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Patient Centric Pharmaceutical Drug Product Design:

Methodological overview and formulation development of solid oral dosage form film coatings for enhanced gliding performance

DOCTORAL THESIS

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STATUTORY DECLARATION

I declare that I have authored this thesis independently, that I have not used other than the declared sources/resources, and that I have explicitly indicated all material that has been quoted either literally or by content from the sources used. The text document uploaded to TUGRAZonline is identical to the present doctoral thesis

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We get these pills to swallow

How they stick

In your throat

Tastes like gold

“No one knows”

Queens Of The Stone Age

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Summary

In recent years, patient centric pharmaceutical drug product development has become more prominent within the pharmaceutical industry and healthcare systems. The one-size-fits-all manufacturing strategy is no longer attainable to current worldwide highly heterogenic societies, especially when considering an increasingly older and frail population living with several comorbidities. As major therapeutic intervention in developed countries, drug delivery administered in the form of solid oral dosage forms (SODF) is therefore increasing the burden of older patients to safely and effectively administer their oral medications, namely large tablets and capsules that need to be swallowed and move throughout the oro-esophageal system. To address this, future pharmaceutical development activities must consider the specific needs of the target patient population and incorporate these into drug product design (e.g., oral dose size reductions). Therefore, special considerations to dosage form and packaging designs, including label information or product leaflets, should also be taken into consideration during development of new medicinal products.

This doctoral thesis addresses the overall topic of patient centric pharmaceutical drug product design, with special emphasis on new patient centric technologies to enhance swallowability of SODF. The introductory section of the thesis includes:

A general overview into the current state of the art for patient centric pharmaceutical development in existing healthcare systems and perspectives for drug product design that can better meet patients' needs. As patient centricity is expected to have a huge impact in the quality of life of future generations, the concerned stakeholders must still adapt existing business development models to integrate a patient centric approach into pharmaceutical development.

A literature review into the available clinical evidence to measure patient appropriateness, acceptability, and preference for drug products among diversified patient populations worldwide. The development of suitable methodologies for the evaluation of drug product appropriateness, including studies investigating patient-drug product interface are still very limited, which suggests that current claims used for age-appropriateness of medicines lack scientific evidence.

A literature and patent reviews on available administration aids and coating materials suggested to enhance SODF swallowability. As scientific evidence demonstrating the benefits of identified coating materials and administration aids in the concerned patient populations are still very limited, the availability for safe, effective, and clinically proven solutions to address the increasing prevalence of swallowing issues in the older patient population are still very limited.

The experimental section of the thesis includes:

A screening on literature-reported methodologies that could be adopted into this framework, which included *in vitro* and *in vivo* studies focusing on mucoadhesive potential of different polymers and esophageal transit of uncoated/coated SODF, respectively. The identified *in vitro* methods using fundamentals based on particle interactions and mechanical forces were applied to measure the mucoadhesive potential of different water-soluble polymers, and generate preliminary data on low mucoadhesive materials that when applied to coating formulations may improve the oro-esophageal gliding performance of SODF. Nevertheless, as none of the *in vitro* methods applied are able to predict the gliding performance or mimic the oro-esophageal transit of SODF, *in vivo* studies in humans remain as the gold standard.

The development of an innovative *in vitro* system that considers the hydrodynamic interactions between coating layers and mucous layers, allowing a detailed gliding performance characterization of different coating formulations and extrapolation of their predictive oro-esophageal transit when combined with multivariate statistical analysis, therefore complementing the limitations previously identified on limited methodology to address this research problem.

The formulation development and manufacturing of different film coating materials, including their gliding performance characterization using the developed *in vitro* system, to identify suitable coating formulation recipes that demonstrate enhanced gliding performance and subsequent desired oro-esophageal transit when applied to SODF. Generally, favorable gliding properties were obtained for coating combinations in which xanthan gum and/or gellan gum were applied as film-forming agents. Sodium alginate and SLS showed beneficial effects when applied as slippery-inducing agent.

Lastly, the main conclusions of this framework are summarized, and perspectives for future work addressed.

Zusammenfassung

Die patientenzentrierte Entwicklung von Arzneimitteln hat in der Pharmaindustrie und im Gesundheitswesen an Bedeutung gewonnen. Die einheitliche Fertigungsstrategie ist für die derzeit weltweit stark heterogenen Gesellschaften nicht mehr erreichbar, insbesondere wenn man eine zunehmend ältere und gebrechliche Bevölkerung betrachtet, die mit mehreren Komorbiditäten lebt. Als wichtige therapeutische Intervention in Industrieländern erhöht die Verabreichung von Arzneimitteln in Form fester oraler Darreichungsformen (SODF) daher die Belastung älterer Patienten, ihre oralen Medikamente, nämlich große Tabletten und Kapseln, die geschluckt werden müssen, sicher und effektiv zu verabreichen Bewegen Sie sich durch das oro-ösophageale System. Um dies anzugehen, müssen zukünftige pharmazeutische Entwicklungsaktivitäten die spezifischen Bedürfnisse der Zielpatientenpopulation berücksichtigen und diese in das Produktdesign einbeziehen (z. B. orale Dosisgrößenreduktionen). Daher sollten bei der Entwicklung neuer Arzneimittel auch besondere Überlegungen zu Darreichungsform und Verpackungsdesigns, einschließlich Etiketteninformationen oder Produktbroschüren, berücksichtigt werden.

Diese Doktorarbeit befasst sich mit dem Gesamtthema des patientenzentrierten pharmazeutischen Produktdesigns, wobei der Schwerpunkt auf neuen patientenzentrierten Technologien zur Verbesserung der Schluckbarkeit von SODF liegt. Der einleitende Teil der Arbeit umfasst:

Ein Überblick über den aktuellen Stand der patientenorientierten pharmazeutischen Entwicklung in bestehenden Gesundheitssystemen und Perspektiven für das Design von Arzneimitteln, die die Bedürfnisse der Patienten besser erfüllen können. Da die Patientenzentrierung voraussichtlich einen großen Einfluss auf die Lebensqualität künftiger Generationen haben wird, müssen die betroffenen Stakeholder bestehende Geschäftsentwicklungsmodelle anpassen, um einen patientenzentrierten Ansatz in die pharmazeutische Entwicklung zu integrieren.

Eine Literaturübersicht über die verfügbaren klinischen Beweise zur Messung der Angemessenheit, Akzeptanz und Präferenz von Patienten für Arzneimittel bei diversifizierten Patientenpopulationen weltweit. Die Entwicklung geeigneter Methoden zur Bewertung der Angemessenheit von Arzneimitteln, einschließlich Studien zur Untersuchung der Schnittstelle zwischen Patient und Arzneimittel, ist noch sehr begrenzt, was darauf hindeutet, dass die derzeit für die Angemessenheit von Arzneimitteln verwendeten Angaben keine wissenschaftlichen Beweise enthalten.

Eine Literatur- und Patentübersicht über verfügbare Verabreichungshilfen und Beschichtungsmaterialien schlug vor, die Schluckbarkeit von SODF zu verbessern. Da wissenschaftliche Belege für die Vorteile identifizierter Beschichtungsmaterialien und

Verabreichungshilfen bei den betroffenen Patientenpopulationen immer noch sehr begrenzt sind, ist die Verfügbarkeit sicherer, wirksamer und klinisch erprobter Lösungen zur Bewältigung der zunehmenden Prävalenz von Schluckproblemen in der älteren Patientenpopulation immer noch sehr hoch begrenzt.

Der experimentelle Teil der Arbeit umfasst:

Ein Screening auf in der Literatur berichtete Methoden, die in diesen Rahmen übernommen werden könnten, einschließlich In-vitro- und In-vivo-Studien, die sich auf das mukoadhäsive Potenzial verschiedener Polymere und den Ösophagustransit von unbeschichtetem / beschichtetem SODF konzentrieren. Die identifizierten In-vitro-Methoden unter Verwendung von Grundlagen, die auf Partikelwechselwirkungen und mechanischen Kräften basieren, wurden angewendet, um das mukoadhäsive Potenzial verschiedener wasserlöslicher Polymere zu messen und vorläufige Daten zu mukoadhäsiven Materialien zu generieren, die bei Anwendung auf Beschichtungsformulierungen die Gleitleistung der Speiseröhre verbessern können von SODF. Da jedoch keine der angewandten In-vitro-Methoden die Gleitleistung vorhersagen oder den oroösophagealen Transit von SODF nachahmen kann, bleiben In-vivo-Studien am Menschen der Goldstandard.

Die Entwicklung eines innovativen In-vitro-Systems, das die hydrodynamischen Wechselwirkungen zwischen Überzugsschichten und Schleimschichten berücksichtigt und eine detaillierte Charakterisierung der Gleitleistung verschiedener Beschichtungsformulierungen und eine Extrapolation ihres prädiktiven oroösophagealen Transits in Kombination mit einer multivariaten statistischen Analyse ermöglicht, ergänzt die Einschränkungen zuvor anhand begrenzter Methoden zur Lösung dieses Forschungsproblems identifiziert.

Die Entwicklung und Herstellung von Formulierungen für verschiedene Filmbeschichtungsmaterialien, einschließlich ihrer Charakterisierung der Gleitleistung unter Verwendung des entwickelten In-vitro-Systems, um geeignete Rezepturen für Beschichtungsformulierungen zu identifizieren, die eine verbesserte Gleitleistung und einen anschließenden gewünschten oroösophagealen Transit bei Anwendung auf SODF zeigen. Im Allgemeinen wurden günstige Gleiteigenschaften für Beschichtungskombinationen erhalten, bei denen Xanthangummi und / oder Gellangummi als Filmbildner angewendet wurden. Natriumalginat und SLS zeigten vorteilhafte Wirkungen, wenn sie als rutschiges Induktionsmittel angewendet wurden.

Zuletzt werden die Schlussfolgerungen dieses Rahmens angesprochen und Arbeitsperspektiven gegeben.

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Background

Solid oral dosage forms (SODF) remain as the most common delivery vehicle for patients to administer drugs into the body. These present several advantages from a patient perspective, as they are the easiest route for drug delivery, non-evasive, and allow independent administration and handling. From a technological point of view, SODF are for decades well established in the pharmaceutical industry and manufacturing activities are cheaper as compared to other delivery technologies (Liu et al., 2014). Furthermore, provided with a wide variety of "smart" excipients on the market, the manufacturing of SODF allow a range of functionalities that can contribute for improved patient compliance. These may include non-functional and functional materials that are applied to SODF for several reasons. Non-functional coatings are usually applied for taste masking to hinder the potential bitter taste of active pharmaceutical ingredients or excipients, for tablet appearance improvement, protection from moisture and better swallowability. On the other hand, functional coatings are controlled and extended systems that are applied to govern the drug release rate from the SODF, reducing dose administration frequency and improving patient acceptability (Felton et al., 2013; Kestur et al., 2016; Palani et al., 2015). The coating of larger SODF is typically performed in perforated drum coaters whereas coating of multiparticulates are conducted in a fluidized bed equipment. For both cases, the coating material is dissolved or suspended in a suitable liquid vehicle and sprayed onto the SODF, leading to the formation of a thin polymer-based film upon evaporation of the solvent. Based on the type of polymer and coating applied, the generated films will then provide functional or non-functional characteristics to the SODF (Cerea et at., 2004; D. Douroumis, 2007; Maderuelo et al., 2019; Saleh et al., 2007). With a wide range of possibilities to improve patient compliance, SODF will continue playing a crucial role during pharmaceutical development of new drug therapies and impact healthcare provision in the upcoming decades.

In recent years, patient centric pharmaceutical drug product development has become a hot topic within the pharmaceutical industry. The assumption that "one size fits all" during drug product development is no longer sustainable in today's world, especially considering that the population lifespan is constantly increasing due to better healthcare systems and drug therapies that can address life-threatening diseases (Stegemann et al., 2016; 2018). Healthy adult populations are typically able to cope and manage independently standard oral dosage forms such as tablets and capsules, including their packaging presentations, however, the same may not be applicable considering special patient populations such as older patients, the cognitively and visually impaired, or patients suffering from specific diseases (e.g., dysphagia, arthritis, Alzheimer, Parkinson) (Atkin et al., 1994; Braun-Münker et al., 2015; Dietlein et al., 2008;

Le Gallez et al., 1984). In addition, these specific populations also tend to present a high incidence of swallowing problems, leading to administration issues and potential cases of drug manipulation to improve swallowability, which may expose the patient to drug toxicity or loss of treatment efficacy (Schiele et al., 2013; 2015). As such, future pharmaceutical development activities should consider the specific needs of the target patient populations in the drug product design. This approach would contribute for drug products that will meet the specific needs of patients, enhancing drug product handling and administration, and contributing for treatments with increased efficacy and safety (Stegemann et al., 2018).

This thesis addresses the subject of patient centric pharmaceutical drug product design and focuses on the development of new *in vitro* methodology to support the screening and characterization of suitable coating technologies with enhanced gliding properties throughout mucosal layers, including their statistical correlation to predictive *in vivo* oro-esophageal transit.

The first half of the thesis is theoretical, and includes: 1) a general introduction into the current state of the art for patient centric pharmaceutical development in existing healthcare systems is addressed and perspectives for future drug product design regarding solid oral dosage forms are discussed; 2) a review into the available clinical evidence and existing methodologies to access patient appropriateness, acceptability, and preference for drug products among all types of patient populations was conducted; and 3) a literature and patent review to assess the availability of surface coating treatments and drug administration aids claimed to enhance SODF swallowability.

The second half of the thesis is experimental and involves: 4) an evaluation of the reduced mucoadhesive properties for different water-soluble polymers using *in vitro* methods based on particle interactions and mechanical forces, including their sensitivity and associated bias for differentiating reduced mucoadhesion to suggest an optimal setup; 5) an overview on *in vitro* and *in vivo* methodology reported in the literature to evaluate mucoadhesion and esophageal transit of oral dosage forms, including their limitations and points to be considered; leading to 6) a new *in vitro* method developed to evaluate and characterize the gliding performance of different film coating materials across mucosal tissue; and culminated in 7) the formulation screening of different SODF film coating compositions for optimized gliding performance using the developed *in vitro* system, including their statistical correlation to predictive *in vivo* oro-esophageal gliding performance.

Lastly, the main conclusions of this doctoral thesis are summarized, and perspectives for future work discussed.

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Perspectives for patient centric pharmaceutical drug product design

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Abstract

Additional costs for healthcare provision are expected for cases where the level of care provided is not according to the patient's needs and demands. To address these issues and reduce costs, fundamental changes need to be made on how healthcare provision is administered to patients, which raises the opportunity for the implementation of patient centric systems. This review addresses the importance of implementing a patient centric approach in current healthcare provision and emphasizes the need to adjust current development and business models for a successful application of patient centric care. To increase awareness and avoid confusion, the purpose of patient centric pharmaceutical drug product design is reviewed in detail and future market opportunities for patient centric drug products are discussed. In the upcoming future, drug product design will focus more on the customization of existing technologies (e.g., dosage form size reduction) to address the needs of specific patient based on patient centric principles for populations such as pediatrics, geriatrics, dysphagia patients or the cognitively impaired.

Keywords: drug product design, healthcare provision, patient centric, patient characteristics, patient needs, pharmaceutical product, product characteristics, solid oral dosage form.

1. Introduction

In current days, the majority of healthcare systems across the industrialized countries are facing global challenges. These challenges are related to the constant increasing costs of basic healthcare provision, with no optimal improvements in the level of care provided to the patients (IBM Corporation, 2006; Levit et al., 2013).

The governmental institutions and involved industries play a crucial role in shaping the way that healthcare is administered to the patients. Yet, their focus is still maintained in keeping healthcare and innovation costs at minimum levels in order to reduce the financial burden, which later is reflected by healthcare solutions that do not always fit the needs of the patients. As a result, additional costs for healthcare provision are expected for cases where the patients are not comfortable with the options offered by healthcare professionals (Iuga and McGuire, 2014; Tang et al., 2004).

To address these issues and reduce healthcare costs, fundamental changes need to be made on how healthcare provision is administered to patients, which raises the opportunity for the implementation of patient centric systems (Chen et al., 2016). A patient centric approach does not require specific rules or guidelines, as it simply

involves patients in their healthcare progression and allows them to receive the most appropriate treatment at a reasonable cost. By placing the patients' needs in first place, the patient centric model will require a high level of both patient and healthcare professional commitment, responsibility and accountability to deliver efficacious treatments while reducing costs (Greene et al., 2012). If successfully applied, this model can benefit every segment of healthcare provision by improving the general health of patients and reducing global expenses for payers and governmental institutions.

The purpose of this review is (i) to address the importance of implementing a patient centric approach in current healthcare provision, (ii) to emphasize the need of modifying current development and business models for a successful application of patient centric care, (iii) to clarify the importance of patient centric pharmaceutical drug product design, and (iv) to discuss future market opportunities in which patient centric pharmaceutical products can bring added value to patients.

2. The patient centric model in healthcare provision

Up till now, the gold standard of patient autonomy and involvement across clinical care as well as research has been mainly based on "consent" rather than "centricity" (Demiris et al., 2008). Therefore, the patient's opinions or preferences are usually omitted and vulnerable to healthcare professionals' decisions (Bien et al., 2017; Brennan and Strombom, 1998). For example, in a routine visit to the clinic, the patient only possesses an active role in the initial phase of the appointment with the doctor, mostly by reporting the reason for the visit and any disease-related symptoms that need to be addressed. From this point on, the doctor frequently takes action and performs a differential diagnosis that may include physical examinations to confirm the patient's complaints, with further prescription of any medicines required to attenuate the patient's symptoms (Altin and Stock, 2016; Pomey et al., 2015). The visit is terminated with the delivery of the prescription to the patient, which demonstrates its passive role during the whole procedure, with no further exchange of feedback or relevant information. As such, a doctor's appointment has become an automated and time-limited process that lasts 5 to 15 min, with no time for the patient to share his ideas or treatment preferences (Backer, 2002; Gupta and Denton, 2008).

The patient typically has access to a more personalized care during the visit to the pharmacy, where the healthcare professional dispensing the prescription is responsible to explain the purpose, duration, posology or administration steps required for the treatment. Moreover, since the interaction between both is not time-dependent, the patient feels more comfortable to ask questions or expose treatment-related

uncertainties that can be promptly clarified by the pharmacists (Davis et al., 2014; Smith, 2009).

Patient centric care is a term that has been increasingly used in recent research reports and clinical settings, however, it is still not very clear what it means. A common assumption is that patient centric relates to the involvement of the patient in the healthcare process and its interaction with healthcare providers (Stegemann et al., 2016). Although correct, patient centricity is a much broader subject that was designed to account patients' individual preferences, values and beliefs in the selection of their therapeutic choices by healthcare professionals (Yeoman et al., 2017). It helps patients and their caregivers to communicate and make informed healthcare decisions, allowing them to have an active voice in assessing which healthcare options are more valuable for each specific case ("PCORI. Patient-centered outcomes research"; Williams et al., 2007). Notwithstanding, if patient centric care is simply related to the patient's involvement in the selection of its treatment or care, then words like "engaged" or "empowered" could easily replace centricity (Robbins et al., 2013). The word centricity is used to demonstrate that the patient is at the center from start to finish during healthcare provision (Fig. 1), and all the involved professionals are invited to help the patient in navigating the decision-making process to make it more personally useful (Curro et al., 2013, 2015).

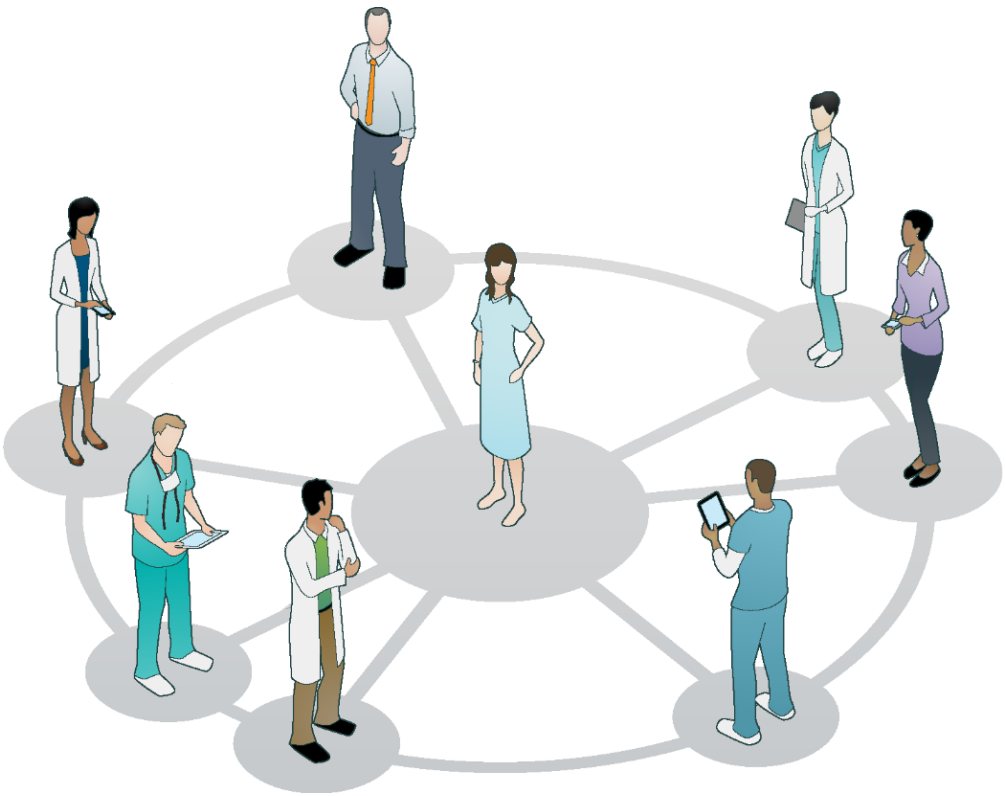

Fig. 1. The patient always at the center during patient centric healthcare provision.

Yet, this process is not simple and requires a deep understanding of the patient's capabilities to codify the information provided from the different healthcare professionals. In order to accomplish this, professionals must guide patients through the different steps involved in healthcare provision and transform complex information into something that can be easily understandable, therefore helping centric patients in taking the right decision for their own health benefits (Huang et al., 2016; Levit et al., 2013).

As patients cannot be instantaneously empowered with knowledge and experience to manage their healthcare alone, the involved professionals need to be adequately informed about patients' health literacy, knowledge, and power disparities, in order to provide them valuable tools that can contribute for an appropriate decision of which therapeutic approach to follow (Fisher, 2008). With this regard, since the final decision relies on the patient, an active participation is highly beneficial and centricity can be supported by constant updates of the healthcare needs of the patient (Vahdat et al., 2014). This approach would contribute for huge savings with healthcare costs since patients are highly involved on their therapeutic choices and can adequately address their needs, increasing the efficacy of prescribed treatments and reducing the incidence of potential hospitalizations (Bertakis and Azari, 2011; Collins et al., 2013).

3. Implementation of a patient centric model requires modification of current development and business patterns

Most of pharmaceutical products remain as single active ingredients formulated as conventional solid dosage forms that are dispensed in bottles or blister packs (Liu et al., 2014). The reason for the lack of innovative progress is highly related to the continuous application of an old pharmaceutical development model that needs to be reconsidered. The model continues to prioritize the compliance with regulatory requirements and return on investment, rather than investing time on the development of pharmaceutical products according to the specific needs of the final consumer – the patient (Schuhmacher et al., 2016; Stegemann and Bresciani, 2014).

The costs related to patients' nonadherence to prescribed therapies is estimated to be approximately 100 billion USD per year (Hughes, 2004). Adherence and effectiveness of treatments were identified to have a great impact on the general health of the population by reducing medical costs related to cases of improper use of drug products, nonadherence or adverse drug reactions (Haynes et al., 2002). The current pharmaceutical business model is one of the main responsible for these costs, as it is no longer adapted to modern healthcare demands (Taylor, 2015). This creates an opening for new critical thinking for redefinition of the model, preferably to one in which the patient

plays a central role (Rao, 2010). Moreover, it launches opportunities for the development of new technologies that can increase adherence and patient compliance to medication regimens (Sabaté, 2003).

New guidelines have addressed the need for drug products to be designed according to the specific needs of the targeted patient population (EMA, 2015). Nevertheless, based on the current model used for clinical trials, the patients' characteristics are not appropriately addressed. Even though the major user group for a new drug product is known, the targeted patient population is usually not represented in the clinical trials conducted (Cerreta et al., 2012). A patient centric approach needs to be adopted, where the patient's needs and preferences are considered from the early stage of drug product development and the targeted patient population is highly represented during clinical studies (Sharma, 2015). This will ultimately lead to the design and development of pharmaceutical products that patients can intuitively understand, manage and administer properly (Leiner et al., 2015). In addition, the implementation of patient-reported outcomes during clinical trials can highly contribute for the development of optimized designs (e.g., dosage form and packaging) based on the patient's feedback and experience with the drug product (Kwan et al., 2016). This approach will contribute for increased patient adherence after the launch of the drug product in the market while reducing treatment costs (Bosworth et al., 2011). With this in mind, a Patient-Centered Outcomes Research Institute was implemented in Washington (USA) in 2010, proving that efforts are being made for the development and expansion of a patient centric healthcare system (Selby et al., 2012).

4. Patient centric pharmaceutical drug product design

Patient centric pharmaceutical drug product design is a broad term that combines the terms "pharmaceutical drug product design" and "patient centricity". The topic was created to address the need of considering the targeted patient population characteristics in the product design. As such, the drug product should include non-complex elements that intuitively lead the patient to use it easily and as intended, preventing adherence problems or administration errors (Stegemann et al., 2016).

The constant improvements in healthcare provision and the continuous discovery of new therapies for several diseases has led to the increase of special patient populations such as very old and multi-morbid, cancer survivors and dementia patients (Nobili et al., 2011). Alongside, medication management with regard to these patients becomes very complex due to an increase in the number of drug products, dosage forms and dosing frequency (Libby et al., 2013). The capability of these patients to manage complex medication regimens is very limited and may have to rely on caregivers (Look and Stone,

2017). This is a predictor for a higher incidence of medication errors and poor adherence for cases where the pharmaceutical product was not designed according to the patient characteristics and needs (Boyd et al., 2014; Ehlenbach et al., 2015; Stenholm et al., 2015). Therefore, patient centric pharmaceutical drug product design plays a crucial role in developing or designing pharmaceutical products according to patients' needs.

A patient centric design approach can be taken by predicting the characteristics (skills, impairments, co-morbidities) of the final consumer and consider them during the initial development and design of pharmaceutical products. As example, patients with limited manual dexterity (e.g., due to arthritis) may not be able to access the medication contained in a specific packaging (Atkin et al., 1994; Carmeli et al., 2003). Other cases can include patients that may experience difficulty in reading the product label or understanding the package leaflet due to poor visual acuity and low literacy, respectively (van Beusekom et al., 2016). By applying a patient centric model, increase attention would be given to the packaging design and opening mechanism during development of the pharmaceutical product. . Therefore, anticipating the characteristics of the targeted patient population at the time of product design is likely to generate an optimized pharmaceutical product that delivers the specific needs of patients in a real-world setting, something which is not taken into account in current randomized clinical trials (Saad et al., 2017).

In order to generate a patient centric basis for guidance during pharmaceutical development, a system composed of design drivers, design inputs and design outputs can be implemented. The design drivers and design inputs are derived from the targeted patient population and can be identified through routine checkups (e.g., geriatric assessments). Subsequently, the involved healthcare professionals (e.g., doctor, nurse, pharmacist, etc.) are responsible to identify the most important design outputs and select the most suited pharmaceutical drug product accordingly. This will then contribute for an optimal interaction between the patient and the drug product, which will ultimately lead to an appropriate use and effective treatment (Onder et al., 2013; Stegemann et al., 2016). Since patients present different health literacies, the efficient delivery of relevant product information by healthcare professionals will also play an important role in the treatment success (Greenhalgh, 2015; Mullen, 2013; Wong et al., 2014). Studies involving patient-reported outcomes will become an integrating tool of patient centric pharmaceutical drug product design, as they will collect feedback on experience of patients with a specific drug treatment and contribute for a greater understanding of product design (Reeve et al., 2013; Rothman et al., 2009).

5. Perspectives for patient centric pharmaceutical design regarding solid oral dosage forms

Over the years, research and development activities in academic, pharmaceutical and research organizations have contributed for new innovative products and scientific know-how. This has led to a constant increase in the number of novel dosage forms and formulation technologies available to the patients. Nevertheless, the majority of drug products available on the market remain as solid oral dosage forms (Liu et al., 2014).

For drugs that can be delivered orally, solid oral dosage forms are and will continue as main drug delivery technology due to its technological applications, which can be applied or adapted to meet patients' needs (e.g., taste masking, extended release). In addition, the development and manufacturing of solid oral dosage forms is very well established in the pharmaceutical industry and it is the technology of choice whenever applicable due to its cheaper price.

With regards to solid oral dosage forms, the subject of patient centric pharmaceutical drug product design will focus more on the customization of existing drug delivery technologies (e.g., dosage form size reduction) to address the needs of specific patient populations such as pediatrics, geriatrics, dysphagia patients or mentally ill patients (Maalouf, 2013).

One frequent issue that affects all these patient populations when practicing drug therapy is their inability to swallow tablets or capsules. In pediatric patients, there is often a fear of chocking during the administration of the dosage form, whereas mentally ill patients often skip their medications by hiding the dosage form in their cheeks (Latha, 2010). Considering geriatric and dysphagic patients, there is a general difficulty to swallow related to a deterioration of the swallowing function due to aging, specific diseases or co-morbidities, which challenges the oral administration of drug products (Stegemann et al., 2012). These situations raise opportunities for patient centric research, as these issues can be addressed with the development of patient centric pharmaceutical drug products that can complement the specific needs of each specific patient, increasing therapy efficacy and patient compliance (Liu et al., 2014).

In the past, dosage form design helped to address the specific needs of geriatric patients through simple variations on the physical appearance related to size, shape or color. In addition, extended-release formulations or combined products have also helped to decrease the dosing frequency and pill burden. A recent breakthrough in patient centric dosage forms was achieved with the development of orally disintegrating tablets (Hannan et al., 2016). It is usually stated that these are easy-to-swallow dosage forms, which allow the administration of a tablet that can be swallowed in the form of a liquid or

suspension. However, considering dysphagic patients, the administration of a liquid formulation can be associated to a higher risk for aspiration when compared to solid forms (Schiele et al., 2015).

Other progresses in patient centric dosage forms were performed to address drug delivery among pediatric populations. Liquid formulations such as syrups and suspensions have for long been considered the most appropriate type of dosage form for young children. Nevertheless, liquid formulations present several problems during administration such as bad taste and dose measuring errors (van Riet-Nales et al., 2011). The introduction of new European Medicine Agency (EMA) guidelines addressing the development of appropriate medicines for the pediatric population (EMA, 2006; The European Parliament and The Council of the European Union, 2006) led to a general understanding that solid oral dosage forms such as multiparticulates and minitablets are suitable patient centric options, enabling proper administration, flexible dosing and high acceptability in young children (Klingmann et al., 2015, 2013; Spomer et al., 2012). In addition to pediatrics, the same approach should be applied to specific patient populations suffering from diseases that affect the activity of voluntary muscles such as Amyotrophic Lateral Sclerosis (ALS) and muscular dystrophy, which will ultimately lead to patients with impaired swallowing function and impact oral administration of drug products.

Considering older adults, a similar approach was recently applied by EMA to encourage the pharmaceutical development of appropriate medicines that can address the specific needs of this special patient population (European Medicines Agency, 2017). Although regulatory proceeding has started, real technology progresses are yet to be made (van Riet-Nales et al., 2016). Since older patients tend to present an aged and deteriorated swallowing function (dysphagia), these may also struggle to swallow large tablets and capsules. Therefore, the patient centric approach currently in development for the pediatric population can also be transferred to the geriatric population, as these patients would benefit from solid oral dosage forms such as minitablets or multiparticulate systems to facilitate oral drug administration and increase efficacy and safety of prescribed treatments by reducing the cases of drug product manipulation to improve swallowability.

During development of solid oral dosage form drug products, a wide range of presentations should be manufactured to meet specific needs of different patient populations. In addition to the typical manufacturing of conventional tablets and capsules that typically meet the needs of the normal adult population, the manufacturing of dosage form size reduction presentations should also be considered and introduced during routine development. This approach will lead to drug products that can globally impact

patients and enhance therapy regimens, as it would not only meet the standard needs of the adult population, but also the needs for pediatrics, older adults, and patients suffering from swallowing issues due to specific conditions (Marconati et al., 2018). For cases of drug products which remain in a conventional tablet or capsule presentation (e.g., high drug loads), a patient centric approach could involve the development of appropriate surface conditions that can aid the swallowability and gliding properties of tablets and capsules during oro-esophageal transit. This can be obtained through the development of new coating technologies that present poor mucoadhesive properties and increased gliding performance across the oro-esophageal system. Since the currently available options still do not meet patients' needs for enhanced swallowability, it is therefore expected an increase in methodological research for the development of appropriate surface coatings that can optimize the swallowing function and administration safety of solid dosage forms.

Patient centricity is expected to have a huge impact in the quality of life of future generations. Consequently, the involved stakeholders need to adapt and integrate a patient centric approach into their visions, which will allow them to remain competitive and deliver innovative solutions for current patient needs. Substantial efforts have already been made through the development of patient centric departments or creation programs to keep a closer relationship with patients. Notwithstanding, the pharmaceutical industry and related organizations are still far from reaching its fully potential, and a higher predominance of patient centricity in healthcare provision will be expected in future years.

6. Conclusions

In the years to come, a higher predominance of patient centric research and patient centric healthcare systems is expected to be established across developed countries. The adoption of a patient centric care is expected to benefit patients and contribute for huge savings with healthcare costs. Through a solid commitment of all parts involved, patients will be highly engaged to their therapeutic choices, as these will appropriately address their specific needs. This will contribute for higher adherence levels and reduced events of medication errors or potential adverse drug reactions, which eventually reflect less number of hospitalizations. The recent updates in regulatory regulations encouraging the developing appropriate medicines for special patient populations (e.g., pediatrics and geriatrics) indicate that patient centric pharmaceutical drug product design is slowly getting shape, with the involved industries also starting to adapt to this new reality. As such, a higher attention and dedication to dosage size reduction during development and manufacturing of solid oral dosage forms will become a standard

routine and drug product presentations in the form of multiparticulate systems or minitablets are expected to be more frequent in the upcoming years.

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- 3 -

Patients' appropriateness, acceptability usability and preferences for pharmaceutical preparations

- Results from a literature review on clinical based evidence -

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Abstract

Patients play an important role in achieving the desired therapeutic outcomes, as they are frequently responsible for their own medication management. To facilitate drug administration and overcome medication issues, the patients' needs and preferences should be considered in the pharmaceutical drug product design. With the aim to evaluate the current state of evidence for patient appropriateness, acceptability, usability and preference for aspects of this design, a literature search was performed. Comparative clinical studies that assessed such endpoints for different patient populations were included and summarized descriptively. The search identified 45 publications that met the inclusion criteria. A detailed analysis of the studies identified two main areas investigating either packaging design (n=10) or dosage form design (n=35). Studies on packaging design showed preferences for wing top and screw cap openings, push-through blisters and suppositories with slide system. Additionally, child-resistant containers should be avoided concerning specific patient populations. Regarding dosage form design, sprinkles and minitablets were the most preferred in studies involving young patients, while preferences varied considerably depending on route of administration and geographical region in studies with adult patients. Review of the methodology used in the studies revealed that ten studies had used well-defined protocols and observational endpoints to investigate patient appropriateness. Studies focusing on methodology for testing the appropriateness and usability of drug products by patients were not found. In conclusion, more interdisciplinary scientific efforts are required to develop and increase research in understanding patient needs and preferences.

Keywords: acceptability, appropriateness, dosage form design, drug product, packaging design, pharmaceutical development, preference.

1. Introduction

The clinical efficacy of medicines for human use is established through randomized clinical trials during the development and subsequent marketing of the drug products. There is growing evidence that the expected clinical outcomes in a real-world treatment setting are often not being achieved. The observed gaps between efficacy and effectiveness have been recently analyzed suggesting that patient perception, therapy management, health literacy, adverse reactions and issues associated with navigating through the health systems play important roles (Eichler et al., 2011). Additionally, the increasing age and multimorbidity of the patients correlates with a higher incidence for

polypharmacy (Charlesworth et al., 2015). Both multimorbidity and polypharmacy significantly increase the burden for patients and their caregivers to manage the growing complexity of the medications as recommended. For the management, handling and administration of medicines, the patients must interface with the drug product across various cognitive, motoric and sensory domains. It has been shown that this interface can be substantially impacted by patients' age or disease patterns, as well as by drug product characteristics that are not appropriate for the target patient or patient populations (Notenboom et al., 2014; Stegemann et al., 2010). For example, patients suffering from arthritis, cognitive decline, or other conditions may struggle to get through pharmaceutical packaging and access the medication contained inside (Beckman et al., 2005; Swanlund, 2010). Additionally, the administration of specific dosage forms might not be feasible in functionally impaired patients or in health illiterate patients who do not understand the instructions (e.g., suppositories, transdermal systems, inhalation products) (Heppner et al., 2006).

The importance of the drug product design was first recognized for the pediatric patient population due to the limited availability of medicines in suitable formulations. Thus, the related high rates of off-label prescribing, or inappropriate modifications of drug products are worldwide concerns (Van Riet-Nales et al., 2010). In order to surpass these limitations, a regulation for pediatric medicines was established in January 2007 (The European Parliament and The Council of the European Union, 2006). Nevertheless, a systematic literature search aiming at comparative studies on product design aspects like the type of dosage form, route of administration, formulation, acceptance and other related aspects for the pediatric population only revealed two studies meeting the expected quality standards for clinical trials (Van Riet-Nales et al., 2010). Another study also confirmed the limited availability of pediatric medicines for a broad range of therapeutic areas (Van Riet-Nales et al., 2011). Recent ICH guidelines have introduced a new quality by design (QbD) concept, which include the requirement that "in all cases, the product should be designed to meet patients' needs" (EMA, 2015). Moreover, the Dutch Regulatory Agency strategic business plan (Medicines Evaluation Board; 2014-2018) has put the patients' interest first, focusing on the entire life cycle of medicinal products from the early development stage until their use in real world practice. These regulatory efforts confirm the need for more interdisciplinary research on how patient needs should be addressed in the drug product design (College ter Beoordeling van Geneesmiddelen, 2013).

A preliminary literature review on the evidence for appropriateness of aspects in the drug product design with respect to older patient populations has already been conducted (Messina et al., 2015). The aim of this study was to perform a literature review

with the purpose of identifying clinical evidence for patient appropriateness, acceptability, and preference for drug products among all the target age populations. A secondary objective of this work was to recognize validated methodology used to determine such endpoints and to identify suitable methodology for testing the appropriateness and usability of drug products by patients.

2. Methods

2.1. Definitions

A list of keywords were collected to develop a suitable search profile. For the sake of clarity, definitions for some of the important terms constantly found in this literature research (Table 1) were used according to Stegemann et al. (Stegemann et al., 2016) and EMA (EMA, 2003). The search also included other terms that are being used in the scientific literature but do not have a commonly agreed definition. Hence, such definitions has been proposed by the authors for use in this review (Table 2).

Table 1. Defined terms used in the literature search.

Term	Definition
Medicine/Drug	Medicinal products from the same company including a specific active substance.
Drug product	Preparation in its container closure system, together with written user instruction (product label and package leaflet).
Preparation	Formulation in a particular strength or, for oral liquids, with specific container contents.
Formulation	Pharmaceutical dosage form with a particular composition and appearance (tablet size, shape, color).
Patient centricity	The recognition of the needs of an individual patient or distinct patient populations and their specific needs as the focal point in the overall design of a medicine including the targeted patients' characteristics.
Pharmaceutical drug product design	The design of the comprehensive presentation of the therapeutic entity to the end user including type of dosage form, formulation, dose, dosing frequency, packaging, medical device, dosing devices, instructions for use.
Patient centric drug product design	The process of identifying the comprehensive needs of individuals or the target patient population and utilizing the identified needs to design pharmaceutical drug products that provide the best overall benefit over the intended duration of treatment.

2.2. Search strategy

A search profile was performed in April 2016 using the PubMed database. Combinations of keywords with their relevant truncations were used to obtain broad searches that could include the majority of relevant publications (Tables 3A-3B).

2.3. Selection process

All studies in English, including those conducted in clinical settings (hospital or nursing centers), as well as those conducted in patients' houses and community settings were considered. Publications written in other languages but with available abstract in English were also considered. No limits were set for the study setting, time frame or date of acceptance/publication.

Table 2. Proposed definitions for important terms addressed in the literature research.*

Term	Definition
Appropriateness	A set of pharmaceutical design characteristics of a drug product that determines within a specific target patient population if a patient and/or its caregivers can use the pharmaceutical drug product as intended.
Acceptability	Sum of positive and negative experiences of a patient and/or caregiver with a pharmaceutical drug product before, during and after use, which will affect the ability and willingness to take or use the drug product as intended.
Usability	The product characteristics and attributes of a pharmaceutical product that enables the patient and/or caregiver in its personal environment and life situation to use the pharmaceutical drug product as intended.
Preference	The personal favored selection of a product attribute over others that is perceived as an advantage whereby all choices are appropriate for the intended patient purpose.

* Acceptability and usability can be considered to fall within the definition of appropriateness while preference is a separate term, which is related to individual preferences regarding specific product elements (e.g., taste, color, etc).

The two co-authors (Drumond and Stegemann) independently performed a primary screening by reviewing the title and abstract of the publications. In the case of being out of the scope of the review, no further evaluations were done and the publication was rejected. The full-text of each remaining article was individually reviewed and screened according to four pre-established inclusion criteria (Table 4). In order to obtain a higher level of evidence, the literature review specifically aimed to retrieve comparative studies (with a minimum of 10 subjects and at least two drug product designs tested) that evaluated and distinguished higher/lower appropriateness, acceptance or preference for distinct drug products, such as the type of dosage form or packaging design. Variables such as appropriateness and acceptability do not possess standard values neither can be quantified, being only measurable by comparison to other references. There were no restrictions for patients' characteristics concerning age or gender. Other studies that evaluated the ability of patients to comply with different types of packaging were included in the review because the packaging has a direct impact on medication usability and is part of the drug product design.

Table 3A. List of keywords used as basis for the defined search profile.

Criteria	Keywords
Drug product terms	delivery system, dosage form, drug, drug delivery, drug formulation, drug product, formulation, generic drug, medication, medicine, pharmaceutical dosage form, pharmaceutical product, pharmaceuticals..
Patient-related outcomes	acceptability, acceptance, adequate, adherence, administration, adolescent, adult, age-appropriate, appropriate, appropriateness, child, compliance, crushing, drug administration, drug effect, drug-related, errors, geriatric, handling, inhaling, injecting, issues, management, manipulation, modification, omission, opening, palatability, patient, patient acceptance, patient centric, patient compliance, pediatric, preference, preferred, problems, route of administration, satisfaction, side effects, skip, skipping, splitting, swallow, swallowing, taking, teenager, tolerability, usage, use, youngster.
Delivery technology	adhesive, auto-injector, buccal, caplets, capsule, conventional tablet, cream, delayed release, delivery system, DPI, dry powder inhaler, emulsion, fast dissolving, film, film coating, film formulation, granules, immediate release, implants, inhalation, inhaler, injectable, injection, intramuscular, intraocular, intravenous, liquid, liquid formulation, lyophilizate, lyophilized powder, melting tablets, meltlets, metered dose inhaler, mini-tablet, mouth dissolving, mucoadhesive, nasal, ocular, ointment, oral, oral disintegrating, orally disintegrating, orodispersible, package, packaging, patches, pellets, pill, powder for reconstitution, prefilled syringe, rectal, sachets, semi-solid, solution, spray, sprinkle, subcutaneous, sublingual, suppositories, suspension, sustained release, syrup, tablet, topical, transdermal.

Table 3B. Search strategy applied in PubMed.

1. "Acceptability" AND "clinical" AND "dosage form"
2. "Appropriateness" AND "clinical" AND "dosage form"
3. "Preference" AND "clinical" AND "dosage form"
4. "Container" AND "packaging" AND "handling" AND "patient"
5. "Container" OR "packaging" AND "opening"
6. "Acceptance" OR "preference" AND "children" AND "mini-tablets"
7. "Acceptance" OR "preference" AND "children" AND "syrup"
8. "Children" AND "randomized" AND "oral" AND "preference"
9. "Children" AND "clinical" AND "sprinkle"
10. "Children" AND "clinical" AND "oral" AND "drops"
11. "Patient" AND "preference" AND "acceptability" AND "dosage form"
12. "Patient" AND "preference" AND "conventional tablet"
13. "Swallowing" AND "size" AND "shape"
14. "Formulation AND "swallowing" AND "satisfaction"
15. "Acceptability" AND "tablet" AND "powder"
16. "Comparison" AND "mini-tablet" AND "tablet"

The obtained studies were further evaluated regarding a list of predefined exclusion criteria (Table 4). To keep the focus on the objective of the review, publications involving medical devices were not included since there are specific guidelines defining relevant studies (FDA, 2011). The appropriateness of dosing aids alone were not considered due to their main dependence on drug product formulation attributes (e.g., color, viscosity). Comparative studies focusing on preferences for specific flavors of liquid formulations (e.g., strawberry, banana) were also not included because they are mainly based on general individual patient and/or regional preferences. Studies comparing different drug substances were not considered since the effect of the different substances might

significantly influence dosage form perception. In addition, retrospective studies were not included since result interpretations cannot be validated due to potential patient's recall bias. Lastly, studies that assessed tablet subdivision were excluded due to the high risk for dosage errors and medication loss, which can lead to incorrect dosing. Such subdivision problems can be impacted by several variables such as disease conditions (Mascarenhas Starling et al., 2015; Wilson et al., 2001), subdivision techniques and accessories used (Van Riet-Nales et al., 2014). Best practices for tablet subdivision were suggested by FDA (U.S. Food and Drug Administration, 2013). Unless otherwise justified, tablet subdivision may be assumed as inappropriate drug product design as it is technically possible to manufacture lower dosed products.

Table 4. Inclusion and exclusion criteria applied to identify suitable publications.

Inclusion criteria	Publications selection criteria
1	Comparative and controlled clinical study design
2	Assessment of two or more distinct dosage forms (placebo or drug) or packaging designs
3	Minimum of 10 volunteers/patients
4	Inclusion of one or more product aspects, patient-related outcomes and delivery technology aspects from Table 2
Exclusion criteria	
1	Investigation in homeopathic, anthroposophic and herbal drug products
2	Comparative studies for medical devices, measuring or administration devices
3	Clinical endpoints only focused on efficacy, safety and PK/PD profiles
4	Appropriateness, acceptability or preferences not measured during the study
5	Comparative studies evaluating different taste preferences for liquid formulations
6	Studies comparing clinical endpoints for different drug substances

2.4. Data analysis

The eligible publications were analyzed and evaluated by the authors (DRU, STE) for the quality of their research target, research methodology and clinical data interpretation. Specific research targets should include a description of formulation, drug delivery technology, dosage form, route of administration and/or frequency of administration used in the study. Validated methodologies with objective endpoint determinations to measure and interpret product design appropriateness, usability or preference in comparison with other pharmaceutical preparations were assessed for their quality. In addition, methodologies used to investigate the appropriateness and

usability of drug products by patients were also investigated. As there was large heterogeneity between the studies, descriptive analysis was used and articles results were summarized in tables (Tables 5-6).

3. Results

3.1. Evaluation of the data collected

The combined publications retrieved from the search syntax (1794 publications) were subjected to the pre-established inclusion and exclusion criteria. Several publications were rejected (1725) because at least one inclusion criterion was missing. After review of the publications potentially eligible for inclusion (69), twenty-six publications (26) were rejected because they were subject to at least one of the exclusion criteria. Forty-three (43) publications were suitable for the review. The references of the included publications were analyzed individually, which lead to the inclusion of two more publications generating a total of forty-five (45) publications included in the review (Tables 5-6).

3.2. Evaluation of the included publications

All of the 45 published studies evaluated different aspects related to drug product design and how patients interact with them. The publications fell into one of two main categories depending on their research focus: packaging design and dosage form design.

3.2.1. Packaging design

This category included 10 publications and was related to studies assessing the ability of patients to cope with different types of packages (Table 5). A total of 958 subjects were enrolled, averaging between 41 and 141 per study. Two main types of populations were targeted, allowing its division in two subcategories: older patients (7 studies) and rheumatic patients (3 studies). Concerning studies with older patients, 38 types of designs were investigated including eyedrop dispensers, blister packs, screw-top containers, childproof containers and others. For studies with rheumatic patients (which also included younger patients), among 37 different packages tested, 28 were containers with different opening features regarding shape and opening mechanism, seven were different suppository packages, while the remaining two were blister and foil packs. The pain experienced during the handling procedure was also measured in two of the studies, being an important factor that should be always considered when assessing rheumatic patients. The obtained results demonstrated that both younger and older patient populations might experience problems when trying to cope with the

different types of packages tested. In addition, child-resistant containers can be very difficult to open (Atkin et al., 1994; Lisberg et al., 1983) and may cause pain, as shown by the studies with rheumatic patients (Le Gallez et al., 1984; Verheggen-Laming et al., 1988).

Table 5. Publications on packaging design included in the review.

	Authors	Research focus	Conclusions
Older patients	Atkin et al., 1994	Ability to handle standard medication packages	Packaging designs significantly impede access to medication
	Braun-Münker et al., 2015	Influence of transparency and tablet/cavity size ratio on patients' handling two different blister materials	Limited movement and shifting space of the dosage form in the blister packaging was the most important factor for fast opening and patient satisfaction
	Dietlein et al., 2008	Ability to apply eyedrops from a single-use container versus standard container	Problems in self-administering eyedrops from single-use containers. Correlation to container size and training administration
	Keram et al., 1988	Quantitative comparison of the difficulty experienced when opening different medication container designs	Ability to open different types of child-resistant containers is variable (30% could not open). Large containers are preferred
	Mühlfeld et al., 2012	Relationship between blister pack designs and utilization problems	Opening force and opening mechanism can impact the usability of blister packs
	Nikolaus et al., 1996	To measure the prevalence of difficulty in opening and removing tablets from a range of common medicine containers	A high rate of failure in opening medication containers was seen. "Push and turn" bottles could not be opened by 2/3 of all tested subjects
	Parkkari et al., 2010	Handling of unit-dose pipettes in comparison to conventional eye drop bottles	Polyethylene unit-dose pipettes were at least as easy to handle as conventional eye drop bottles
Rheumatic patients	Gallez et al., 1984	Ability to handle different tablet containers	Flip off tops, tops with long threads requiring many turns, small and glass containers were unfavorable
	Lisberg et al., 1983	Ability to open a range of reclosable tablet containers and unit dose packs	Child-resistant containers, especially the "click-loc" type, and smaller containers were less easy to open
	Verheggen-Laming et al., 1988	Difficulties involved in removing suppositories from the package	Patients have problems in opening suppository packages

Some drug packaging designs were identified as being more suitable or easier to handle. Eyedrop bottles were preferred compared to single-use eyedrop containers, with a positive correlation observed for the size of the tested product. Bottles with higher surface area were seen as easier to handle and subsequently to administer eyedrops (Dietlein et al., 2008). In another study, polyethylene unit-dose pipettes were at least as easy to manage as conventional eyedrop bottles and appeared to be better for the population studied (Parkkari et al., 2010). A common problem raised with multi-use eyedrop bottles is the presence of preservatives in the formulation. In cases where no preference is manifested, patients could be suggested to use preservative-free

medications in unit-dose pipettes. Containers having tall bases and angulated tops or wing top openings were preferred to other opening designs (Le Gallez et al., 1984). Conventional screw cap tablet bottles were also easier to open when compared to other opening systems such as click-loc closures (Lisberg et al., 1983). Suppositories with slide system were easier to open compared to plastic/aluminum wrappings (Verheggen-Laming et al., 1988). Additionally, push-through blisters were found easier to handle than peel-push blisters, with the last being very difficult to open. For all studies, a positive correlation was found between visual acuity and ability to cope with the packaging technology. Impaired cognitive function and low manual dexterity were other causes for inability to open medicine packaging (Nikolaus et al., 1996). Another positive correlation was observed regarding the size of the packaging design, which proved to have huge impact on proper handling. Smaller packages were more difficult to handle for older patients and patients with impaired hand dexterity (Dietlein et al., 2008; Lisberg et al., 1983).

The methods used for assessment of the packaging design were mainly based in physician/investigator observations (Atkin et al., 1994; Dietlein et al., 2008; Lisberg et al., 1983; Nikolaus et al., 1996) and patient's preference questionnaire (Le Gallez et al., 1984; Mühlfeld et al., 2012; Verheggen-Laming et al., 1988). Only one study used a combination of both methods, with visual observation and patient preference assessment (Keram and Williams, 1988). A schematic image for the studies on packaging design is visualized in Figure 1.

3.2.2. Dosage form design

This category included 35 publications and comprised studies comparing the appropriateness, acceptability or preference for different dosage form designs. Two main types of populations were targeted allowing its division in subcategories: young patients (≤ 18 years, 10 studies) and adult patients (> 18 years, 25 studies).

The studies on young patients were specific to dosage forms for oral administration. Eight types of dosage forms were tested, namely minitablets, syrup, suspension, microspheres, lyophilizates, powders, sprinkles and drops (Table 6). A total of 1396 young patients were enrolled, encompassing all age phases (preterm neonates included in one study). The mean age for all studied patients was 4.93 years. Most of the studies included children younger than 6 years and only one study exclusively enrolled adolescents (10-18 years, McCrindle et al., 1997). Drug-free products were used in four studies in order to evaluate acceptance, appropriateness and swallowability of minitablets in healthy volunteers (Klingmann et al., 2015, 2013; Spomer et al., 2012; Van Riet-Nales et al., 2013). When compared to liquid dosage forms, minitablets commonly

showed better acceptance and no major issues were observed regarding administration and swallowing. Six studies involved patients with a certain type of disease or condition, and medication references were used considering each specific case. Patients suffering from epilepsy and anemia showed better acceptance for a sprinkle formulation in comparison to syrup formulation (Cloyd et al., 1992) and oral drops (Zlotkin et al., 2003), respectively. Another study showed that a tablet formulation was preferred to a powder form considering patients with hypocholesteremia. In patients with nocturnal enuresis, a lyophilizate formulation was better accepted when compared to a tablet form (Lottmann et al., 2007), while minimicrospheres were seen as easier to take for children suffering from cystic fibrosis (Patchell et al., 2002). Lastly, a study with African HIV-infected children showed that minitab sprinkles were better accepted than syrup in younger children, while older children preferred tablets (Musiime et al., 2014).

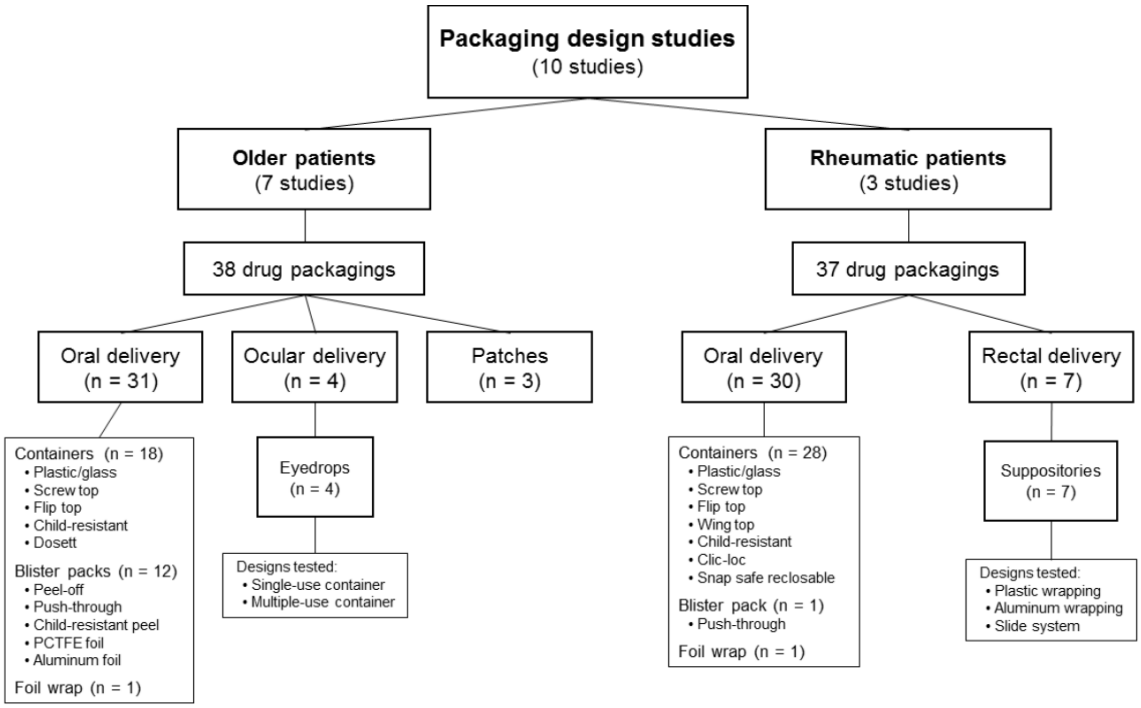

Figure 1. Schematic representation of publications addressing packaging designs.

Two assessment methods for patient's preference and appropriateness were used. In cases where the population was younger than 6 years, measurements were based on investigator or caregiver observations and included their reporting on the outcomes (Klingmann et al., 2015, 2013; Spomer et al., 2012; Van Riet-Nales et al., 2013; Zlotkin et al., 2003). For the remaining studies that included children older than 6 years, self-preferences were measured through oral or written questionnaires (Cloyd et al., 1992; Lottmann et al., 2007; McCrindle et al., 1997; Musiime et al., 2014; Patchell et al., 2002).

Table 6. Publications on dosage form design involving young patients.

	Authors	Research focus	Conclusions
Young patients	Cloyd et al., 1992	Preference: sprinkle versus syrup formulations	Sprinkle formulation rated as the preferred
	Klingman et al., 2013	Acceptability: mini-tablets versus syrup	Mini-tablets were more acceptable compared with liquid formulation.
	Klingman et al., 2015	Acceptability: mini-tablets versus syrup	Mini-tablets were a valuable alternative
	Lottmann et al., 2007	Preference: lyophilisates versus tablet	Preference for oral lyophilizate formulation
	McCrindle et al., 1997	Acceptability: pill versus powder formulation	Pills increased acceptability
	Musiime et al., 2014	Preference: minitab sprinkles versus tablets and syrups	Minitab sprinkles were more acceptable than syrup for younger children but older children preferred tablets
	Patchell et al., 2002	Preference: minimicrospheres versus microspheres formulations	Minimicrospheres are easier to take and were preferred
	Riet-Nales et al., 2013	Acceptability: mini-tablet versus powder versus suspension versus syrup	Tablets were better accepted. Tablets and syrup were the most preferred formulations.
	Spomer et al., 2012	Acceptability: mini-tablets versus syrup	Higher or at least equal acceptance for mini-tablets
	Zlotkin et al., 2003	Acceptability: sprinkle versus drops formulation	Sprinkles were well accepted without complications

The publications on adult patients approached different dosage forms for different routes of administration e.g., oral, vaginal, rectal and topical drug delivery (Tables 7A-7B). Eleven publications exclusively assessed dosage forms for the oral route. Four studies only used placebos and evaluated the swallowing preferences among healthy volunteers (Hayakawa et al., 2016; Overgaard et al., 2001) and dysphagic patients (Carnaby-Mann and Crary, 2005; Schiele et al., 2015). No correlation was found between the size and shape of oral dosage forms and swallowability in stroke-induced dysphagic patients (Schiele et al., 2015). Capsules and coated tablets (Overgaard et al., 2001), orodispersible tablets (Carnaby-Mann and Crary, 2005) and minitablets (Hayakawa et al., 2016) were found as being easier to swallow when compared to conventional tablets. In the other studies, conventional tablets were also used as comparator. Patients with neurological pathologies such as Parkinson's disease, schizophrenia or mood disorders showed preference for orodispersible tablets (Bitter et al., 2010; Nausieda et al., 2005; Sajatovic et al., 2013). Liquid-dispersible tablets were more accepted in dysphagic parkinsonian patients (Bayer et al., 1988), patients with breast cancer receiving highly emetogenic chemotherapy showed preference for a film formulation of dexamethasone (Nishigaki et al., 2012) and hemodialysis patients showed preference for a gel cap formulation (Kaplan et al., 2002). Lastly, bone marrow transplant recipients showed higher acceptability for a rinse formulation when compared to thin and thick gels, in a

study evaluating topical approaches for the management of oral mucositis (Bellm et al., 2001).

Table 7A. Publications on dosage form design including adult patients.

	Authors	Research focus	Conclusions
Adult patients	Aubeny et al., 2000	Acceptability: vaginal capsule versus pessary form	Ease of use and acceptance was higher for the capsule
	Baxter et al., 2014	Preference and acceptability: tablets versus chewable tablets versus powder	Conventional tablets were the most accepted and successful delivery vehicle
	Bayer et al., 1988	Acceptability: capsules versus dispersible tablet formulations	The dispersible formulation offered practical benefits
	Bellm et al., 2001	Acceptability of topical formulations: rinse versus thin gel versus thick gel	The rinse was selected as the most acceptable formulation
	Bitter et al., 2010	Preference: orodispersible tablet versus conventional tablet	Majority of patients preferred the orodispersible tablet
	Blesa et al., 2007	Preference: patches versus capsules	Caregivers indicated greater satisfaction and less interference with the patch formulation
	Carnaby-Mann et al., 2005	Preference: orodispersible tablet versus conventional tablet	The orodispersible tablet was the most preferred
	Creinin et al., 2008	Acceptability: contraceptive ring versus contraceptive patch	Ring users preferred the ring to the oral contraceptive and patch users preferred the oral contraceptive to the patch
	Dowson et al., 2007	Preference: conventional tablet versus orodispersible tablet versus nasal spray	The orodispersible formulation was the most convenient
	Fennell et al., 2010	Preference: injectable versus implantable depot	Most patients preferred the injectable over the implantable form
	Hayakawa et al., 2016	Ease of taking: mini-tablet versus orodispersible mini-tablet versus conventional tablet versus conventional orodispersible tablet	Mini-tablets were easier to take and required less amount of water
	Kaplan et al., 2002	Preference: gelcaps versus tablets	The gelcap was the most preferred among patients

Supplementation formulations to be taken by pregnant women and osteoporotic patients were investigated in four studies. Tablets were more acceptable compared to powdered prenatal supplements with regard to pregnant woman (Baxter et al., 2014; Young et al., 2010) whereas chewable tablets were preferred to effervescent powders in osteoporotic patients (Den Uyl et al., 2010; Reginster et al., 2005). In another studies, androgen deficient men preferred an injectable depot over an implantable form for testosterone replacement therapy (Fennell et al., 2010), a topical suspension was preferred to an ointment in patients with psoriasis (Sandoval et al., 2015) and an orodispersible tablet was considered more convenient for migraine patients (Dowson et al., 2007). Caregivers of Alzheimer's patients preferred a dermal patch to capsules with respect to ease of use and interference with daily life (Blesa et al., 2007) and a vaginal

capsule was preferred to a pessary as local spermicidal contraception (Aubeny et al., 2000). With regard to female hormonal therapy, a contraceptive ring and an intranasal solution were preferred to oral and dermal (patch) administrations, respectively (Creinin et al., 2008; Lopes et al., 2001).

Table 7B. Publications on dosage form design including adult patients (*cont.*).

	Authors	Research focus	Conclusions
Adult patients	Lopes et al., 2001	Preference: intranasal solution versus transdermal patch	Levels of user preference were higher for the intranasal dosage form
	Minnis et al., 2013	Acceptability: vaginal gel versus oral tablets	Women in USA favored tablets. Preferences varied in South Africa and Uganda
	Nausieda et al., 2005	Preference: orodispersible tablets versus conventional tablets	The orodispersible tablet provided convenience, ease of use and may be valuable depending on patient preferences
	Nel et al., 2011	Preference: vaginal film versus vaginal tablet versus vaginal soft-gel capsule	Women in Burkina Faso and Tanzania preferred the soft-gel capsule. Zambian women preferred the film formulation
	Nishigaki et al., 2012	Acceptability: film versus tablet formulations	Patient's impressions were better for the film formulation
	Overgaard et al., 2001	Acceptability: tablets and capsules based on size, shape and surface	The ideal tablet is small, strongly arched circular and coated
	Pines et al., 2013	Acceptability: enema versus lubricant-filled applicator versus suppository	The applicator ranked as the highest considering acceptability
	Reginster et al., 2005	Preference and acceptability: chewable tablet versus effervescent powder	The chewable was preferred by a significant majority of the patients
	Sajatovic et al., 2013	Satisfaction and convenience: orodispersible tablet versus immediate-release tablet	Both formulations were associated with good satisfaction but the orodispersible tablet was more convenient to administer
	Sandoval et al., 2015	Preference: topical suspension versus ointment	The topical suspension was preferred over the ointment
	Schiele et al., 2015	Swallowing difficulties: round tablets versus oval tablets versus oblong tablets versus capsules	Capsules and round tablets had more probability to be lodged in the throat
	Uyl et al., 2010	Preference and acceptability: chewable tablets versus sachets	A greater number of patients considered the chewable tablet as preferable/accepted
	Young et al., 2010	Acceptability: powder to dissolve in water versus sprinkles versus tablets	Tablets and sprinkles were most acceptable. Tablets were preferred over sprinkles

In studies aiming at HIV prevention, a lubricant-filled applicator was preferred for rectal microbicide delivery when compared to enema and suppository forms (Pines et al., 2013). Most women in the USA favored orally administered tablets over a vaginal gel while preferences varied in African sites (Minnis et al., 2013). Another study showed that Zambian women preferred a vaginal film formulation while women in Burkina Faso and Tanzania optioned for a vaginal soft-gel capsule, with the vaginal tablet formulation being the least preferred (Nel et al., 2011). Tablet formulations are generally perceived as

being the most acceptable dosage form for patient populations due to its easy administration and independent use. Nevertheless, patient's geographical and cultural experiences with product formulations should be considered when evaluating the appropriateness of drug products.

The methodology used for evaluation of the studies on dosage form design applied a combination of observational endpoints (Carnaby-Mann and Crary, 2005; Schiele et al., 2015), questionnaire/interview assessments (Baxter et al., 2014; Bayer et al., 1988; Bellm et al., 2001; Bitter et al., 2010; Blesa et al., 2007; Creinin et al., 2008; Den Uyl et al., 2010; Dowson et al., 2007; Fennell et al., 2010; Hayakawa et al., 2016; Kaplan et al., 2002; Lopes et al., 2001; Minnis et al., 2013; Nausieda et al., 2005; Nel et al., 2011; Nishigaki et al., 2012; Overgaard et al., 2001; Pines et al., 2013; Reginster et al., 2005; Sajatovic et al., 2013; Sandoval et al., 2015; Young et al., 2010) and home visits with pill counting (Aubeny et al., 2000). A schematic image for the studies in this category is visualized in Figure 2.

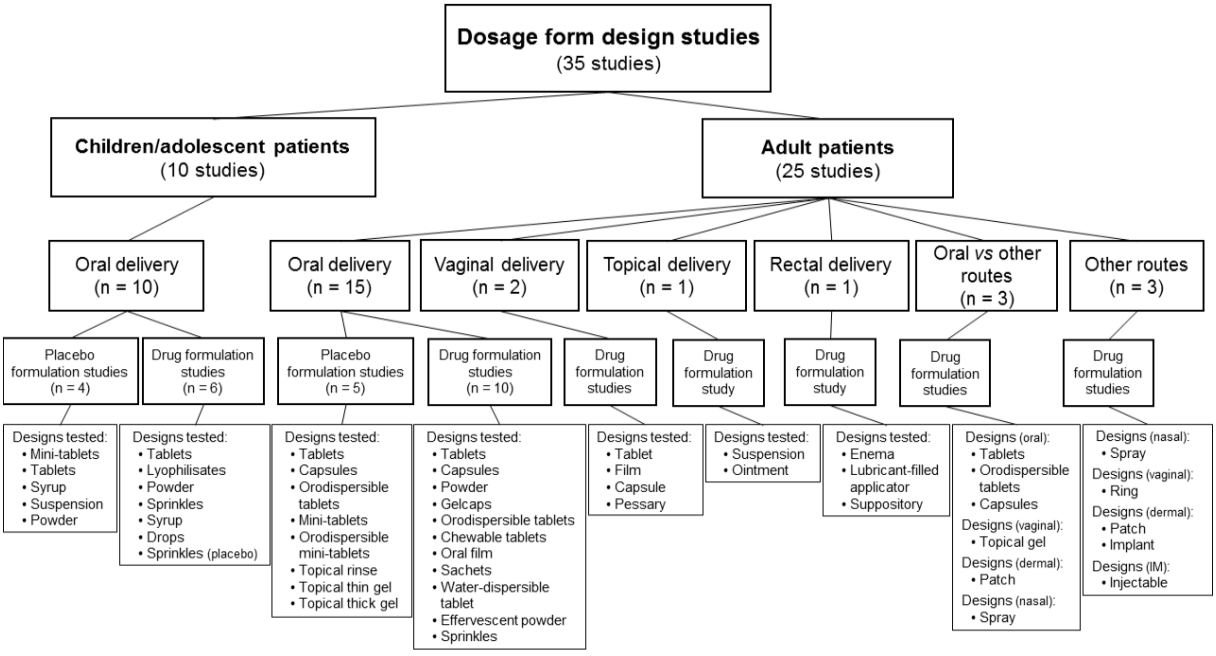

Figure 2. Schematic representation for the publications addressing dosage form designs.

4. Discussion

4.1. Literature review results

Results from an earlier preliminary review on clinical evidence for appropriateness of pharmaceutical preparations, dosage forms and other product designs limited to patients 65 years and older only identified 34 publications through the search criteria, with none being according to the established inclusion and exclusion criteria suggesting

that scientific evidence for claims being made are lacking (Messina et al., 2015). These surprising findings suggested the need to perform a broader literature review that could include all age groups, nonrestrictive inclusion and exclusion criteria, an adequate list of keywords and a search in all major databases. In order to prepare for such extensive work, an initial review was conducted in the PubMed database. The search identified 45 publications that were according to the pre-established inclusion and exclusion criteria. The applied criteria was based on the previous publication (Messina et al., 2015), with additional inclusion of studies assessing patients' appropriateness, acceptability, usability or preference for dosage forms and packaging designs.

A limited set of common aspects were found among the studies, which allowed the categorization in two main areas: studies comparing different drug packaging designs (handling problems) and studies comparing dosage forms designs. In addition, subcategories were created according to the target patient populations. Populations included in the category on drug packaging designs were older patients and patients suffering from rheumatoid conditions. The exclusive focus on these specific populations is meaningful, as they are more prone to suffer from impaired dexterity and handling issues. Positive correlations for the size and surface area of the packaging design were associated with better handling and acceptance regarding eyedrop bottles (Dietlein et al., 2008). Containers with tall bases, angulated tops, wing tops or screw cap openings were reported to be easier to open (Le Gallez et al., 1984; Lisberg et al., 1983). In addition, suppositories with slide system were preferred to plastic/aluminum wrappings (Verheggen-Laming et al., 1988) and push-through blisters were found easier to handle than peel-push blisters.

Careful attention must be given to the forces required to reach the medication. Higher resistance forces for push-through and peel-push blisters may hinder older and rheumatic patients to disrupt or open the blister and remove the dosage form (Mühlfeld et al., 2012). Other factors like perfect fitting of the dosage form in the blister cavity and visibility of the dosage form were also considered important when handling blister packages (Braun-Münker and Ecker, 2015).

Considering the category on dosage form designs, subcategories included young patient and heterogeneous adult populations. In young patient population studies, children and caregivers showed preference for oral solid dosage forms such as multiparticulates (sprinkles and lyophilizates) and minitablets when compared to liquid dosage forms (syrup and oral drops). These findings support the idea that liquid dosage forms are no longer the formulation of election for pediatric populations. According to the studies with adult populations and thanks to the continuous development of pharmaceutical technologies to deliver drugs, conventional (uncoated) tablets are

becoming the least preferred dosage form for oral administration. In either healthy or drug-medicated patients, preferences were displayed for the alternative dosage form tested. Higher acceptability was seen for orodispersible technologies, with this effect being usually independent of the patient disease pattern. Acceptability and preferences were variable regarding other potential routes of administration and can be affected by additional circumstances (e.g. geographical region and religious beliefs), proving that more efforts and interdisciplinary research are required for the development of patient centric drug products in a world scale.

4.2. Data analysis

All studies included detailed information regarding their specific research objectives. Information concerning the demographic characteristics of the patients enrolled were provided in the majority of cases. Information regarding the impact of treatment duration on the acceptability of drug products was neglected in the studies. In addition, no relevant information was found concerning the quantification or qualification of disease-specific and formulation-related factors within reference populations.

The used methodologies were thoroughly analyzed and revealed that the type of assessment was dependent on the population studied. Preference questionnaires were commonly used within adult patients while assessment methods used in young patients were variable depending on their age. In cases where children were not able to respond to questionnaires due to younger age, observational studies were applied and performed either by trained investigators (physicians) or by the parents. The questionnaires used to assess patient perception were either quantitative scales (e.g., 1-5, 1-12) or qualitative scales (e.g., very good, good, bad). Nevertheless, these studies did not provide further details on how the questions and questionnaires were developed and validated. This could be considered a critical weakness of these studies, as the questionnaires to capture true patients' feedback should be specific to the research subject and should follow a sequence of several steps (Patrick et al., 2011a, 2011b). Moreover, potential interviewer bias must be considered through the questions and the way of asking these to the concerned patients (Dukala and Polczyk, 2014).

4.2.1. Methodology used to assess patient appropriateness and preference for product design

The review revealed that only ten studies used validated methodology to investigate patient appropriateness: five studies on packaging design (Atkin et al., 1994; Braun-Münker and Ecker, 2015; Dietlein et al., 2008; Keram and Williams, 1988; Lisberg et al.,

1983) and five studies on dosage form design (Carnaby-Mann and Crary, 2005; Klingmann et al., 2015, 2013; Schiele et al., 2015; Spomer et al., 2012).

4.2.1.1. Packaging design studies

For the studies on packaging design, methodologies included experienced investigators who were responsible for observing and evaluating how patients handled the drug products. Three studies used a "step by step" methodology based on an objective 2-point scale (able versus unable), which involved opening and closure of the container, with additional dosage form removal. Different drug packages and opening designs were tested, with results reinforcing the non-suitability of child-resistant openings for older patients. Time and grip strength were also some of the variables measured (Atkin et al., 1994; Keram and Williams, 1988; Lisberg et al., 1983). In another study, two investigators simultaneously observed and documented practical problems experienced by patients when administering eyedrops. The method consisted of the opening and self-application from different container types (single-use versus standard). Endpoints evaluated the ability to open the container, the successful application of a drop into the conjunctival sac, the scratching or touching of the eyedrop container to the patient's eye and the time taken to fulfil the task. Information obtained showed that successful administration is dependent on the size of the container (Dietlein et al., 2008). The last study used video documentation to record and study patients' handling movements when opening two different types of blister packages (PCTFE opaque foil versus aluminum foil). Assessment was based on a three-step test, analyzing efficiency (opening a package within 5 min), effectiveness (opening same package opened within 1 min) and patient's satisfaction (scale ranging from -2 to +2) with opening procedure (Braun- Münker and Ecker, 2015).

Despite the availability of studies performed more than 20 years ago demonstrating incidence of handling issues for specific drug packaging designs among special populations, not much has been done until today to develop alternatives that can be more user-friendly. Drug packaging technologies generally remain the same over the years and attention must be given to the development of designs that can be easily handled by rheumatic and older patients. Ordinary packaging designs should also be adapted for these special populations in order to facilitate access to medication and their proper administration.

4.2.1.2. Dosage form design studies

As the participants and endpoints assessed were nearly identical, similar methodologies were used in the three studies on dosage form design for young children.

The studies involved an experienced physician approaching similar criteria and endpoints that relied on children's capacity to swallow minitablets. After each deglutition, the participant's mouth was inspected with a flashlight. This would allow the detection of dosage form residuals and evaluate if the swallowing was safe and successful (Klingmann et al., 2015, 2013; Spomer et al., 2012). The remaining two studies on dosage form design for adult populations were also specific of oral delivery. These evaluated the safety and swallowing differences experienced by patients with dysphagia, which are at increased risk for penetration and unintended aspiration of dosage forms. The studies included experienced physicians who evaluated the swallowability of different oral dosage forms designs, by using different medical examinations and endpoints. Techniques used included video-endoscopy, surface electromyography and respiratory flow measurements. Additionally, endpoints were based on validated medical methods for evaluation of the swallowing function.

4.3. Pediatric medicines: regulatory modifications and novel drug product designs

The evolution in patient centric research is reflected by some of the recent publications included in the dosage form design category, related to studies that focused on the appropriateness and acceptability of solid dosage forms among young children. Oral liquid dosage forms, such as syrups and suspensions, have for long been considered as the most appropriate type of dosage form for young children. However, liquid medicines have several disadvantages such as bad taste, potential refrigeration, portability and measuring errors (Van Riet-Nales et al., 2013). The introduction of new EMA guidelines for pediatric medicines (The European Parliament and The Council of the European Union, 2006), together with WHO's endorsement for treatments with oral solid forms (World Health Organization, 2008) and other related-campaigns (World Health Organization, 2010, 2007) contributed to the increased research and development activities for appropriate pediatric medicines. This recent research provided evidence that solid oral dosage forms such as multiparticulates and minitablets are appropriate options for the pediatric population, enabling easily administrable drug vehicles with prolonged stability and flexible dosing (Klingmann et al., 2015, 2013; Patchell et al., 2002; Spomer et al., 2012; Van Riet-Nales et al., 2013). Such developments in pediatric research should be taken as example and extended to other target patient populations (e.g., elderly patients), encouraging multidisciplinary research towards the development of age-appropriate medicines.

4.4. Influence of geographical and cultural experiences on drug product preferences

An important finding to retain from this literature review is that different populations have different preferences and the appropriateness of drug products is not solely dependent on the product design. Conventional forms and known/familiar product designs may be better accepted depending on patients' geographical and cultural experiences with pharmaceutical preparations (Buckalew and Coffield, 1982; Horne et al., 2004; Morgan et al., 2011). This important variable must be considered when evaluating the appropriateness of drug products, especially in countries where patients have limited access to healthcare provision and lack of prior medication experience, as it was shown by the results obtained in studies that included participants from African sites. Additionally, some studies were driven by the urgent need of reducing HIV incidence among these populations (efficacy and effectiveness), which triggered research on the important aspect of dosage form usability and acceptability for patient's adherence to HIV prevention treatments and helped researchers to understand which type of dosage forms were preferred (Minnis et al., 2013; Nel et al., 2011; Pines et al., 2013).

4.5. Points to consider towards the improvement of patient centric research

Within drug product development, the traditional priority on drug efficacy to support approval and prescription of the products by healthcare professionals seems to be one of the main reasons for the undervaluation of patient centric research. Patient usability and administration is usually considered to be sufficiently addressed by the user instructions in the package leaflet. This is also supported by the observation that the increasing number of publications on appropriateness, acceptability and preference correlates with the recent pediatric regulatory initiatives that emphasized the importance of the appropriateness of the dosage form for this patient population. The gap between efficacy and effectiveness also gained more visibility in regulatory reviews in the past years, not only to be considered a major reason for poor therapeutic outcomes (Eichler et al., 2011) but also due to the increasing pressure from healthcare providers towards a pay-for-performance reimbursement (Van Herck et al., 2010; Wouters et al., 2016). Such poor outcomes encouraged the development of comparative trials between different dosage forms in HIV prevention among African states, as HIV is the leading cause for death in these regions (Minnis et al., 2013; Nel et al., 2011; Pines et al., 2013).

Several domains of drug product design that impact on patients' usability, independent administration, drug adherence and drug safety/effectiveness are still not yet explored. In addition, the majority of studies are problem descriptive in nature, and

studies performed to improve or compare drug product design are still very limited. One of the major reasons found in this work might be related to the limited availability of methodology, or studies into methodology, regarding drug product design appropriateness and acceptability for different patient populations.

The results obtained in this literature research followed the same pattern obtained in previous works, with little attention being given to the study of drug products appropriateness, acceptability, usability or preference for the targeted patient population. Other available reviews in the literature that tried to address the availability of appropriate medicines for pediatric and geriatric populations have also shown that clinical evidence on appropriateness is still very limited (Messina et al., 2015; Van Riet-Nales et al., 2013, 2011). The small amount of publications addressing proper methodology for testing the appropriateness of drug products shows that further work has to be done in order to improve drug therapy and provide appropriate medicines to meet patient's needs.

4.6. Strengths and weaknesses of this review

This work provides a useful review on the clinical evidence available for acceptability, appropriateness, usability and preferences for pharmaceutical preparations. A better understanding of these aspects may improve the interface between patients and drug products, contributing to easier administrations and ultimately to effective therapies. In addition, such valuable information can help pharmaceutical scientists in the product design and development, as they reveal the actual knowledge as well as the gaps which can be considered opportunities for enhanced pharmaceutical products. Nevertheless, this literature review also has some limitations. Even though a careful and exhaustive literature search was performed in PubMed database, the authors would like to alert for the possibility of not considering relevant publications. In addition, due to the established inclusion and exclusion criteria, there is also potential for omitting significant publications (e.g. studies with fewer patients). Nonetheless, the authors are convinced that existing publications within the scope of the literature review were captured and potentially missed publications will not change the general conclusion of this review.

5. Conclusion

A literature review identified 45 articles on clinical evidence for patients' appropriateness, acceptability, usability or preference for pharmaceutical preparations. The majority of studies were problem descriptive rather than targeted towards comparative evaluations. The lack of a common language and scientific terms within patient centric research was identified as a major challenge to establish comprehensive

search profiles. Clear definitions and the use of an agreed taxonomy are urgently required. Definitions for some relevant keywords/terms were proposed for further multidisciplinary discussions. According to the defined search profile and criteria, only ten studies used scientific methodology that could provide quality data on the user appropriateness. The results of this review follow previous publications, with little attention being given to the development of suitable methodologies for the evaluation of drug products appropriateness among different patient populations, as well as studies investigating the patient-drug product interface for appropriateness. This also suggests that claims used for age-appropriateness of medicines today lack in scientific evidence.

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- 4 -

Better medicines for older patients: Considerations between patient characteristics and solid oral dosage form designs to improve swallowing experience

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Abstract

Oral drug administration provided as solid oral dosage forms (SODF) remains the major route of drug therapy in primary and secondary care. There is clear evidence for a growing number of clinically relevant swallowing issues (e.g., dysphagia) in the older patient population, especially when considering the multimorbid, frail, and polymedicated patients. Swallowing impairments have a negative impact on SODF administration, which leads to poor adherence and inappropriate alterations (e.g., crushing, splitting). Different strategies have been proposed over the years in order to enhance the swallowing experience with SODF, by using conventional administration techniques or applying swallowing aids and devices. Nevertheless, new formulation designs must be considered by implementing a patient centric approach in order to efficiently improve SODF administration by older patient populations. Together with appropriate SODF size reductions, innovative film coating materials that can be applied to SODF and provide swallowing safety and efficacy with little effort being required by the patients are still needed. With that in mind, a literature review was conducted in order to identify the availability of patient centric coating materials claiming to shorten esophageal transit times and improve the overall SODF swallowing experience for older patients. The majority of coating technologies were identified in patent applications, and they mainly included well-known water soluble polymers that are commonly applied into pharmaceutical coatings. Nevertheless, scientific evidence demonstrating the benefits of given SODF coating materials in the concerned patient populations are still very limited. Consequently, the availability for safe, effective, and clinically proven solutions to address the increasing prevalence of swallowing issues in the older patient population is still limited.

Keywords: administration aids, administration devices, dysphagia, film coating materials, older patients, patient centric drug product design, solid oral dosage forms, swallowing problems

1. Introduction

The improvements in modern healthcare provision, combined with the availability of new effective drug therapies, are both contributing to a continuous increase in average life expectancy (Stegemann et al., 2012). Ageing is associated with an increasing incidence of chronic diseases and co-morbidities, which leads to the practice of polypharmacy amongst the majority of the older patients (Perrie et al., 2012). This topic raises safety concerns, as it was previously reported that a least 16.5% of older patients

under polypharmacy regimens have gone through hospitalization, or even death, as an outcome of medication-related issues (e.g., drug interactions) (Galato et al., 2010; Husson et al., 2014).

The oral route is considered to be, by far, the most preferred and convenient for the majority of patients, as it is non-invasive in, and allows for, independent usage and handling (Helliwell et al., 1993; Domb et al., 2014). Nevertheless, one must consider that the swallowing function in older patients is expected to be impaired, due to ageing and chronic conditions (dysphagia), which may raise challenges to swallow solid oral dosage forms (SODF) effectively and safely (Forough et al., 2018; Liu et al., 2016). Swallowability and palatability are attributes that impact the acceptability of SODF by patients (Barczi et al. 2000; Leder et al., 2009; Nicosia et al., 2000), which can be affected by the SODF physical properties upon deglutition and esophageal transit time (Stegemann et al., 2012; Barczi et al., 2000; Ekberg et al., 1996; Barer et al., 1989; Calcagno et al., 2002; Coates et al., 1997; De Pauw et al., 200; Gordon et al., 1987; Mann et al., 1999; Spechler et al., 1999; Daniels et al., 2006; Alvarenga et al., 2014; Kendall et al., 2004; Palmer et al., 2000; Balzer et al., 2000). As such, more effort needs to be put into the design of patient centric drug products that can benefit older patients and their experience with prescribed medicines (Liu et al., 2016; Page et al., 2016; Vallet et al., 2020).

This literature review provides an overview on physical characteristics of older patients that can impact the administration and acceptability of drug therapies that are provided in SODF, including their relation to specific SODF designs. Descriptions of conventional techniques, swallowing aids, and administration devices targeting this special patient population in order to improve their swallowing experience with SODF are also given. Moreover, the importance of using a patient centric drug product design approach when developing appropriate SODF for the older patient population is also discussed, being supported by a literature review on the film coating materials designed to enhance the swallowing experience and acceptability of SODF for older patients with impaired swallowing functions, including their clinical evidence for improved efficacy and safety.

2. Swallowing problems in the older patient population

Dysphagia is a growing concern for the health of older and multimorbid patient populations, as it tends to remain an underestimated symptom (Forster et al., 2011; Crary et al., 2012; Kim et al., 2020). Previous findings suggested that 46% of patients with dysphagia do not inform their doctor regarding their condition, while 70.4% of

patients are not properly diagnosed as having dysphagia (Wilkins et al., 2007). In addition, patients report that their pharmacists and doctors rarely inquire about their swallowing function (Masilamoney et al., 2018; Sestili et al., 2018). Therefore, it is important that healthcare professionals question older patients regarding their swallowing function (and rule out dysphagia as a symptom) in order to ensure that appropriate solid dosage form designs are being provided (Sestili et al., 2018; Marquis et al., 2013; Schiele et al., 2013; Ekberg et al., 2002).

2.1. Prevalence of dysphagia

Swallowing problems are predicted to affect one out of 25 adults. Previous surveys have identified that approximately 9.5 million adults (mean age: 52.1 years) report swallowing problems yearly, with women being more likely to report the problem as compared to men. In USA, it is expected that more than six-million older adults experience swallowing issues (Nicosia et al., 2000; Bhattacharyya et al., 2014). Other reports have suggested that more than 15% of the older population suffers from dysphagia worldwide, from which only 22.7% visited their healthcare professional in order to address the condition (Ekberg et al., 2002). Therefore, a continuous growth is expected in the prevalence of swallowing disorders regarding older patients, as life expectancy is expected to increase in the future.

2.2. Factors contributing to dysphagia

There are many reasons and underlying etiologies that contribute to the development of swallowing problems. These can be classified into age-related, disease-related, and drug-related dysphagia.

2.2.1. Age-related dysphagia

Age-related changes in the swallowing physiology are predisposing factors for dysphagia in the older patient population (Spechler et al., 1999; Marik et al., 2003). These are typically related to anatomic, motoric, and sensory alterations, which become less efficient when responding to the body stimulus and they lead to a subtle decay in the swallowing function with increasing age (Marquis et al., 2013; Pauloski et al., 2002; Starmer et al., 2013). The diagnosis of dysphagia in older patients usually remains asymptomatic and it only becomes visible in advanced stages of deterioration or when associated to other clinical conditions (Stegemann et al., 2012).

2.2.2. Disease-related dysphagia

Dysphagia can also develop as a co-morbidity, due to an increasing incidence of chronic conditions or disease-specific patterns in older patients (Table 1). Examples include neurological disorders and neurological damage (e.g., Parkinson's disease, Alzheimer's disease, dementia, multiple sclerosis, muscular dystrophy, stroke, and spinal cord injury), chronic obstructive pulmonary disease, congestive heart failure, and xerostomia (Barer et al., 1989; Calcagno et al., 2002; Coates et al., 1997; De Pauw et al., 2002; Gordon et al., 1987; Mann et al., 1999; Spechler et al., 1999; Daniels et al., 2006; Alvarenga et al., 2014; Wilkins et al., 2007). Furthermore, conditions that impact the swallowing reflex (e.g., osteoarthritis, thyroid disease, hypertension, hypercholesterolemia, gastroesophageal reflux, and depression) may also predispose patients to dysphagia, due to their association with prolonged pharyngeal and oropharyngeal transit times upon swallowing (Kendall et al., 2004; Palmer et al., 2000).

Table 1. Disease-related conditions as predisposition for developing dysphagia.

Predisposition	*Condition*
Neurologic disorders and stroke	Cerebral infarction
	Brain-stem infarction
	Intracranial hemorrhage
	Parkinson's disease
	Multiple sclerosis
	Amyotrophic lateral sclerosis
	Poliomyelitis
	Myasthenia gravis
	Dementia
Structural lesions	Thyromegaly
	Cervical hyperostosis
	Congenital web
	Zenker's diverticulum
	Ingestion of caustic material
	Neoplasm
Psychiatric disorder	Psychogenic dysphagia
Connective tissue diseases	Polymyositis
	Muscular dystrophy
Iatrogenic causes	Surgical resection
	Radiation fibrosis
	Medications

2.2.3. Drug-related dysphagia

Patients with long-term exposure to certain classes of drugs are more susceptible to developing swallowing problems as a result of their pharmacological activity, the likelihood of adverse drug reactions (ADRs), and medication-induced esophageal injury (Balzer et al., 2000). ADRs are usually associated with drugs that affect the smooth/striated muscle function (Sengupta et al., 2006). Immunosuppressive drugs, antineoplastic agents, and antibiotics have been identified to increase the incidence of

dysphagia as a complication of its pharmacological effects (Stoschus et al., 1993). Finally, esophageal injury can also be induced by medications that have a direct erosive effect in the mucosa (dose dependent) or an indirect modification of the physiological pH of the esophagus (Fields et al., 2015). Some examples include anti-infective drugs (e.g., tetracyclines, penicillin, and macrolides), steroidal anti-inflammatory drugs (e.g., piroxicam, acetylsalicylic acid), emepronium bromide, and quinidine (Table 2). Medication-induced dysphagia is expected to be one of the leading etiologies for esophageal motility disorders in older patients (Palmer et al., 2000; Bott et al., 1987; Jaspersen et al., 2000).

Table 2. Medication that may affect swallowing function.

Physiological condition	*Class of drugs*
Sedation, pharyngeal weakness, dystonia	Benzodiazepines
	Neuroleptics
	Anticonvulsants
Myopathy	Corticosteroids
	Lipid-lowering drugs
Xerostomia	Anticholinergics
	Antihypertensives
	Antihistamines
	Antipsychotics
	Narcotics
	Anticonvulsants
	Antiparkinsonian agents
	Antineoplastics
	Antidepressants
	Anxiolytics
	Muscle relaxants
	Diuretics
Inflammation (from tablet irritation)	Tetracycline
	Doxycycline
	Iron preparations
	Quinidine
	Nonsteroidal anti-inflammatory drugs
	Potassium
Impaired motility or gastroesophageal reflux	Anticholinergics
	Calcium channel blockers
	Theophylline
Esophagitis (related to immunosuppression)	Corticosteroids

2.3. Perception of dysphagia by older patients

The extent to which older patients are aware of a possible deterioration of their swallowing function remains unknown. Some findings point out that patients experience an impairment in swallowability; however, it is unclear how they perceive this (Pauloski et al., 2002). Discrepancies between patient complaints and objective swallowing diagnosis have been reported, while positive associations were identified in other studies (Bálint et al., 1991; Newton et al., 1994; Witterick et al., 1995; Anselmino et al., 1997; Nathadwarawala et al., 1994; Rhodus et al., 1995). Notwithstanding, one significant

correlation has been pointed out, which is related to a reported difficulty in swallowing by the patients and their measured swallowing efficiency values (Rogus-Pulia et al., 2014).

3. Administration of SODF by older patients

The majority of available drug therapies on the market are SODF (65–70%), such as tablets and capsules with different sizes and shapes. SODF remain very popular for manufacturing companies, due to different reasons (e.g., cheap manufacturing, accurate dosing, patient acceptability, and taste masking) (Heppner et al., 2006; Nunn et al., 2005; Singh et al., 2008). However, when considering older patients and their incidence for polypharmacy, the administration of SODF can become a daunting task (Logrippo et al., 2017; Tahaineh et al., 2017). Previous research has identified that one in three patients experience situations of vomiting, gagging, or choking when administering SODF (Figure 1). Furthermore, it has been noted that, during SODF administration, older patients with dysphagia demonstrate longer swallowing times, a higher number of swallows, and the need of water to support the SODF bolus (Carnaby-Mann et al., 2005). The combination between impaired swallowing function and poor dosage form design (e.g., large round tablets) may contribute to an unpleasant patient experience, due to potential adherence or lodging of the SODF in the esophagus, reducing the acceptability and compliance for prescribed treatments (Schiele et al., 2013; Andersen et al., 1995; Kikendall et al., 1991; Llorca, 2011; Simpson et al., 2006). Subsequently, older patients cope with the situation by either skipping doses or modifying the SODF (e.g., crushing and splitting tablets, opening capsules) for an easier swallowing experience (Kirkevold et al., 2010; Paradiso et al., 2002; Van Welie et al., 2016; Oberoi et al., 2018; Lau et al., 2018).

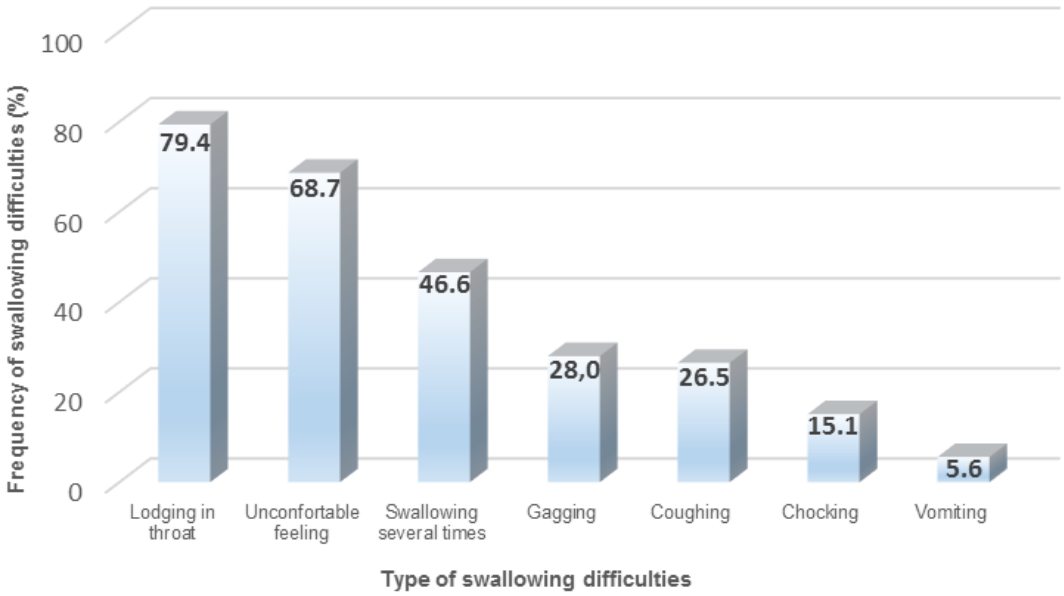

Figure 1. Common types of swallowing difficulties when administering SODF.

SODF modifications are seen as the most common technique that is used by older patients and their caregivers to improve the. administration of SODF (Ekberg et al., 1996). A survey in Germany showed that 58.8% of dysphagia-affected patients manipulate their drugs for easier administration (Schiele et al., 2013). Dosage form modifications should be avoided if not specified in the drug product label. Improper manipulations can endure the unpleasant taste of masked ingredients and modify the controlled release properties, which can lead to poor efficacy or clinically relevant ADRs (Kelly et al., 2010; Schier et al., 2003; Griffith et al., 2007).

3.1. Conventional administration techniques to improve swallowability

A study that was conducted in Germany investigated the efficacy of swallowing large tablets and capsules by applying two distinct administration strategies. The “pop-bottle” method was applied in order to swallow large tablets, whereas the “lean-forward” technique was applied for large capsules (Figure 2). The “pop-bottle” is a method where the tablet is placed on the tongue, the lips are tightly closed around the opening of a plastic bottle, and the tablet is swallowed in a swift suction movement in order to overcome the initial, volitional step of the swallowing act (Fowler, 1986). In the “lean forward” technique, capsules are swallowed in upright position with the subject’s head bent forward (MacLeod et al., 2003). The SODF were swallowed with 20 ml of water and the overall swallowing experience was evaluated through a questionnaire. The obtained results revealed that both of the techniques significantly improved SODF administration and, as such, this study was the first to demonstrate that conventional techniques for SODF administration can be adopted (Schiele et al., 2014). Nevertheless, these methods require training, and they are highly dependent on the patient’s characteristics, which may restrict their use in general practice. In addition, the approval to apply such administration techniques should first be confirmed first by a physician, as there is an expected risk of aspiration considering older patients with dysphagia (Sakuma et al., 2010).

Other studies have shown that body position can influence the esophageal transit time of tablets, which confirms that a correct body posture must be adopted when administering SODF (Alghadir et al., 2017). Longer transit times were observed for patients taking SODF in supine position as compared to the upright position. This is a matter of concern for bedridden patients, as these may be subjected to esophageal injury, due to slower transit times regarding the SODF taken (Channer & Virjee, 1985; 1986).

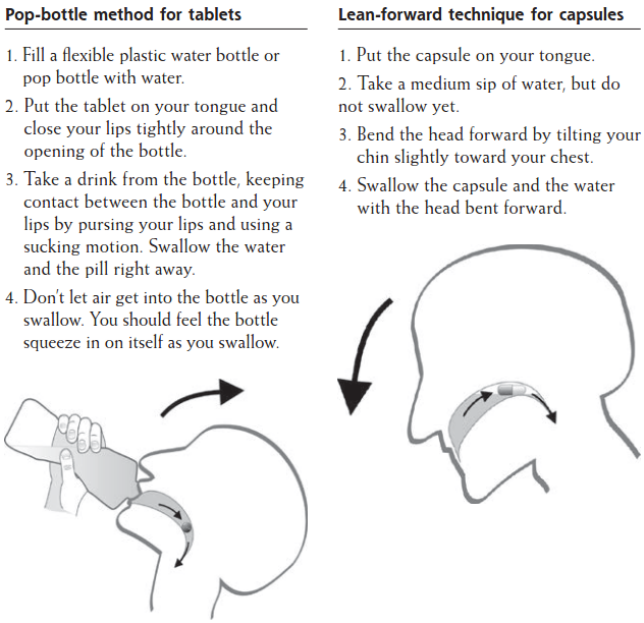

Figure 2. Patient information handout on conventional techniques to swallow SODF.

3.2. Application of administration aids and devices to improve swallowability

3.2.1. Oral jellies

Food aids with semi-solid consistency such as oral jellies, are commonly applied as an administration vehicle by older patients, because their rheological properties allow for the formation of a bolus that incorporates the SODF and promotes a better swallowing experience (Manrique et al., 2016; Malouh et al., 2020; Oh et al., 2020; Patel et al., 2020; Harada et al., 2015). Different reports have shown that the use of viscous oral jellies in the replacement of water tend to reduce the cases of aspiration and choking with large SODF for older patients with dysphagia (Satyanarayana et al., 2011). Another study in Japan investigated the applicability of a swallowing aid that consists of two sections: an upper part containing the SODF to be swallowed and a bottom part, including an amount of oral jelly (e.g., xanthan gum) to support administration (Figure 3). The majority of the participants agreed that the administration vehicle (GT packaging) was convenient and supported swallowability (Table 3) (Sadamoto et al., 2012). Intellectual property (Table 4) while using jelly-based administration vehicles to assist SODF administration have been also reported (Guomin et al., 2014; Morimoto et al., 2014; Craig et al., 2009).

3.2.2. Pill Glide®

A flavored spray was developed in order to provide a better experience during swallowing of SODF (Figure 4). The spraying of Pill-Glide® into the mouth and tongue of the patient generates a mucosa-coated surface that becomes slippery and later

facilitates the swallowing of the SODF (Gaskell, 2016; Jagani et al., 2016). In a clinical assessment (Table 3), Pill Glide® improved the SODF swallowing experience in adolescents (Diamond et al., 2010). Although data is only reported for young patients, the product is recommended to people of all ages that struggle with SODF swallowability, including older patients (Pill Glide, 2009). A patent disclosing an anti-stick formula that is delivered by spray (Table 4) in order to facilitate swallowing is also reported (Lenk et al., 2007).

Figure 3. Packaged jelly formulation to aid tablet swallowing.

Table 3. Scientific articles addressing administration aids to assist SODF swallowability.

Authors	*Title*	*Year*	*Reference*
Diamond et al.	Experience with a pill-swallowing enhancement aid	2010	[89]
Uloza et al.	A randomized cross-over study to evaluate the swallow-enhancing and taste-masking properties of a novel coating for oral tablets	2010	[93]
Sadamoto et al.	Innovative Tool for Taking Large Pills for the Elderly and Patients with Swallowing Difficulties	2012	[83]

Table 4. Patents addressing administration aids to assist swallowability of SODF.

Author(s)	*Patent number*	*Related invention*	*Year*	*Reference*
L.A. Lenk	US2007275053A1	Anti-stick formula delivered by spray process to facilitate swallowing of solid object, such as pill, tablet, capsule or caplet	2007	[91]
Craig et al.	WO2009098520A2	Composition and method for assisting swallowing	2009	[86]
Axelsson et al.	WOUS2018311108	A new coating composition and use thereof	2010	[94]
Guomin et al.	CN103721264A	Gel for assisting swallow of oral solid medicinal preparation	2014	[84]
Morimoto et al.	WO2014064840A1	Device for oral drug administration	2014	[85]
Nappi Bryan	US2018311108A1	Pill coating apparatus and method	2018	[95]

Figure 4. Schematic representation on how to use *Pill Glide*® to aid swallowing of SODF.

3.2.3. SODF Coating Devices

3.2.3.1. MedCoat®

MedCoat® is an administration aid device that was designed to allow patients to independently apply coatings to their SODF before swallowing (Figure 5). The coating contains maltitol (sweetener), vegetable fats (coconut and palm oils), gelatin, sugar esters of fatty acids (emulsifiers), citric acid, and lemon flavor additives for taste masking and saliva stimulation. The coating is applied by passing the tablet through a ring that is covered by a gelatinous film before administration (MedCoat AB, 2002). A clinical trial that was conducted in Lithuania (Table 3) has shown that SODF coated with MedCoat® were easier to swallow for older patients presenting swallowing issues (Uloza et al., 2010). A patent disclosing this technology (Table 4) was reported in 2010 (Axelsson et al., 2010).

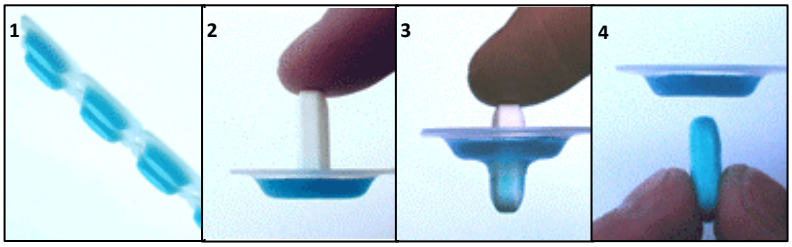

Figure 5. Schematic representation on how to apply *MedCoat*® onto SODF.

3.2.3.2. Coating container

A vessel system in which the SODF can be inserted and coated was developed (Figure 6). The vessel system is composed of the container, contained cap, and internal closure assembly. The container can be filled with a coating liquid that is sealed by the closure assembly and cap (Nappi, 2018). The SODF are fitted between the cap and valve closure assembly, followed by the fitting of the closure assembly on the container.

The coating liquid is composed of vegetable oils, surfactants, and flavoring agents that alter the surface properties of the SODF, thus improving swallowability (Table 4).

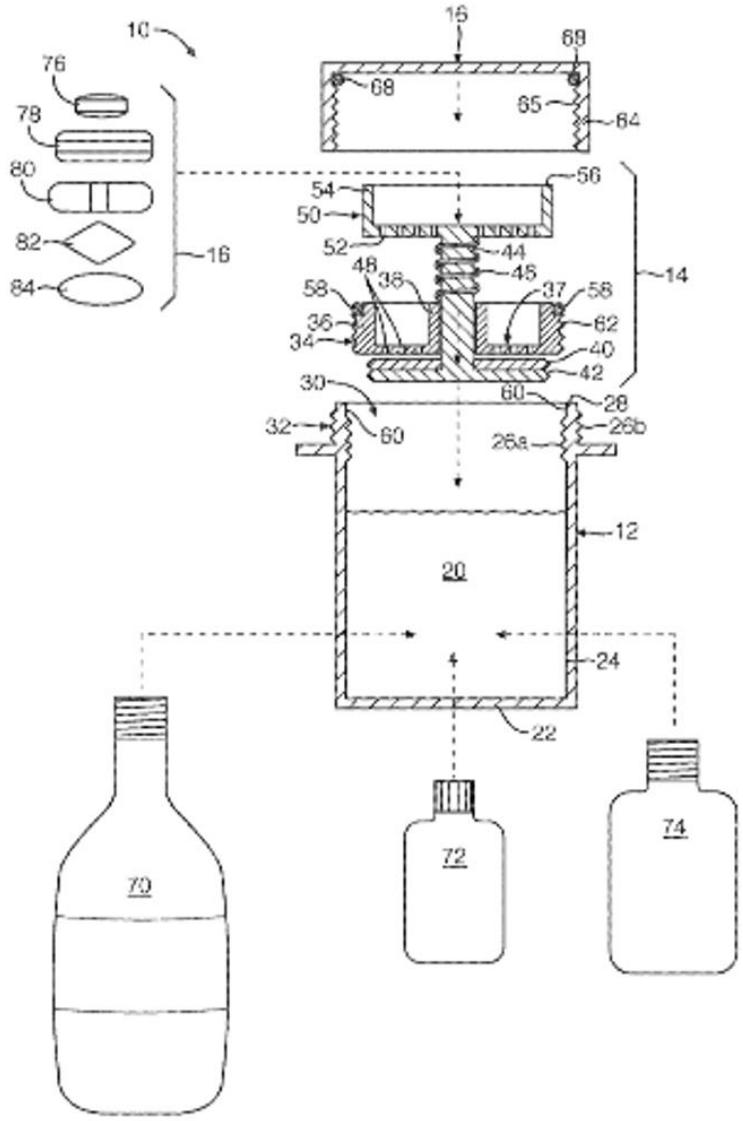

Figure 5. Schematic representation of container to coat SODF [95].

3.3. Influence of SODF design on patients' adherence and swallowing experience

Previous reports detailed that the adherence to self-administering drug therapies is around 50%, with the decrease being related to an increased complexity, inconvenience, or duration of the regimen (McDonald et al., 2002). Another study identified swallowability as being the most important characteristic of SODF for improving acceptability for older patients (Brotherman et al., 2004). Swallowability and esophageal transit time can both be impacted by the physical attributes and technology-related characteristics of SODF. Physical attributes, such as tablet size, shape, thickness, color, and surface roughness, were strongly associated to medication adherence (Kelly et al., 2010; Tucker et al., 2002), from which tablet size, shape, and thickness were identified as critical attributes

for proper handling and swallowability (Yoder et al., 2014). Technology-related characteristics of SODF, such as disintegration time, surface roughness (e.g., film coating), and propensity for swelling, were other important parameters that were also identified with impact swallowing performance (U.S. Department of Health, 2013; Yamamoto et al., 2014).

3.3.1. Color

Specific SODF colors can be associated to taste and flavor by older patients. The pink color tends to be linked to sweet flavors, whereas yellow tablets can be perceived to have a salty taste, irrespective of formulation ingredients (Srivastava et al., 2010). The color of SODF are an important criteria for patients with specific conditions (e.g., epileptic), since its modification can lead to cases of non-adherence (Kesselheim et al., 2013). Overall, the white color is recognized as the most popular choice for tablets, while the most disliked colors are purple and brown (Brotherman et al., 2004). Although color appears to be of least importance for patient adherence, it is, on the other hand, considered to be the most distinctive and memorable attribute for a SODF (Yoder et al., 2014).

3.3.2. Size

A usual approach for increasing patient compliance and reducing pill burden is done by increasing the SODF size in order to accommodate a higher dose strength (Hey et al., 1982). This rule does not apply to older patients, as these perceive SODF as being more difficult to swallow with increasing size and consider the size of the SODF to be the most important physical attribute for swallowing safety (Vallet et al., 2020; U.S. Department of Health, 2013; Srivastava et al., 2010). This is supported by a study that identified a correlation between higher esophageal muscle effort with an increasing size of the SODF to be administered. Other studies have also shown that larger SODF administered by elderly patients tend to present longer esophageal transit times (Channer & Virjee, 1985; 1986; Brotherman et al., 2004; U.S. Department of Health, 2013; Yamamoto et al., 2014; Mangoni et al., 2004; Overgaard et al., 2001). With regards to handling and easiness of swallowing, a study that was conducted in Japan showed that 7–8 mm tablets were perceived to be the most desirable size for old frail patients (Miura et al., 2007).

3.3.3. Shape

Several studies have evaluated the impact of different SODF shapes on older patients' swallowing experience. Flat-shaped tablets were seen as being more likely to

adhere to the esophagus when compared to convex-shaped tablets (U.S. Department of Health, 2013; Overgaard et al., 2001), whereas oval and oblong tablets have shown faster esophageal transits as compared to round tablets with the same density. The oblong shape was seen to be the preferred for SODF, as it was reported to provide a better administration experience regarding patients with swallowing issues (Stegemann et al., 2012; Yamamoto et al., 2014; Hey et al., 1982). The shape of SODF is also considered to be the most memorable characteristic for older patients, alongside the color (Yoder et al., 2014).

3.3.4. Taste and smell

Previous studies have identified that the bad taste of SODF was the fourth major complaint of patients, behind size, surface, and shape (Andersen et al., 1995). Furthermore, cases of non-adherence have also been reported, due to the potential bad taste and smell of SODF (Overgaard et al., 2001). Taste masking is a very common technique that is applied during granulation and coating processes, as there are many drugs with bitter taste (e.g., Ibuprofen) (Becker et al., 2016).

3.3.5. Density

SODF with higher density typically were shown to present faster transit times when compared to similarly-sized tablets with less density (U.S. Department of Health, 2013). Large and dense capsules are related with quicker esophageal transit times when administered by patients in an upright position, whereas capsules with lower densities exhibited the same profile when swallowed in the supine position (Channer & Virjee, 1985). A positive correlation between the density of capsules and their tendency to stick in the patient's esophagus was also identified (Overgaard et al., 2001).

3.3.6. Surface characteristics

Several studies have assessed the impact of SODF coated surfaces and their relation to the patient swallowing experience. It was observed that coated tablets reduce the number of swallows and the strength of swallowing regarding patients with dysphagia. A higher esophageal contraction force was required by the patients in order swallow large uncoated tablets, whereas the presence surface coating in the SODF reduced their swallowing effort. The transit time was also reduced when a coating surface was present in the SODF (Yamamoto et al., 2014). A higher risk for the lodging of SODF in the esophagus was also identified for uncoated tablets when compared to the identical coated tablets (U.S. Department of Health, 2013). The surface roughness of SODF may also increase their likelihood for sticking in the esophagus, leading to an

unpleasant swallowing experience for older patients. The stickiness was also positively correlated to the SODF surface area, while the presence of SODF film coatings led to an improvement in their transit times (Channer & Virjee, 1985). Overall, the SODF coatings have demonstrated to considerably reduce the cases of non-adherence and SODF manipulation to enhance swallowability, and they should always be integrated into SODF product design (Stegemann et al., 2012; Brotherman et al., 2004; Yoder et al., 2014; Yamamoto et al., 2014).

4. Development of SODF for older patients requires a patient centric drug product design approach

It is a general understanding regarding drug product design a “one size fits all” approach cannot address the specific needs of heterogeneous older patient populations worldwide (Page et al., 2016; Stegemann, 2016; Du Plessis et al., 2017; Liu et al., 2014). Previous reports suggested that a tablet weight within 300–450 mg provides a good balance between the handling and swallowing experience (Yoder et al., 2014). However, such an approach only covers a limited number of drugs and it does not apply to SODF requiring a higher dose strength (e.g., 1000 mg tablets). It is generally perceived by older patients that a better swallowing experience can be achieved with coated SODF that are small, oblong, and strongly convex. In addition, for SODF requiring higher doses, the preferred shape tends to be oblong and/or oval (Kelly et al., 2010; Overgaard et al., 2001).

New guidelines that were published by the European Medicines Agency (EMA) were implemented in order to encourage the development of drug product designs that can address the specific needs of older patients (EMA, 2017). Nevertheless, although regulatory incentives have been initiated, the availability of SODF designs that can really benefit older patients are still lacking (Van Riet-Nales et al., 2016; Burke et al., 2019; Stegemann et al., 2018; Radhakrishnan et al., 2019).

Recent developments in patient-friendly dosage forms were achieved with the development of orally disintegrating tablets (ODTs) (Hannan et al., 2016; Rehman et al., 2018). These are easy-to-swallow dosage forms that disintegrate within seconds upon uptake of saliva in the mouth, and they can be therefore swallowed in the form of a liquid or suspension (Hesari et al., 2016; Aslani et al., 2016; Chandrasekaran et al., 2016; Sotoyama et al., 2019; Glezer, 2016; Rustemkyzy et al., 2015). Notwithstanding, the administration of non-solid formulation can be associated with a higher risk for aspiration regarding dysphagic patients, as compared to conventional SODF (Schiele et al., 2015; Curtis et al., 2020).

As it is well understood that older patients struggle to swallow large SODF, a simple patient-centric approach could focus on the manufacturing of reduced dosage form sizes in order to enhance swallowing experience and patient compliance (Vallet et al., 2020; Marconati et al., 2018; Maalouf et al., 2013; Reeve et al., 2013; Hanning et al., 2016; Menditto et al., 2020; Timpe et al., 2020). Following this concept, and for a given pharmaceutical drug product, a wide range of SODF presentations should be available on the market to meet the heterogeneous needs of the older patient population (Goyanes et al., 2017; Duggan et al., 2015; Ho et al., 2020; Govender et al., 2020). Examples may include not only minitablets (Alshetaili et al., 2016; Freerks et al., 2020; Aleksovski et al., 2015; Chen et al., 2017) and multiparticulate systems (Ito et al., 2015; Marconati et al., 2019; Mohylyuk et al., 2020; Al-Hashimi et al., 2018; Hofmanová et al., 2020), which are patient centric for supporting a better swallowing experience and flexible dosing (Shariff et al., 2020; Robbins et al., 2013), but also chewable tablets (Dille et al., 2017) and buccal films (Uddin et al., 2019; Kumar et al., 2020; Speer et al., 2019). For cases of drug products that remain in a conventional SODF presentation (e.g., tablets or capsules), a patient-centric approach for addressing older patients could involve the development of appropriate film coating materials that can contribute for faster transit times and reduce their likelihood to stick or lodge in the esophagus (Smart et al., 2013). New non-mucoadhesive film coating materials that exhibit enhanced gliding performance throughout the oro-esophageal system are still required to address this (Hofmanová et al., 2019; Smart et al., 2015).

5. Film coating materials designed to enhance SODF swallowing experience

A literature review on available scientific articles and patents that described film coating materials (and their polymer compositions) targeting swallowability enhancement for SODF was performed in May 2015 by an experienced librarian while using established methodology (Khan et al., 2003). A list of suitable keywords and relevant truncations were developed in order to support the search using different search engines (e.g., Scifinder, Web of Science, Medline). The patents were searched by using the self-programmed Retrieval-Engine available from Espacenet. In December 2020, a complementary literature review was conducted while using PubMed database to update the search strategy regarding the time frame between 2015 and 2020. All of the searches were performed with no date of publication, language, or geographic restrictions. The term “palatability” was not included in the search strategy in order to avoid biased results

representing patient acceptability with regards to flavoring agents (e.g., taste) because the main focus of the review was targeted on swallowability enhancement.

5.1. Selection process and obtained results

The authors (Drumond and Stegemann) independently performed a primary screening by reviewing the title and abstract for the retrieved publications. Articles with no relevant content, as decided by the two authors, were eliminated from the search result. The full text of the remaining articles was individually reviewed and screened according to pre-established inclusion and exclusion criteria (Table 5). The resulting publications were analyzed and evaluated by the authors for their research target, research methodology, and data interpretation.

Table 5. Inclusion and exclusion criteria used in the review.

Priority order	Inclusion	Exclusion
1	Oral drug delivery	Other routes for drug delivery
2	Capsules and tablets	Powders, granules, sachets, multiparticulates, effervescent tablets
3	Tablets swallowed intact (e.g., non-dispersible, bulk tablets)	Dispersible tablets (e.g., dispersible, effervescent, orodispersible)
4	Interventions to facilitate swallowing of tablets and capsules	Dosage form manipulations
5	Coatings to enhance swallowing of tablets and capsules	Other functional coatings

The combined literature searches that were performed at the different time frames using the relevant databases and search criteria resulted in 425 citations. The preliminary examination of their potential relevance led to the exclusion of 282 references. Publications that were related to the remaining 143 citations were screened while using the established inclusion and exclusion criteria. This resulted in the exclusion of 113 citations, with the remaining 30 references being included in the review. From the included references, two were scientific articles (Table 6) and twenty-eight were patents (Table 7). It is worth noting the limited availability of scientific articles, which contrasts with the large number of patent applications aiming at retaining intellectual property and reducing competitiveness, as the formulations that are employed to manufacture SODF coatings are composed of well-known polymers that are present in the market for decades.

Table 6. Scientific articles addressing coating materials to aid swallowability of SODF.

Authors	*Title*	*Year*	*Reference*
Okabe et al.	Development of an easily swallowed film formulation	2008	[161]
Ito et al.	Investigation of Oral Preparation That Is Expected to Improve Medication Administration: Preparation and Evaluation of Oral Gelling Tablet Using Sodium Alginate	2017	[179]

5.1.1. Polyvinyl alcohol-based coatings (PVA)

Researchers in Japan developed a swellable tablet coating that was composed of PVA and carboxyvinyl polymer (Okabe et al., 2008). A patent application has also been disclosed for this technology (Sugiura et al., 2012). Another two patents have also described PVA combinations with polyacrylic acid/ glycerin and guar gum/triglycerides, respectively (Kata et al., 2009; Jeffrey et al., 2018).

5.1.2. Cellulose-based coatings

Different hydroxypropyl methylcellulose films (HPMC) were suggested alone (Kawasumi et al., 2007, and in combinations with triacetin (John et al., 1981) or ethyl cellulose (EC)/polyvinylpyrrolidone (PVP) (Tencza et al., 1987).

5.1.3. Gum-based coatings

Coating materials comprising gum arabic in association with gelatin (Clark et al., 1878) and sodium alginate/methylcellulose (MC) have been defined (Sato et al., 1986). Other formulations described the use of gellan gum (Flanagan et al., 2002), and its further combinations with polyethylene glycol (PEG)/sodium lauryl sulfate (SLS) (Flanagan et al., 2003) or pullulan/mannitol (Nitsuto et al., 2002). In addition, a formulation comprising xanthan gum with sodium alginate/citric acid was also reported (Mizuhara et al., 2014).

5.1.4. Gelatin-based coatings

Gelatin has been applied as individual coating material in order to achieve reduced stickiness and glutinous behavior (Becker et al., 1992). Other combinations of gelatin with lubricants (Imanishi, 1997), sodium alginate/vegetable oil (Yinjian, 2018), carrageenan/HPMC/starch/polymethacrylate (Waldman, 2012), and glycerin/glucose/gum arabic have also been published (Yinjian, 2018).

5.1.5. Sodium alginate-based coatings

Sodium alginate has been applied as a thickening agent in order to manufacture a coating material that swells and forms a gel upon the uptake of water (Ito et al., 2017).

Table 7. Patents addressing new coating materials to enhance swallowability of SODF.

Author(s)	*Patent number*	*Year*	*Related invention*	*Reference*
William N. Clark	US209654A	1878	Improvement in soluble coatings for pills	[168]
Secora et al.	US3390049A	1968	Pharmaceutical tablets coated with wax-free ammonia solubilized water soluble shellac	[181]
John et al.	US4302440A	1981	Easily-swallowed aspirin tablet thinly-coated with HPMC and aqueous spray-coating preparation	[166]
Motoaki Sato	JPS61161215A	1986	Method of making solid material easily swallowable	[169]
Tencza et al.	CA1217140A	1987	Thin film coated tablets	[167]
Becker et al.	US5114720A	1992	Gelatin coated tablets and method for producing same	[174]
S. Imanishi	JPH09104621A	1997	Medicine coated with gelatinizing agent, lubricating agent and lubricant	[175]
Peter Gruber	WO9806385A1	1998	Easy to swallow oral medicament composition	[184]
Nitsuto et al.	JP2002275054A	2002	Easily administrable solid preparation	[172]
Flanagan et al.	US6395298B1	2002	Gellan gum tablet coating	[170]
Flanagan et al.	US6635282B1	2003	Gellan gum tablet film coating	[171]
Tsukioka et al.	JP2007070344A	2007	Internal medicine	[186]
Jerry Robertson	US20070259038A1	2007	Solid medicament dosage form consumption aid	[189]
Kawasumi et al.	JP2007015950A	2007	Easily-swallowable film-coated preparations containing antacids	[165]
Eramo Lincoln	US2007243246A1	2007	Lubricious coatings for pharmaceutical applications	[185]
Kata et al.	JP2009120497A	2009	Film for assisting deglutition and method for producing the same	[163]
Kata et al.	JP2010120877A	2010	Oral administration preparation	[183]
Fujioka et al.	JP2011195569A	2011	Easily swallowable tablet	[187]
Chen et al.	TW 201121586A	2011	Oral tablet	[180]
Joel Waldman	WO2012024360A2	2012	Tablet sleeve for improved performance	[177]
Yang et al.	CN102652738A	2012	Novel medicinal outer wrapper facilitating swallowing	[188]
Sugiura et al.	CN102361652A	2012	Adhesion preventing composition, solid preparation and method for producing the same	[162]
Li et al.	CN102430124A	2013	Pill coating with ultralow friction coefficient and preparation method	[190]
Mizuhara et al.	JP2014227391A	2014	Water-swellable laminated film and swallowable substance-coated body	[173]
Takano et al.	JP2014189547A	2014	Swallowable film-coated cover for oral drug delivery	[182]
Bao Yinjian	CN108543072A	2018	Coating composition and related used thereof	[176]
Bao Yinjian	CN108578704A	2018	Composition used for swallowing and relevant applications of composition	[178]
Jeffrey et al.	US2018036413A1	2018	Easy to swallow coatings and substrates coated therewith	[164]

5.1.6. Wax-based coatings

An anti-adhesive coating of beeswax and talc to obtain good slip properties has been disclosed in a patent (Chen et al., 2011).

5.1.7. Shellac-based coatings

A material that is composed of water-soluble shellac has been proposed to contribute for pharmaceutically elegant tablets that enhance swallowability (Secora et al., 1968). Another patent described a solution comprising a mixture of shellac/PVP/hydroxypropyl cellulose (HPC)/PEG/sucralose (Takano, 2014).

5.1.8. Polyacrylate-based coatings

A two-layered polyacrylic acid coating material in combination with sodium carboxymethylcellulose (CMC)/PVP, which forms a viscous surface after absorbing saliva, was suggested (Imanishi, 1997). Furthermore, an acrylic acid copolymer formulation has also been described (Gruber, 1998).

5.1.9. Polyethylene oxide-based coatings

A polyethylene oxide (PEO) coating has been proposed as lubricious material for pharmaceutical applications. The coating can be applied by dipping the SODF in the coating solution, followed by curing process with ultraviolet light (Lincoln, 2007).

5.1.10. Carrageenan-based coatings

A film composed of carrageenan and trehalose that converted to an easy-to-swallow smooth surface was disclosed in a patent (Tsukioka et al., 2007). A complex mixture comprising carrageenan/sodium alginate/xanthan gum/HPMC/crospovidone has been proposed as coating material in order to enhance tablet swallowability (Fujioka et al., 2011). Other combinations, including carrageenan/agar/gelatin, were also reported (Yang et al., 2012).

5.1.11. Polysaccharide-based coatings

A flavored coating solution containing viscous and lubricant materials (e.g., polysaccharides, polyols) that can be applied to SODF by spraying or dipping was previously detailed in a patent record (Robertson, 2007). In addition, a coating gel that was obtained by polymerization and crosslinking of different polysaccharides that contributes to reduced esophageal friction was also suggested (Li et al., 2012).

5.2. Clinical Evidence of Proposed Coating Compositions for Enhanced Swallowability

Clinical studies involving healthy volunteers have been performed for some of the described coatings compositions. Fluoroscopic measurements with 10 healthy volunteers while using the PVA/carboxyvinyl coating combination provided evidence for the accelerated transit time of the coated SODF as compared to gelatin capsules (Okabe et al., 2008). The mixture of PVA/polyacrylic acid/glycerin was assessed in a study with five volunteers, which confirmed a good swallowing experience that was provided by the coating (Kata et al., 2009). Five healthy volunteers were also enrolled in an *in vivo* trial that assessed gellan gum/pullulan/mannitol coatings (Nitsuto et al., 2002).

Another clinical study has shown that shellac/PVP/HPC/sucralose-based coatings can reduce the tendency of SODF to adhere into the oral cavity of patients (Takano, 2014). Improved taste and optimal swallowing experience upon SODF administration was identified through sensory assessments for both the polyacrylic acid/CMC/PVP and acrylic acid copolymer coatings (Gruber, 1998; Kata et al., 2010). Lastly, a clinical trial with 30 subjects reported an improvement in SODF swallowability though a significant reduction of involuntary gag reflexes for lubricant coatings that are composed of polysaccharides/polyols (Robertson, 2007).

6. Reflections on available administration aids and devices to enhance SODF swallowability in older patient populations

Two of the identified administration aids/devices are currently marketed as swallowing-enhancing technologies for SODF. These can be sub-grouped into distinct co-administration mechanisms involving SODF suction with jelly vehicles (Sadamoto et al., 2012), spraying of the SODF and patient's mouth and/or tongue with lubricants (Diamond et al., 2010), and the manual application of a gelatinous coating onto the SODF before administration (McDonald et al., 2002). Semi solid vehicles are typically recommended for patients with swallowing issues, as their rheological properties allow for the formation of a bolus that is smooth to swallow and prevents cases of aspiration (Satyanarayana et al., 2011; Clavé et al., 2008). When embedded into the semi-solid vehicles, the SODF are not recognized as a bulk solid by the patients and they do not directly interfere with their oro-esophageal system, therefore preventing cases of mucosal sticking and gag reflex. Nevertheless, the co-administration with such type of swallowing aids requires the proper handling and it might be limited by the patient's sip volume, as well as the number of daily doses to be administered, which may limit their use by older patients.

The swallowing-enhancing properties of the spraying solution (Pill Glide®) are supported by specific formulation ingredients, namely xanthan gum and glycerin, as their film-forming and plasticizing effects are expected to coat the oral mucosa and the SODF, reducing the friction and improving the swallowing experience for the patient (Suput et al., 2016; Schwartz et al., 2000).

The flexible integrity of MedCoat® conferred by gelatin allows for the manual application of the coating onto the SODF, while the swallowing-enhancing properties of the material are exerted by a combination of the slippery attribute of vegetable oils, the surfactant effect of fatty acid sugar esters, and the saliva stimulation provided by citric acid (Rahman, 2007; Otoni et al., 2017). Moreover, the maltitol and lemon flavor ingredients are expected to increase the palatability and improve the acceptability of the SODF by older patients (Sohi et al., 2004).

The clinical evaluations for the GT packaging and MedCoat® administration aids were directed to older patient populations. The endpoints and assessments instruments varied, according to the type of administration aid tested, with a general use of qualitative scales for swallowing experience being adopted in all studies. A three-step sensory test was used for the GT packaging, which included opening (breaking the film cover), pushing the gel with the fingers, and preference of co-administration with the packaging. On the other hand, the easiness of swallowing and SODF palatability were the endpoints that were reported by the patients during the trials with MedCoat® (Sadamoto et al., 2012; Uloza et al., 2010).

7. Reflections on identified film coating materials to enhance SODF swallowability in older patient populations

The modification of the surface properties of SODF to improve the swallowing experience for older patients can be achieved with pharmaceutical coatings. The identified coating technologies were mainly focused on water-soluble polymers, in combination with excipients providing additional functions. The swallow-enhancing mechanism for PVA-based coatings is related quick hydration, due to the formation of hydrogen bonds between the saliva water molecules and OH groups in the polymer monomer units (Satokawa et al., 2008). Further combinations of PVA with carboxyvinyl polymers and polyacrylic acid/glycerin will increase the water absorbing and swelling properties of the coating, promoting a gel-forming surface and increasing the slip effect of the SODF in the esophagus (Okabe et al., 2008; Al-Harthi et al., 2016).

The cellulose-based coatings were mainly HPMC-derived, as modified celluloses are predicted to hydrate and uptake water more efficiently, due to the increased

hydrophilicity granted by hydroxypropyl groups, contributing to the formation of a gel-like surface in the SODF (Stephen et al., 2006). Additional combinations of HPMC with ethyl cellulose/PVP are also expected to increase the slip properties of the coating surface, due to a combination of hydrophobic and binder properties, respectively (Yang et al., 2014).

The gelling and emulsifying capabilities of gelatin alone are expected to contribute for a better swallowing experience when administering SODF. However, the gliding properties of gelatin coatings can be further optimized with additives, such as HPMC and polysaccharides, in which their hydroxyl and carboxyl groups will increase the water binding and optimize wettability (Sahoo et al., 2015; Zaikov, 2005).

The swallowing enhancement mechanism for gum-based coating are mainly related to their swelling properties, which are conferred by water binding capacity and quick hydration. The level of water binding can be increased depending on the gum applied in the coating formulation, and higher binding capacity can be achieved with xanthan gum. Guar gum and sodium alginate, as stand-alone coating materials, will present lower binding capabilities and, as such, associations with water-soluble additives, surfactants (e.g., SLS) and saliva promoting agents (e.g., citric acid) will contribute to an improvement in their gliding performances (Sánchez et al., 1995).

The gelling properties of carrageenan are associated with the presence of anhydro galactose units, with a higher softness and gelling elasticity being achieved for ι-carrageenan, due to its lower content in units when compared to with κ-carrageenan. In addition, further combinations with water-soluble additives are expected to promote the gelling effect of carrageenan (Dos Santos et al., 2015).

The enhancing SODF swallowing experience with wax and shellac-based coatings is associated with the hydrophobic nature of these molecules, as their expected smooth surface will reduce the coefficient of friction and increase slip properties (Tracton, 2006). Last but not least, the fast emulsifying properties of polyacrylates will generate a swellable SODF coating surface when in contact with saliva, and they are expected to entail suitable viscosity for a better swallowing experience. Further combinations with water-soluble additives (e.g., CMC and PVP) will increase the coating water uptake and promote a better SODF gliding surface (Medina-Torres et al., 2014).

Although the majority of the identified coating materials allege to enhance SODF swallowability, their clinical evidence to support such claims is still very limited. Furthermore, the available literature published in recent years has tended to focus more on observational studies to measure overall patient acceptability in older patient populations, rather than investigating SODF characteristics and their critical endpoints for swallowability enhancement. Therefore, the current lack of research on developing

relevant evidence on the relationship between the physical characteristics of SODF and their direct correlation to swallowability appears to be the main reason for the limited number of scientific articles that were identified within this literature review (Vallet et al., 2018; 2020; Shariff et al., 2020; 2020; Belissa et al., 2019).

Along with the development of technical approaches and solutions, the collection of clinical data for the concerned patient populations will be required in order to confirm the theoretical models underlying the scientific and technical rationale for drug products that make claims of enhanced swallowability or appropriateness for special patient populations. As such, further clinical assessments are required for validating their potential to overcome swallowing issues (Marconati et al., 2018; 2019; Smart et al., 2015).

8. Concluding remarks

Swallowing issues with SODF are being increasingly recognized as a growing health condition throughout healthcare professionals. There is a consensus that the size, shape, color, taste, and mouthfeel have a significant impact on drug product swallowability and acceptance. In order to achieve good compliance, as well as effective, safe, and independent pharmacotherapy, it is important for physicians and pharmaceutical professionals to be informed regarding potential problems that are related to a patient's inability to swallow SODF, in order to prescribe/dispense suitable drug formulations and/or designs that can better meet the specific needs of each patient (Vallet et al., 2020; Sestili et al., 2018; Chandrasekaran et al., 2016).

Technologies for improving the swallowability of SODF have been developed and tested throughout the years; nevertheless, these often require preparative steps by the patient and, as such, remain very dependent on user's handling capabilities. When considering the older, multimorbid, frail, and polymedicated patients; this might further increase the therapeutic complexity and lead to non-compliance or medication errors (Atkin et al., 1994; Dietlein et al., 2008; Braun-Münker et al., 2016; Notenboom et al., 2014). It was noticed that all of the clinical assessments were sponsored, or at least supported, by companies owning the swallowing enhancing technology under investigation. Other studies that were financed by public funds or independent research groups comparing different swallowing enhancing technologies with scientific or clinical endpoints were not identified.

More attention has been given to the development of new coating technologies for SODF. A large number of patents claiming new intellectual property were published, disclosing new coating formulations and its relative-preparation methods. The coatings

can be applied to oral solid forms and they have been suggested to provide enhanced swallowing experience to both healthy and dysphagic patients. However, clinical evidence confirming the swallowing benefits of the coating formulations in the concerned patient populations are still very limited. In addition, very few of the suggested technologies have been introduced in the market, with evidence of their potential to overcome swallowing issues in the most vulnerable, older patient population being very limited. In this respect, the “gold standard” HPMC coating must still be considered to be state of the art in tablet coating, even though it does not specifically enhance swallowability when compared to other SODF (U.S. Department of Health, 2013; Overgaard et al., 2001).

When it comes to older patients with dysphagia, nowadays SODF administration still remains an unresolved challenge within the subject of pharmaceutical technology. Besides the development of technical approaches and solutions, clinical data in the concerned patient populations will be required to confirm the theoretical models underlying the scientific and technical rationales for drug products claiming enhanced swallowability or appropriateness for older patient populations (Stegemann, 2019; Wahlich et al., 2019; Stegemann et al., 2020)

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Polymer adhesion predictions for oral dosage forms to enhance drug administration safety.

Part 1: *In vitro* approach using particle interaction methods

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All authors have read and agreed to the published version of the manuscript.

Abstract

Solid oral dosage forms (SODF) are drug vehicles commonly prescribed by physicists in primary and secondary cares, as they are the most convenient for the patient and facilitate therapy management. Concerns regarding unintended adhesion of SODF during oro-esophageal transit remain, especially in multimorbid patients, bedridden patients and patients suffering from dysphagia. Hence, this factor should be considered during the development of SODF, and more attention should be given on the design of appropriate surface conditions considering patients with swallowing problems. The aim of this work was to estimate the low mucoadhesion strength of different pharmaceutical polymers frequently used in coating technologies, since this property is thought to have impact on the mucoadhesive profile of SODF during oro-esophageal transit. In an approach using *in vitro* methods based on particle interactions, polyethylene glycol grades (PEG) showed the lowest interaction forces suggesting a more favorable *in vivo* performance than hydroxypropyl methylcellulose (HPMC), which was found to have the highest particle interaction. Preference should be given to coating formulations with lower concentrations of polymer and grades with low molecular weight. In addition, rheological measurements should be adopted when targeting poor mucoadhesive polymers.

Keywords: particle interaction methods, polymer coatings, reduced mucoadhesion, rheological measurements, solid oral dosage forms, swallowing safety

1. Introduction

Despite the increasing number of novel dosage forms and formulation technologies over the years, the majority of medicines remain as solid oral dosage forms (SODF) in primary and secondary cares (Liu et al., 2014). SODF such as tablets and capsules are still very popular nowadays due to technological (accurate dosing, taste masking, controlled release) and economical (easy and efficient manufacturing) reasons. Moreover, it is common practice for physicians to prescribe drug regimens with SODF, since the oral route of administration is seen as the most convenient for patients and facilitates both therapy management and drug administration.

Patients with declined swallowing functions (e.g., dysphagia) may struggle to administer SODF on a daily basis by experiencing recurrent situations of vomiting, gagging or chocking (Schiele et al., 2013). In addition, esophageal motility problems may prompt the adhesion of the SODF to the esophageal mucosa, increasing the risk of drug-induced injury and leading to the feeling of having tablets lodged in the throat (Palmer et

al., 2000). To overcome these issues, patients (and their caregivers) feel tempted to modify SODF (crushing and splitting of larger tablets, opening of capsules) in order to facilitate their administration (Kirkevold and Engedal, 2010; Paradiso et al., 2002).

The prescription of suitable dosage form designs according to patients needs is key to achieve therapeutic effectiveness (Heppner et al., 2006). Drug formulation characteristics such as size and shape have revealed to affect the swallowing performance and influence the adhesion of the dosage form to the esophagus (Channer and Virjee, 1986, 1985; Yamamoto et al., 2014). The surface properties of SODF are also important, as the absence of a film coating has shown to increase the swallowing effort and the transit time of tablets in the esophagus (FDA, 2015). Film-coated tablets present a lower tendency in adhering to the esophageal mucosa, however this effect is highly dependent on the polymer used for coating (Channer and Virjee, 1985; Overgaard et al., 2001). Therefore, predicting the risk of unintended mucoadhesion for SODF coatings during oro-esophageal transit through adequate *in vitro* models should be considered an important tool during formulation development, as it would facilitate oral drug administration regarding patients with swallowing impairments.

Different methods that estimate the interaction strength of polymers to mucous and/or biological membranes (e.g., esophageal tissue) have been proposed over the years, mainly for the development of mucoadhesive drug delivery systems. Methods based on particle interactions estimate the amount of polymer adhering to mucous (e.g., saliva) and provide information about their relative adhesive strength (Woertz et al., 2013). Considering that the majority of available methods were not developed to differentiate reduced mucoadhesion, the sensitivity of particle interaction methods to measure such properties should be investigated. The identification of an suitable method would contribute with valid predictions for the *in vivo* performance of SODF coatings regarding safe swallowing and oro-esophageal transit (Smart et al., 2013).

The aim of this work was to investigate the reduced mucoadhesive properties of different water-soluble polymers using *in vitro* methods based on particle interactions. The polymers tested were polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), polyethylene glycol (PEG) and hydroxypropyl methylcellulose (HPMC, positive control). Features of polymers such as molecular weight and concentration were also assessed for their impact in obtaining a low mucoadhesive profile. The sensitivity of particle interaction methods to differentiate reduced mucoadhesion was evaluated to identify an optimal predictive set up.

2. Materials and Methods

2.1. Materials

PVA grades (EG-03P, EG-05PW, EG-18P, EG-30PW and EG-40P) were obtained from Nippon Gohsei (Düsseldorf, Germany). Plasdone grades (PVP K-15, K-25, K-29/32, K-60, K-90 and K-120) and HPMC E15 were donated by IMCD (Wien, Austria). PEG 1000, PEG 1500 and PEG 4000 were purchased from Alfa Aesar (Lancashire, UK). Lyophilized mucin from porcine stomach and PEG 3350 were purchased from Sigma-Aldrich (Munich, Germany). PEG 6000 was obtained from Baxter (Vienna, Austria). Sodium phosphate monobasic (NaH_2PO_4), Sodium phosphate dibasic (Na_2HPO_4), sodium chloride (NaCl), calcium chloride ($CaCl_2$) and PEG 2000 were provided from Capsugel (Colmar, France). The water used was of Millipore quality.

2.2. Preparation of simulated artificial saliva

For the preparation of simulated salivary buffer, 0.021 M of Na_2HPO_4/NaH_2PO_4, 0.036 M NaCl and 0.00096 M $CaCl_2$ were dissolved in distilled water. Subsequently, 5 mg/ml of lyophilized mucin from porcine stomach were added, and the mixture was allowed to stir overnight at room temperature (Teubl et al., 2013).

2.3. Preparation of polymer samples

For each polymer, aqueous stock solutions of 6% (w/v) were prepared at room temperature. The remaining concentrations (1-5%) were obtained by performing dilutions of the stock solutions.

2.4. Rheological measurements

One-part artificial salivary buffer and one part polymer solution were mixed together at 400 rpm for 30 min prior to analysis. Polymer solutions and artificial saliva were also measured alone as references. The measurements (in duplicates) were performed with a Physica MCR rheometer (model MCR 300), using a 26.66 mm cylindrical probe (Anton Paar GmbH, Graz, Austria). The temperature was set to 37°C and the rheometer was automatically equilibrated before starting each measurement. Shear rates ranged from 5 s^{-1} to 25 s^{-1}, and ten replicates were recorded for each point.

2.5. Turbidimetric measurements

2.5.1. Treatment of simulated artificial saliva

The simulated artificial saliva was placed in a sonication bath for 3 h, and later centrifuged at 15,000 RPM for 30 min. Subsequently, the supernatant fraction was collected to be used in the experiments.

2.5.2. Evaluation procedure for turbidimetric measurements

Equal volumes of polymer solution and artificial saliva were mixed together by vortexing, and later incubated at 37°C for 1 h with constant agitation (200 RPM). The absorbance of the mixtures was determined with a Lambda 950 UV/Vis Spectrophotometer at a wavelength of 500 nm (PerkinElmer, Massachusetts, EUA). Each polymer sample was measured in duplicate and simulated artificial saliva was used as a reference (blank).

2.6. Particle size and zeta potential measurements

2.6.1. Treatment of simulated artificial saliva

The simulated artificial saliva was centrifuged at 40,000 RPM for 30 min, using an Optima L-100 XP ultracentrifuge (Beckman Coulter, California, USA). Subsequently, the supernatant fraction was collected to be used in the experiments.

2.6.2. Evaluation procedure for particle size and zeta potential measurements

Equal volumes of polymer solution (in concentrations of 2, 4 and 6%) and artificial saliva were mixed together by vortexing, and later incubated at 37°C for 1 h with constant agitation (200 RPM). The particle size and zeta potential of the mucin particles was determined using a Zetasizer Nano ZS (Malvern Instruments, UK). Considering HPMC mixtures, the particle size was measured with a Mastersizer 2000 (Malvern Instruments, UK). After an equilibration period of 1 min, three measurements were performed (per sample) at 37°C. For each analysis, 7 and 20 runs were conducted for particle size and zeta potential, respectively.

2.6.3. Measurement of pH

The pH of the polymer-mucin mixtures was determined using a HandyLab 860 pH meter (SI Analytics, Mainz, Germany), calibrated at regular intervals with technical buffer solutions (pH 4.01 and pH 7.0).

2.7. Particle interaction methods evaluation

2.7.1. Sensitivity of particle interaction methods to measure low levels of mucoadhesion

The mucoadhesive results obtained for the tested polymer grades were normalized and expressed in percentage (%) to allow a direct comparison between particle interaction methods. Sensitivity and magnitude discrepancies were evaluated, especially at the lower level of polymer adhesive potential, with purpose of identifying an optimal

method that can provide better predictions for the impact of SODF coatings on safe swallowing and oro-esophageal transit.

2.7.2. Method comparison studies – Bland Altman plots

The degree of agreement between the different methods was evaluated using the analysis proposed by Bland and Altman (Bland and Altman, 1999). The bias or systematic error, as well as the lower and upper limits of agreement were calculated based on the normalized values of mucoadhesion obtained with a sample concentration of 6% for each method.

3. Results

3.1. Rheological measurements

Based on the viscosities measured, the interaction strength with artificial saliva was determined for all polymers at different concentrations and respective MWs. The values obtained for standard deviation (SD) were omitted (no significant differences, SD ± 0.001) to improve graphical visualness. With respect to the PVP grades, increases in concentration or MW led to increases in viscosity (Fig. 1).

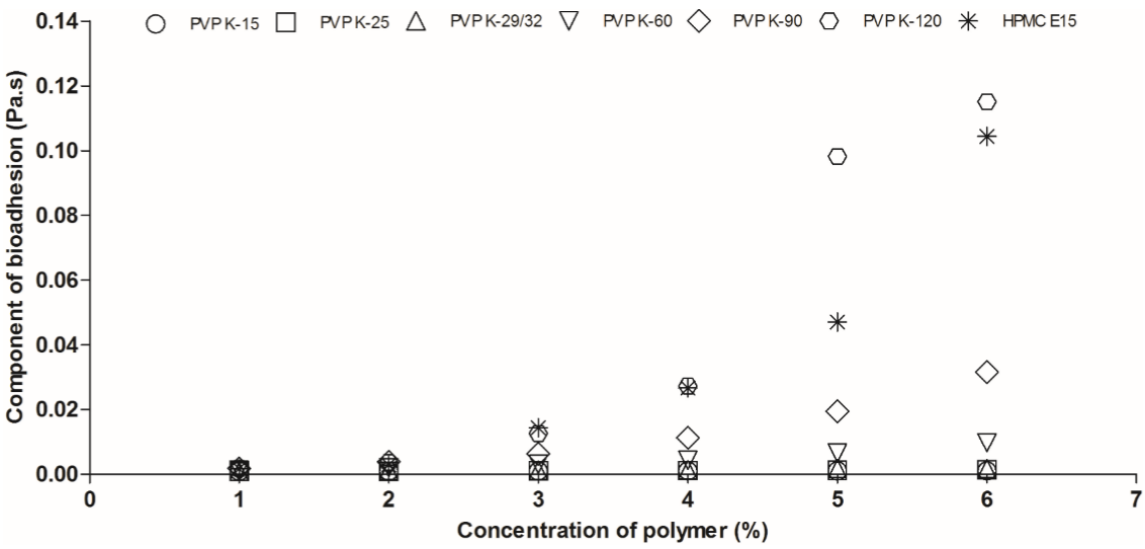

Figure 1. Component of bioadhesion for PVP grades as compared to HPMC (positive control).

Maximum levels were obtained for PVP K-120, which displayed a degree of interaction comparable to the one obtained for HPMC (for concentrations within 4-6%). Grades PVP K-90 and PVP K-60 also showed good levels of interaction based on their viscosity profiles. Low MW grades (PVP K-15, PVP K-25, PVP K-29/32) presented poor

viscosity levels that can be correlated to a weak interaction strength with mucin. PVA grades exhibited similar profiles, with higher MWs and concentrations leading to increasing viscosity values (Fig. 2). Superior viscosity levels were obtained for PVA EG-40P, which showed a similar profile to HPMC. Significant interactions were also predicted for the EG-30PW and EG-18P grades. PVA EG-03P and EG-05P exhibited lower viscosity values that are indicative of poor interactions with mucin. With regard to PEG polymers, all grades displayed extremely low levels of viscosity indicating a negligible interaction with mucin (Fig. 3A). In addition, the concentration of the polymers did not seem to have an impact on the viscosity profile (Fig. 3B).

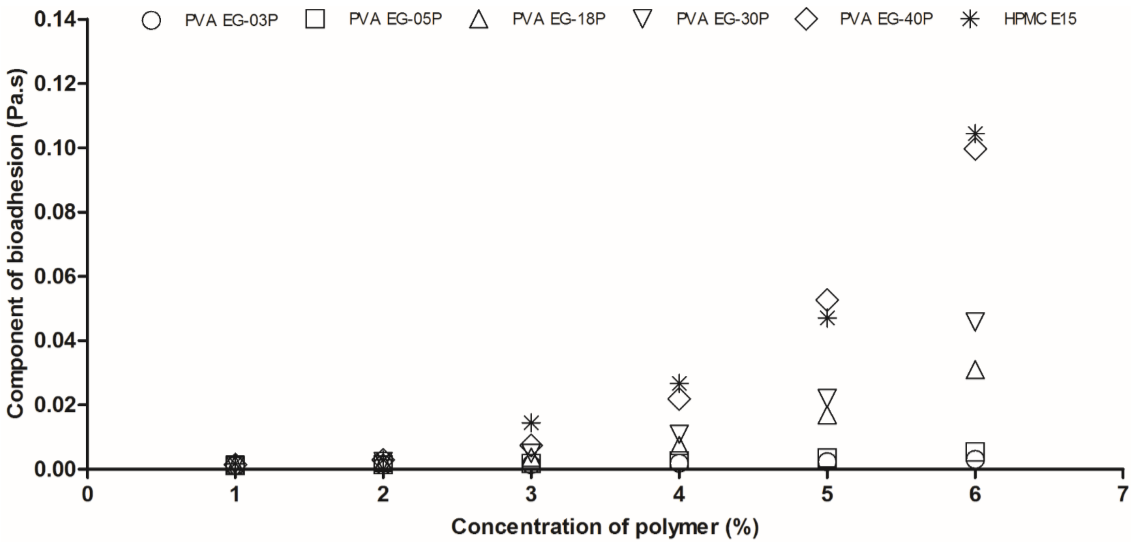

Figure 2. Component of bioadhesion for PVA grades as compared to HPMC (positive control).

3.2. Turbidimetric measurements

The absorbance measured for the mixtures of artificial saliva with the different polymer grades and respective concentrations is shown in figure 4. With regard to PVP grades (Fig. 4A), an overall increase in the absorbance values was observed for higher MWs. However, no correlation was found between the measured absorbance and the polymer grade concentration, with exception for the PVP K-120 grade (highest MW). A similar pattern was observed for PVA grades, with increased absorbance values correlating with higher MW and concentration (Fig. 4B). No relation was detected between the concentration of the polymer and the turbidity of the sample regarding low molecular grades (PVA EG-03P and PVA EG-05P). The slight increase in the absorbance values measured for PVP grades would suggest higher interaction forces as compared with PVA grades. PEG grades showed the lowest absorbance values, which indicates lack of interactions with artificial saliva. Furthermore, no correlations

were found between absorbance strength, MW and concentration (Fig. 4C). The strongest interactions between polymer and mucin are expected for HPMC (positive control), where a perfect correlation between concentration and absorbance strength was observed.

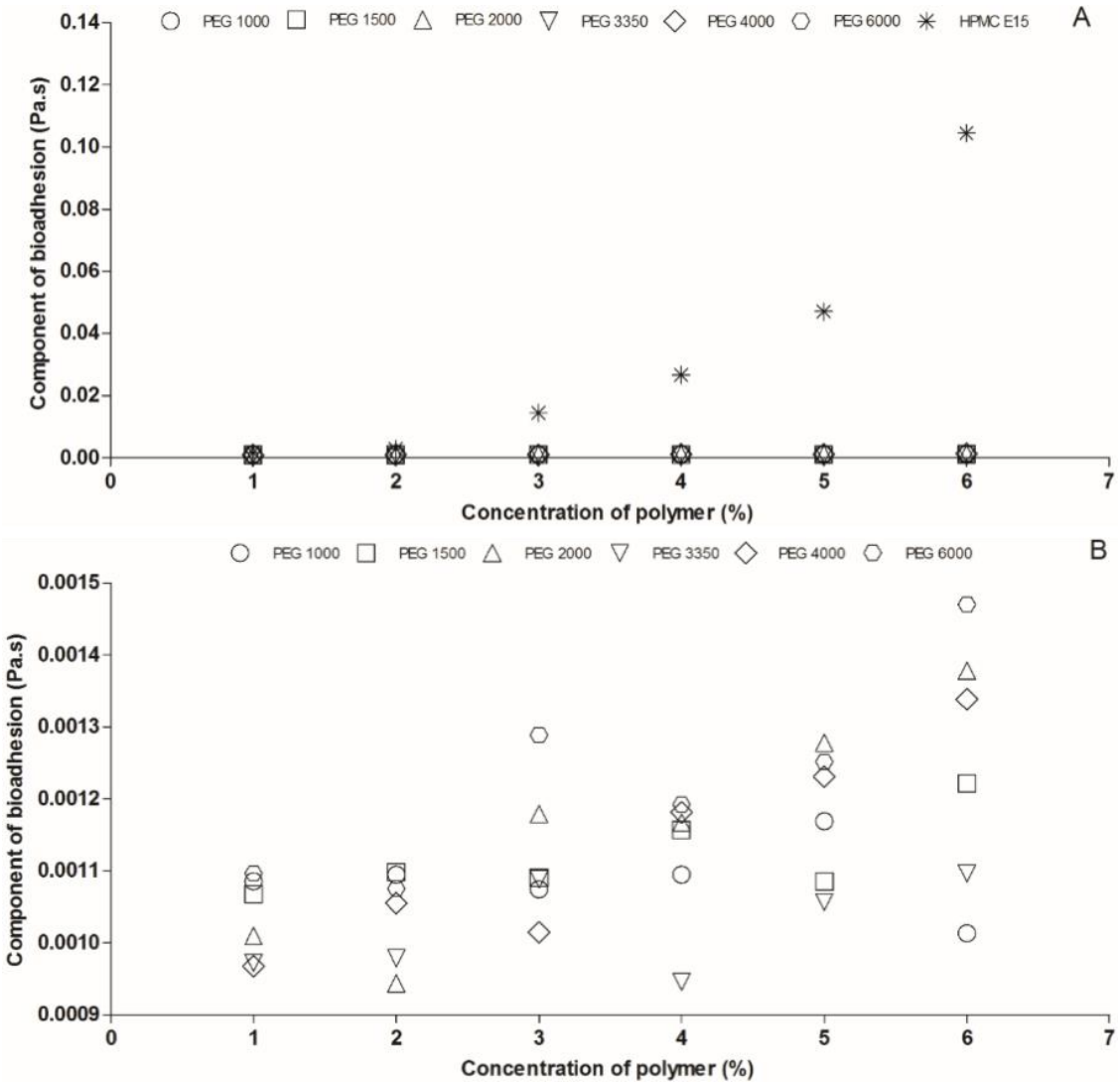

Figure 3. Component of bioadhesion for PEG grades. A: *vs* HPMC, B: PEG grades only.

3.3. Particle size and zeta potential measurements

The particle size and zeta potential of the mucin particles were measured before mixing with the polymers to allow a direct comparison. The obtained results were particle size ± SD: 0.1932 ± 9.34 µm and zeta potential ± SD: -5.78 ± 0.14 mV. Subsequently, the same procedure was applied to the polymer-mucin mixtures. Complementary pH measurements were also performed and can be visualized in table 1.

Table 1. Results obtained for the pH of the polymer-mucin mixtures.

	pH		
Polymer (% m/v)	**2**	**4**	**6**
PVP K-15	6.67	6.63	6.57
PVP K-25	6.72	6.71	6.67
PVP K-29/32	6.84	6.82	6.79
PVP K-60	6.78	6.76	6.73
PVP K-90	6.85	6.84	6.83
PVP K-120	6.92	6.90	6.89
PVA EG-03P	6.87	6.83	6.81
PVA EG-05P	6.89	6.86	6.85
PVA EG-18P	6.97	6.95	6.92
PVA EG-30P	6.86	6.83	6.81
PVA EG-40P	6.91	6.89	6.86
PEG 1000	6.98	6.95	6.94
PEG 1500	6.97	6.94	6.92
PEG 2000	6.95	6.93	6.90
PEG 3350	6.96	6.94	6.91
PEG 4000	6.98	6.96	6.95
PEG 6000	6.94	6.92	6.89
HPMC E15	6.80	6.78	6.75

Regarding PVP grades (Fig. 5A), although it was detected a tendency for the particle size to increase with higher concentrations, no identical correlation was observed considering the MW. At specific concentrations, the increase in MW was not always correlated to higher particle size (especially for PVP K-60, K-90 and K-120). Nevertheless, the influence of the MW on the zeta potential was clearly visible, with higher grades leading to stronger reductions on the negative charge of mucin particles. The same observation is valid for increasing concentrations, with exception for the lower MW grades (PVP K-15 and PVP K-25). A positive correlation between MW and particle size was noted for all PVA grades (Fig. 5B). Additionally, the particle size increased as the concentration increased. Regarding zeta potential, a stronger correlation to concentration is more likely for higher MWs (PVA EG-30P and PVA EG-40P). As such, both MW and concentration seem to impact on the interaction forces of PVA grades with mucin particles. In opposition, no correlation between the studied variables and increasing particle size was observed for PEG grades (Fig. 5C). Nevertheless, when assessing the zeta potential charge, positive correlations with concentration and MW were noticed regarding the majority of the grades. Lastly, superior interaction forces were predicted for the positive control (HPMC), with this effect being highly correlated to the concentration of polymer.

3.3. Particle interaction methods evaluation

3.3.1. Sensitivity of particle interaction methods to measure low levels of mucoadhesion

For each method used, the results were normalized according to the concentration of the tested polymer (2%, 4% or 6%). In order to investigate the sensitivity of the different methods in measuring reduced mucoadhesion, a theoretical range for poor adhesive potential was established for the lower limit of normalization (0 to 10%). The obtained values (in percentage) can be visualized in table 2. Poor sensitivity in measuring lower levels of mucoadhesion was observed for the particle size and zeta potential methods. Considering the first, the analysis is unsatisfactory especially in cases where there is a high difference for the obtained particle size values (e.g., polymer concentrations of 6%). Regarding the latter, the sensitivity to measure mucoadhesion at lower levels is unsatisfactory. Some degree of differentiation can be obtained when measuring mucoadhesion with turbidimetric measurements. Nevertheless, the method seems only to respond properly among polymer species (e.g., PVA, PVP) and is not so critical when evaluating polymer grades within the same specie or different concentrations for the same grade (e.g., PVP K-15, PVP K-25).

Higher levels of differentiation to measure the low mucoadhesive potential of the polymers tested were obtained with rheological measurements. With this method, it is possible to distinguish reduced mucoadhesion between polymer species and it is sensitive enough to discriminate within polymer grades from the same specie (e.g., PEG grades, PVP and PVA low molecular grades). All the assessed methods measured mucoadhesion in a similar extent with exception for the turbidimetric method that measured lower mucoadhesion for PVA grades in compassion to PVP grades.

3.3.2. Method comparison studies – Bland Altman plots

An analysis based on Bland Altman plots was applied to obtain general information on the degree of agreement for mucoadhesive measurements using particle interaction methods. As no standard method for *in vitro* mucoadhesive evaluation has been yet defined in the available literature, all particle interaction methods were compared with one another. The obtained results can be visualized on Table 3.

The plots consist of the average of the paired values from each method along the x-axis with the difference of each pair of readings along the y-axis. The overall mean difference in the obtained values from the two methods is called the bias. The bias and the confidence limits for the bias are displayed as solid and dotted horizontal lines, respectively. The bias quantifies how much higher (positive bias) or lower (negative bias)

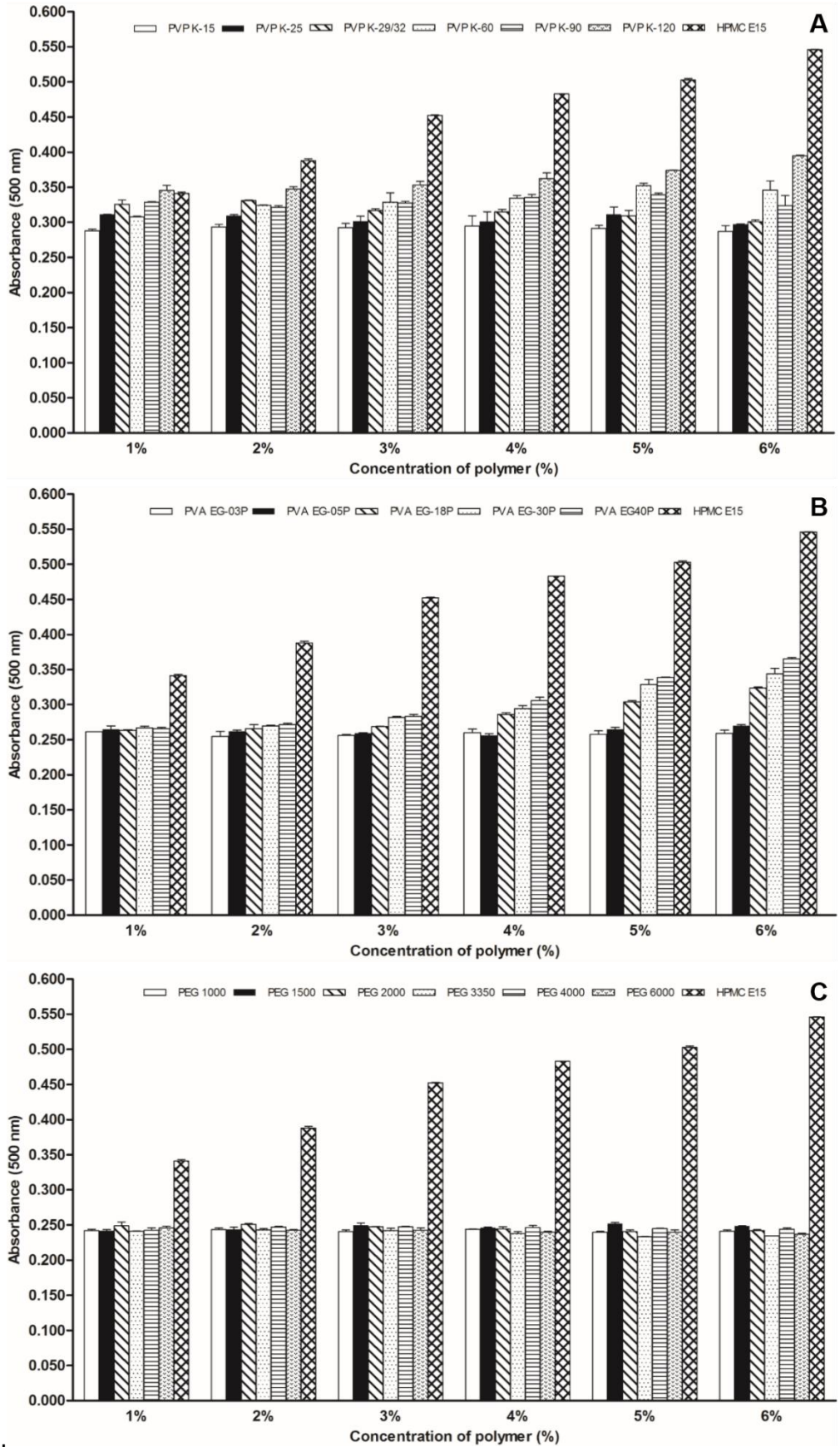

Figure 4. Analysis of absorbance for mixtures with A: PVP grades, B: PVA grades, C: PEG grades and its comparison to HPMC (positive control).

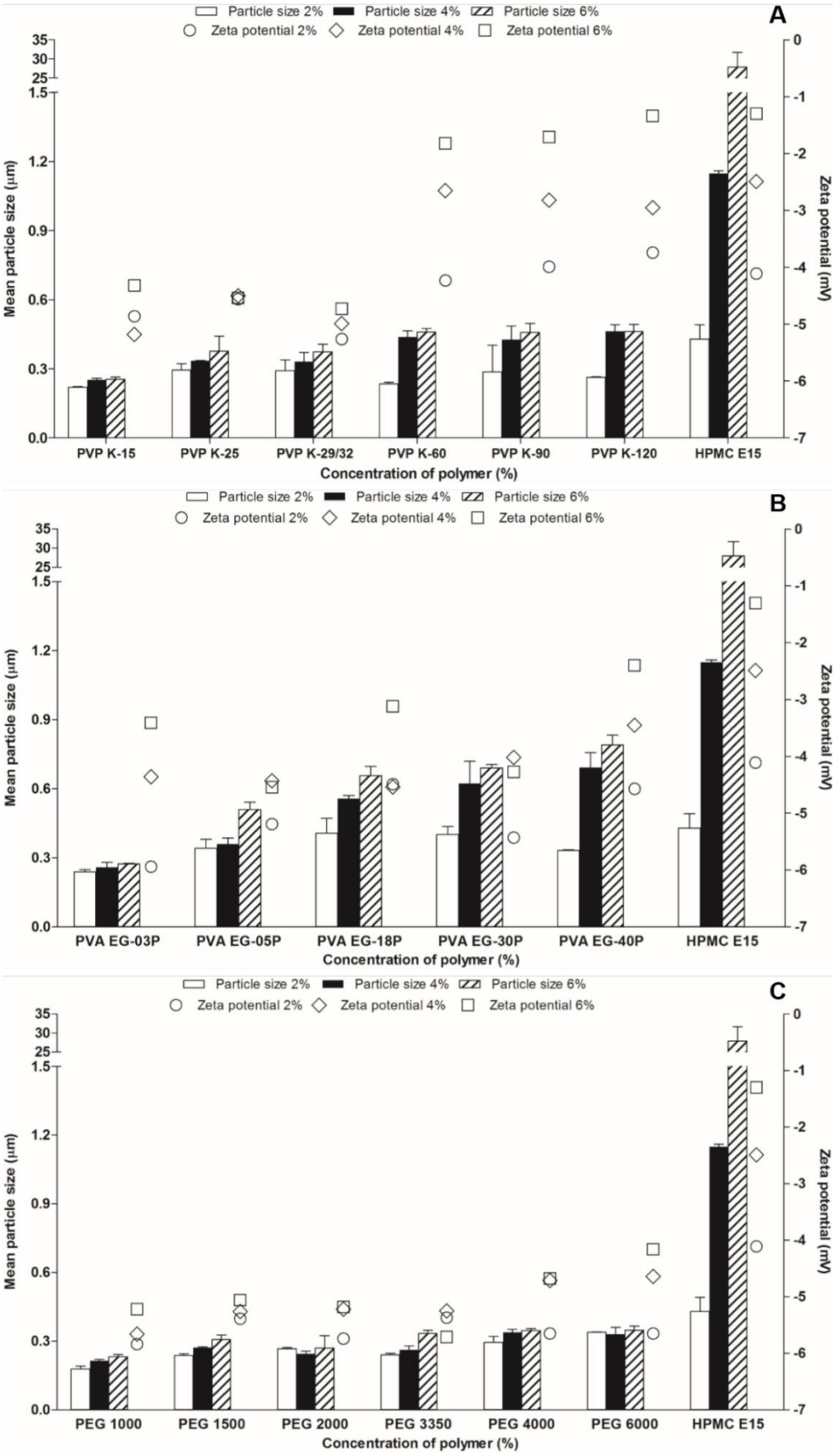

Figure 5. Particle size and zeta potential of mucin particles for mixtures with A: PVP grades, B: PVA grades, C: PEG grades and its comparison to HPMC (positive control).

Table 2. Normalization of polymer grade results according to concentration and particle interaction method used.

	Particle interaction methods											
	Rheological measurements			Turbidimetric measurements			Particle size measurements			Zeta potential measurements		
Polymer (% m/v)	2	4	6	2	4	6	2	4	6	2	4	6
PVP K-15	2.09	0.74	0.12	34.91	23.29	16.88	12.29	4.56	0.00	37.15	0.00	22.29
PVP K-25	1.82	0.92	0.40	45.90	25.75	20.14	43.31	12.04	0.37	73.20	15.66	21.22
PVP K-29/32	7.41	1.97	0.73	60.56	31.48	21.31	46.76	11.58	0.33	27.43	24.04	13.74
PVP K-60	39.34	13.06	7.68	56.03	39.51	35.87	50.84	27.65	0.57	70.85	100.0	89.08
PVP K-90	100.0	39.39	26.83	54.03	39.79	28.70	55.27	14.18	0.55	100.0	88.90	91.68
PVP K-120	93.03	100.00	100.0	72.02	50.90	51.50	18.38	19.16	0.52	86.36	78.67	100.0
PVA EG-03P	13.53	3.57	1.77	8.51	9.21	7.88	16.83	7.18	0.16	0.00	41.68	43.28
PVA EG-05P	17.23	6.17	3.85	13.39	7.52	11.33	67.43	18.55	0.94	25.86	50.68	23.44
PVA EG-18P	40.59	24.37	26.34	15.79	19.80	28.74	100.0	40.65	1.38	86.05	23.18	52.82
PVA EG-30P	49.58	37.87	39.25	18.68	23.00	35.13	75.17	36.66	1.51	59.25	51.54	32.90
PVA EG-40P	49.58	37.87	39.25	20.01	27.89	41.98	43.51	44.90	1.46	80.88	80.89	75.80
PEG 1000	5.12	0.57	0.00	34.91	23.29	16.88	0.00	0.00	0.04	26.65	8.02	16.26
PEG 1500	5.22	0.80	0.18	0.62	3.50	4.48	10.98	6.37	0.31	34.17	12.08	20.15
PEG 2000	0.00	0.84	0.32	5.56	2.79	2.54	17.97	6.29	0.32	12.07	5.06	12.14
PEG 3350	1.19	0.00	0.07	0.21	0.00	0.00	15.43	7.24	0.30	35.11	3.95	0.00
PEG 4000	3.76	0.89	0.29	3.06	3.55	3.08	33.74	13.67	0.35	21.94	23.92	23.59
PEG 6000	4.48	0.93	0.40	0.00	0.77	0.77	38.75	12.72	0.43	11.60	10.97	39.85
HPMC E15	67.14	97.73	90.60	100.0	100.0	100.0	96.82	100.0	100.0	91.22	88.41	95.88

Table 3. Particle interaction method-comparisons using Bland Altman plots.

Methods-comparison	Limits of agreement	Bias	No. of outliers
Rheology vs. Turbidimetric (A)	-36.24 to 26.33	-4.95	1
Rheology vs. Particle size (B)	-37.86 to 63.25	12.70	1
Rheology vs. Zeta potential (C)	-67.99 to 19.54	-24.22	1
Turbidimetric vs. Particle size (D)	-12.97 to 48.27	17.65	1
Turbidimetric vs. Zeta potential (E)	-61.75 to 23.20	-19.27	1
Particle size vs. Zeta potential (F)	-98.97 to 25.13	-36.92	0

the values are measured by method B as compared to method A (standard). A positive mean bias difference indicates that method A is measuring mucoadhesion higher, while

a negative value indicates that method B yielded higher measurements (Fig. 6). Additionally, the limits of agreement represent the range within which the values of method B (approximately 95% ± 1.96 SD) agree with the values of method A (Giavarina, 2015; Hanneman, 2010).

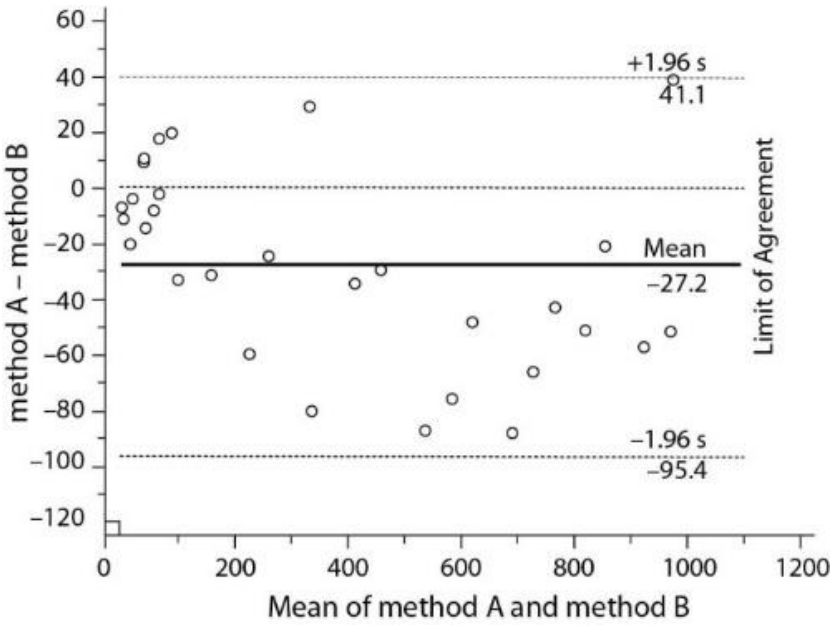

Figure 6. Example of a Bland Altman plot evaluating method A *vs* method B.

The zeta potential method has measured higher mucoadhesive potential when compared to all other three methods (comparisons C, E and F), the particle size method has measured mucoadhesion in a lower extent to both rheology and turbidimetric methods (comparisons B and D), and the turbidimetric method measured superior mucoadhesion in relation to the rheology method (comparison A). These conclusions can be drawn from the evaluation of the bias values obtained for the comparisons. Comparison A showed the lowest bias, which indicates that both rheology and turbidimetric methods were closer during measurements, while the higher values for bias obtained for all other comparisons is indicative of mucoadhesion measuring differences. All comparisons presented one data point outside of the limits of agreement (outlier) with exception for comparison F.

4. Discussion

The integrity of the mucosal tissues within in the human body is maintained by a continuous flow of mucous. With regard to the oro-esophageal system, the mucous layer is conferred by saliva. An important constituent of saliva are glycoproteins (mucins).

These are high MW proteins with ability to adhere to the surface of mucosal tissues, contributing for lubrication and additional protection against pathogens.

Previous works have characterized different commercially available mucins (porcine gastric and bovine submaxillary mucins) and compared them to the mucins present in human saliva regarding chemical and morphological similarities (Teubl et al., 2013). Porcine gastric mucin is constituted by two gel-forming mucins (MUC5AC and MUC6) and two cell surface mucins (MUC1 and MUC16). The gastric mucin MUC5AC has showed increased similarities to the human salivary mucin, MUC5B. In addition, MUC1 and MUC16 can also be found in the tracheobronchial tract. Considering bovine submaxillary mucin, significant differences to human mucins were observed due to formation of thick fibers that agglomerate (Bettelheim and Dey, 1965; Nielsen et al., 1997; Teubl et al., 2013; Wickström et al., 1998). For these reasons, mucin from porcine stomach was chosen as base mucin for the preparation of the simulated salivary buffer, with the formulation being developed according to previous publications (Park et al., 2007; Roblegg et al., 2012).

The degree of interaction of SODF surfaces with the oro-esophageal mucous layer (saliva) is an important factor that should be considered during formulation development, and polymers that produce weak to no interactions should be considered to enhance drug administration safety. In order to study this variable, an *in vitro* approach based on particle interaction methods was used, under similar conditions, to predict the poor interaction strength of different water-soluble polymers with simulated artificial saliva.

The viscosity of a mucin colloidal dispersion is highly depended on noncovalent interactions at the intermolecular level, related to the formation of electrostatic, hydrogen and hydrophobic bonds (Bohdanecky and Kovar, 1982). These interactions are identical to the ones involved in the process of mucin-polymer adhesion (Peppas et al., 2009), which allow the monitoring of adhesive forces by evaluating the viscosity changes in the system. The rheological method quantifies these interactions by applying equation 1, where ηt is the viscosity coefficient of the system and ηm/ηp are the individual viscosity coefficients of artificial saliva and polymer, respectively. Subsequently, ηi is the viscosity coefficient related to the mucin-polymer interaction, and can be obtained by rearranging the equation (Hassan and Gallo, 1990; Ivarsson and Wahlgren, 2012).

Equation 1. $\eta t = \eta m + \eta p + \eta i$

The turbidity degree of a polymer-mucin mixture is another factor that can be used to roughly estimate the adhesive capacity of polymers. In case of high interaction forces, the mucin particles may aggregate into a system where the polymer acts as linkage,

leading to an increase in the turbidity of the mixture as compared to the initial turbidity of the mucin sample alone (Rossi et al., 2000; Thongborisute and Takeuchi, 2008). The changes in particle size and zeta potential of the original mucin particles can also be monitored to presume about the adhesive properties of polymers. Because mucin is a negatively charged molecule, a strong interaction with polymers will lead to changes alterations on its surface properties and ultimately to differences in the zeta potential values. As the zeta potential is highly dependent on the pH, this parameter should also be examined during the assessments. Considering that neutral polymers were used in this study, an increase in the zeta potential is expected for the mucin particles when in mixture with adhesive polymers. Moreover, the mucin particles may tend to aggregate in the presence of adhesive polymers and increase its particle size as compared to the initial one (Takeuchi et al., 2005, 1999). Physicochemical properties such as hydrogen-bonding motifs, ionizable groups and flexible chains are expected to impact on the interaction profile of the polymers with the mucous layer. Moreover, the MW grade and the concentration used are other attributes that can influence the extent of interaction, reason why these parameters were investigated during the course of this study (Boddupalli et al., 2010; Russo et al., 2016; Tiwari et al., 1999).

Based on the different methods assessed, substantial interaction forces with artificial saliva were obtained for concentrations of 3-6% regarding PVP and PVA grades. In addition, the concentration effect was more pronounced with increasing MWs. Poor interactions forces were estimated for PEG grades, with no correlation being found to MW or concentration. HPMC showed the highest interaction forces with mucin regarding all tested methods. Some degree of variability was observed for the turbidimetric method, since it predicted lower adhesive strength for PVA grades in comparison to PVP grades, and the opposite result was observed when using the other methods.

An optimal method that supports a high degree of differentiation when measuring at lower levels of mucoadhesion is required to provide realistic predictions about the *in vivo* performance of polymers, as it would contribute for the development of suitable coatings that can increase safety when swallowing SODF. As the experimental condition (e.g., measuring temperature) and materials (e.g., polymers, mucin) used were kept the same when testing with the different methods, a normalization of the obtained results was performed to deduce about the sensitivity of the methods in measuring reduced mucoadhesion. The evaluation showed that the rheological method is the most sensitive of all particle interaction methods tested, since it was efficient to differentiate lower mucoadhesion between polymer species and within polymer grades. Therefore, rheological measurements should be applied when investigating poor mucoadhesive polymers with particle interaction methods. The analysis with Bland Altman plots showed

that the available particle interaction methods are not equivalent and may measure mucoadhesion differently. Nevertheless, the results obtained are dependent on different factors such as the types of polymers tested, the experimental settings and the conditions applied.

To summarize, the suitability of particle interaction methods to measure poor mucoadhesion was investigated in this work, as there are no currently available methods specifically developed to quantify this property at lower levels. This was the first study to evaluate the degree of differentiation to which particle interaction methods are capable of assessing the low adhesive potential of polymer coatings, and contribute for better predictions towards safe swallowing of SODF. Nevertheless, the usage of a single type of mucin should be considered a weakness of this study.

5. Conclusion

The oral administration of conventional SODF is threatened by the growing age of the population and its increased incidence of swallowing problems. These issues need to be urgently addressed during development of pharmaceutical coatings, as they will contribute for SODF with increase patient compliance and avoid unnecessary drug modifications. Based on the results obtained in this work, PEG grades should be highly considered during the development of dosage forms with such properties. In addition, preference should be given to reduced concentrations of polymer and grades with low molecular weight. The use of HMPC is not recommended due to its strong interaction with the simulated salivary buffer. Rheological measurements should be adopted when investigating the low mucoadhesive potential of polymers with particle interaction methods, since it was shown that better predictions for safe swallowing could be extrapolated. On the other hand, all particle interaction methods appear to measure mucoadhesion distinctively, which can explain the current lack of a standard method when applying this type of methodology.

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Polymer adhesion predictions for oral dosage forms to enhance drug administration safety.

Part 2: *In vitro* approach using mechanical force methods

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All authors have read and agreed to the published version of the manuscript.

Abstract

Predicting the potential for unintended adhesion of solid oral dosage forms (SODF) to mucosal tissue is an important aspect that should be considered during drug product development. Previous investigations into low strength mucoadhesion based on particle interactions methods provided evidence that rheological measurements could be used to obtain valid predictions for the development of SODF coatings that can be safely swallowed. The aim of this second work was to estimate the low mucoadhesive strength properties of different polymers using *in vitro* methods based in mechanical forces, and to identify which methods are more precise when measuring reduced mucoadhesion. Another aim was to compare the obtained results to the ones achieved with *in vitro* particle interaction methods in order to evaluate which methodology can provide stronger predictions. The combined results correlate between particle interaction methods and mechanical force measurements. The polyethylene glycol grades (PEG) and carnauba wax showed the lowest adhesive potential and are predicted to support safe swallowing. Hydroxypropyl methylcellulose (HPMC) along with high molecular grades of polyvinylpyrrolidone (PVP) and polyvinyl alcohol (PVA) exhibited strong *in vitro* mucoadhesive strength. The combination of rheological and force tensiometer measurements should be considered when assessing the reduced mucoadhesion of polymer coatings to support safe swallowing of SODF.

Keywords: mechanical force methods, polymer coatings, reduced mucoadhesion, solid oral dosage forms, swallowing safety, tensiometry measurements

1. Introduction

Surface properties of solid oral dosage forms (SODF) are suggested to affect the extent of interaction with mucosal tissues, which can contribute to unintended mucoadhesion and injuries in the oro-esophageal tract. *In vitro* methods based on particle interactions have been reviewed recently to estimate the safe swallowability and oro-esophageal transit behavior of SODF coatings. The collected data showed that rheological measurements could be adopted to predict the reduced adhesive potential of polymers. The method revealed higher sensitivity when measuring at lower limits of mucoadhesion and might contribute with suitable predictions for the development of SODF coatings that can facilitate oral drug administration regarding special patient populations (e.g., older patients, patients with swallowing impairments). Nevertheless, when measuring mucoadhesion with particle interaction methods, the *in vivo* conditions might not be reflected adequately since aqueous solutions of the polymers are used. For

this reason, further evaluations with methods that estimate the mechanical forces between a mucin layer and the targeted polymers coatings were performed in this study. The mechanical force measurements are based on the forces required to break the adhesive bond between a polymer film coating and the mucous/mucosal tissue, reflecting the mucoadhesive potential of the polymer (Woertz et al., 2013). The sensitivity of the applied methods to discern reduced mucoadhesion was assessed to identify an optimal methodology for the predictive behavior of polymer coatings. Furthermore, the results obtained with particle interaction methods and mechanical force methods were compared to establish a strong correlation and predictive power of interaction.

2. Materials and Methods

2.1. Materials

PVA grades (EG-03P, EG-05P, EG-18P, EG-30PW and EG-40P) were a kind gift from Nippon Gohsei (Düsseldorf, Germany). Plasdone grades (PVP K-15, K-25, K-29/32, K-60, K-90 and K-120) were donated by IMCD (Wien, Austria). Carnauba wax, PEG 1000, PEG 1500 and PEG 4000 were purchased from Alfa Aesar (Lancashire, UK). PEG 3350 and lyophilized mucin from porcine stomach were purchased from Sigma-Aldrich (Munich, Germany). PEG 6000 was obtained from Baxter (Vienna, Austria). Sodium phosphate monobasic (NaH_2PO_4), Sodium phosphate dibasic (Na_2HPO_4), sodium chloride (NaCl), calcium chloride ($CaCl_2$) and PEG 2000 were provided from Capsugel (Colmar, France). HPMC was donated by Ashland. The water used was of Millipore quality.

2.2. Preparation of simulated artificial saliva

For the preparation of simulated salivary buffer, 0.021 M of Na_2HPO_4/NaH_2PO_4, 0.036 M NaCl and 0.00096 M $CaCl_2$ were dissolved in purified water. Subsequently, 5mg/ml of lyophilized mucin from porcine stomach were added and the mixture was allowed to stir overnight at room temperature.

2.3. Preparation of mucin discs

Mucin discs were prepared by compression of a known weight of lyophilized mucin (250 mg) using a Laboratory Tablet Press 102i with a 13-mm diameter die (Fette Compacting, Schwarzenbek, Germany).

2.4. Preparation of polymer films

Aqueous solutions were prepared for HPMC, PVP and PVA grades (10%, w/v) at room temperature. Subsequently, 20 mL of each polymer solution were placed on a petri

plate coated with polytetrafluoroethylene (PTFE) and allowed to dry overnight at 70ºC, until formation of a thin film.

2.5. Preparation of PEG and wax melts

PEG grades and carnauba wax were melted in a hot plate at 70 ºC and 90 ºC, respectively. The produced melts were later transferred to silicone molds and able to cool down at room temperature, until complete solidification.

2.6. Measurements with force tensiometer

The force tensiometer method (Fig. 1) is based on the Wilhelm plate technique used for surface tension determinations and consists of a polymer film connected to a microforce balance (Sam et al., 1992; Smart et al., 1984). A 10 mL glass beaker containing the simulated artificial saliva (37 ºC) was placed in the platform, which was later elevated at a rate of 3 mm/min until the film had penetrated the sample by a depth of 5 mm. After a contact time of 60 s, the platform was lowered at the same rate and the maximum detachment force was recorded with a K100 force tensiometer (KRÜSS GmbH, Hamburg, Germany). Measurements were performed in triplicates for all testing materials.

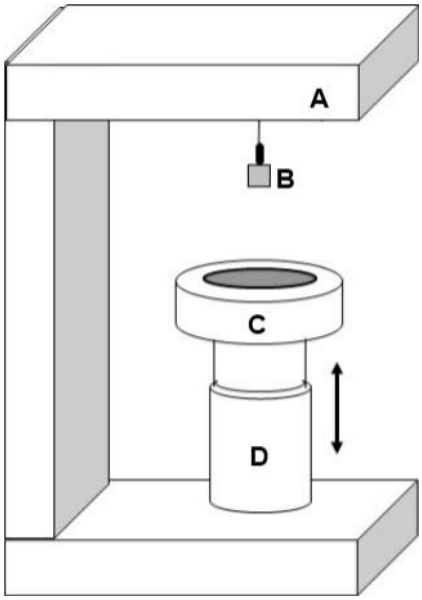

Figure 1. Force tensiometer determinations. A: microforce balance aparatus, B: polymer film/wax, C: container with simulated artificial saliva, D: platform moving vertically.

2.7. Measurements with texture analyzer

The method consisted of determining the force required to separate a polymer film (attached to the upper cylindrical probe with double-sided adhesive tape) from a hydrated

mucin disc (with 50 µl of artificial saliva at 37 °C) that was firmly attached to the lower stationary platform of the equipment (Baloglu et al., 2011; Bruschi et al., 2007). The measurements were performed using a texture analyzer TA.XT Plus (Stable Micro Systems Ltd., Surrey, UK) equipped with a load cell of 5 kg and a cylinder probe of 10 mm (P/10, 10 mm Delrin). A schematic image of the determination can be visualized in Fig. 2A (Kharenko et al., 2008; Thirawong et al., 2007). In the first phase, the probe with the attached polymer film was lowered at constant velocity (0.2 mm/s). As soon as the pressure on the mucin disc reached 1 N (corresponding to an applied mass load of 102 g), the movement was stopped and the film was left in contact with the mucin disc for 60 s (phase 2). Subsequently, in phase 3, the probe was raised (0.1 mm/s) and the force required to separate both surfaces (maximum detachment force; F_{max}) was measured by the equipment's software (Texture Exponent 32). Additionally, the total amount of forces involved in the separation of both surfaces (work of adhesion; Wad) was calculated from the area under the curve obtained during the measurement (Fig. 2B). Both parameters were used to compare the mucoadhesive potential for the different polymers tested (Kerimoğlu et al., 2015; Shakweh et al., 2007).

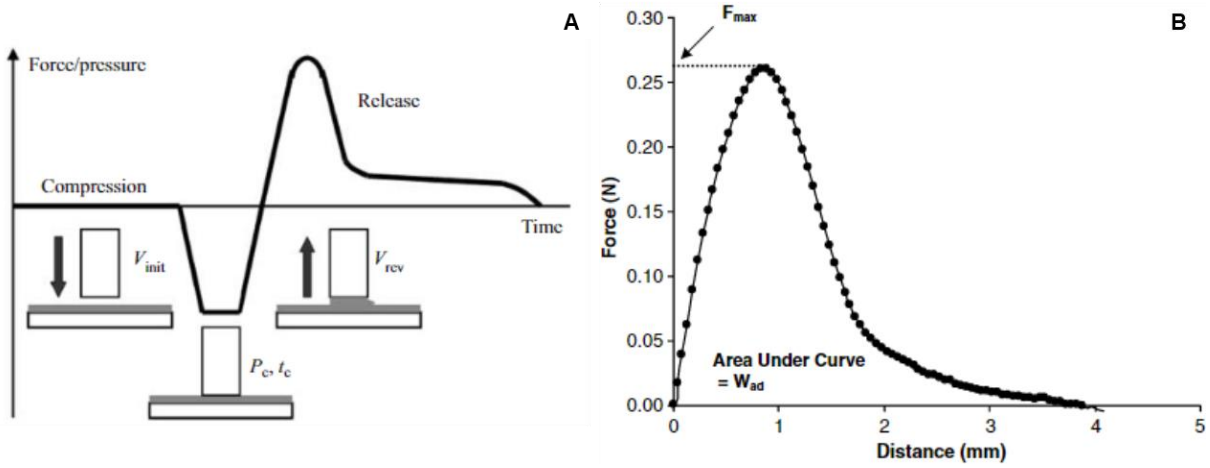

Figure 2. Texture analyzer determinations. A: measurement phases for mucoadhesive potential (*Karenko et al.*), B: parameters extrapolated from the curve (*Thirawong et al.*).

2.8. Measurements with tensile tester

The method consisted of determining the load required to rupture an adhesive bond between the polymer film and the mucin disc (Bruschi et al., 2007), in tension mode (Fig. 3). Measurements were performed using an Universal Testing Machine (Instron, High Wycombe, UK), equipped with a cylindrical probe of 20 mm attached to the load cell (10 N) (Bonacucina et al., 2006, 2004; Mccargar et al., 2001). Before each evaluation, the film was fixed to the probe with double-sided adhesive tape and the mucin disc was glued

to the stationary platform with cyanoacrylate glue (Fig. 3). Additionally, 50 µl of artificial saliva (37 °C) were used to moisture the surface of the mucin disc. Subsequently, the probe was lowered at constant velocity (0.1 cm/s), with the movement being stopped when a load of 1 N was applied to the mucin disc. After a contact time of 60 s, the probe automatically moved upwards at the same speed and the maximum load (L_{max}) required to break the adhesive bond was determined with the equipment's testing software (Bluehill®).

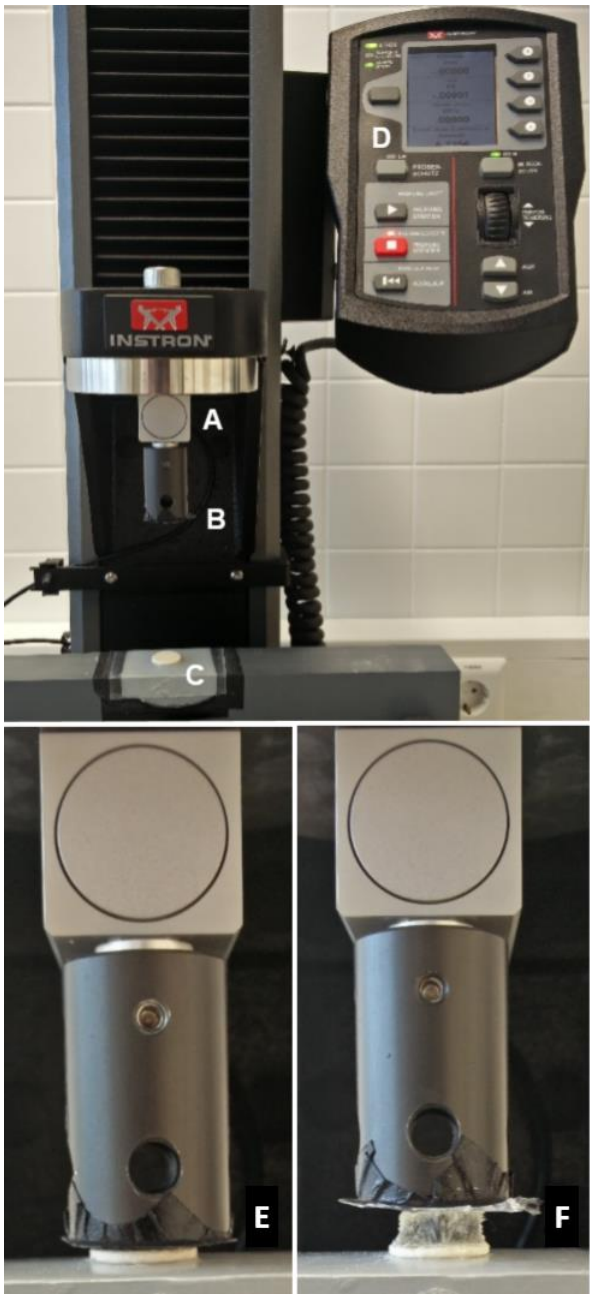

Figure 3. Tensile tester determinations. A: measuring head, B: cylindrical probe containing the polymer film, C: mucin disc attached to the stationary platform, D: Instron live display, E: contact between polymer film and mucin disc, F: rupture of adhesion.

2.9. Mechanical force methods evaluation

2.9.1. Sensitivity of mechanical force methods to measure low levels of mucoadhesion

The detachment loads obtained for the tested polymers were normalized and expressed in percentage (%) to allow a direct comparison between mechanical force methods. Sensitivity and magnitude discrepancies were evaluated when measuring reduced mucoadhesion, with the purpose of identifying optimal methods that can give better coating predictions for safe swallowing of SODF. Furthermore, the mechanical force methods used in this work were compared to the already tested particle interaction methods in order to examine which methodology can contribute with stronger predictions.

2.9.2. Method comparison studies – Bland Altman plots

The degree of agreement between the different methods was evaluated using the analysis proposed by Bland and Altman (Bland and Altman, 1999). The bias or systematic error, as well as the lower and upper limits of agreement were calculated based on the normalized values of mucoadhesion obtained for each method.

3. Results

3.1. Measurements with force tensiometer

An increase in the mean maximum force was observed with increasing molecular weight concerning PVA and PVP grades (Fig. 4). The high molecular grades of PVA (EG 40) and PVP (K-120) had approximate adhesive forces to the positive control, HPMC. PEG grades presented the lowest mean maximum force values and a poor correlation to the molecular weight grade was seen. Lastly, the adhesive force obtained for carnauba wax was poor and comparable to the ones obtained for PEG grades.

3.2. Measurements with texture analyzer

The maximum detachment forces and the total work of adhesion obtained for the texture analyzer measurements can be visualized in Fig. 5. Greater forces were generally associated to higher molecular weights regarding the tested polymers. HPMC showed higher F_{max} and W_{ad} when compared to all other polymers, which was reflected by a strong adhesion to the mucin disc (Fig. 6). In addition, PVA grades exhibited higher F_{max} and W_{ad} in comparison to PVP grades. Low values of F_{max} and W_{ad} were obtained for PEG grades, indicating a lack of bioadhesive bonds to the mucin disc. The same profile was expected for carnauba wax due to its hydrophobic characteristics.

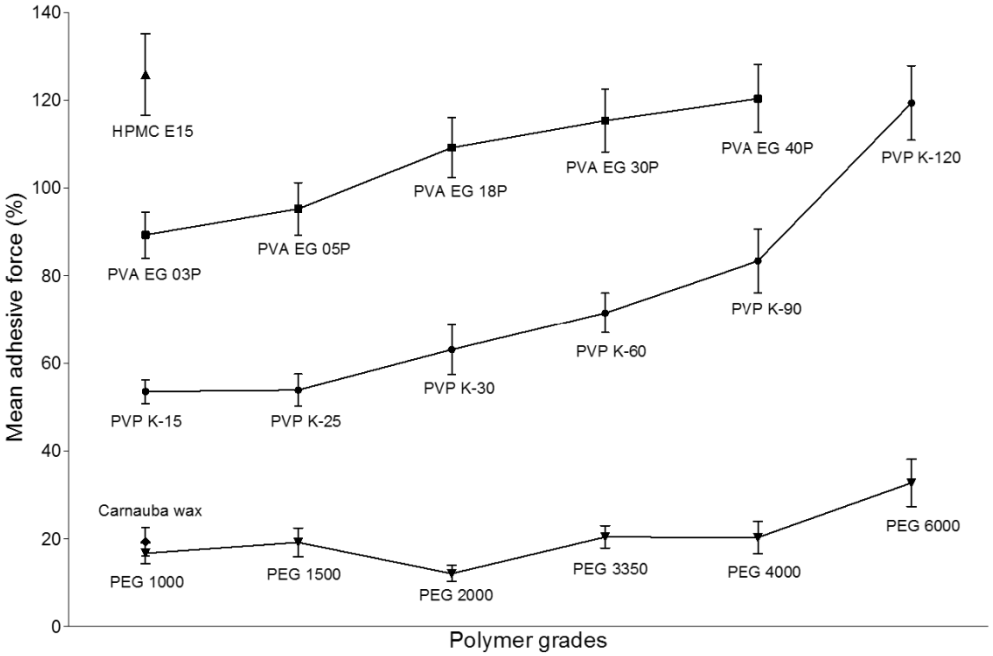

Figure 4. Mean adhesive force (%) obtained for the tested polymers with force tensiometer measurements.

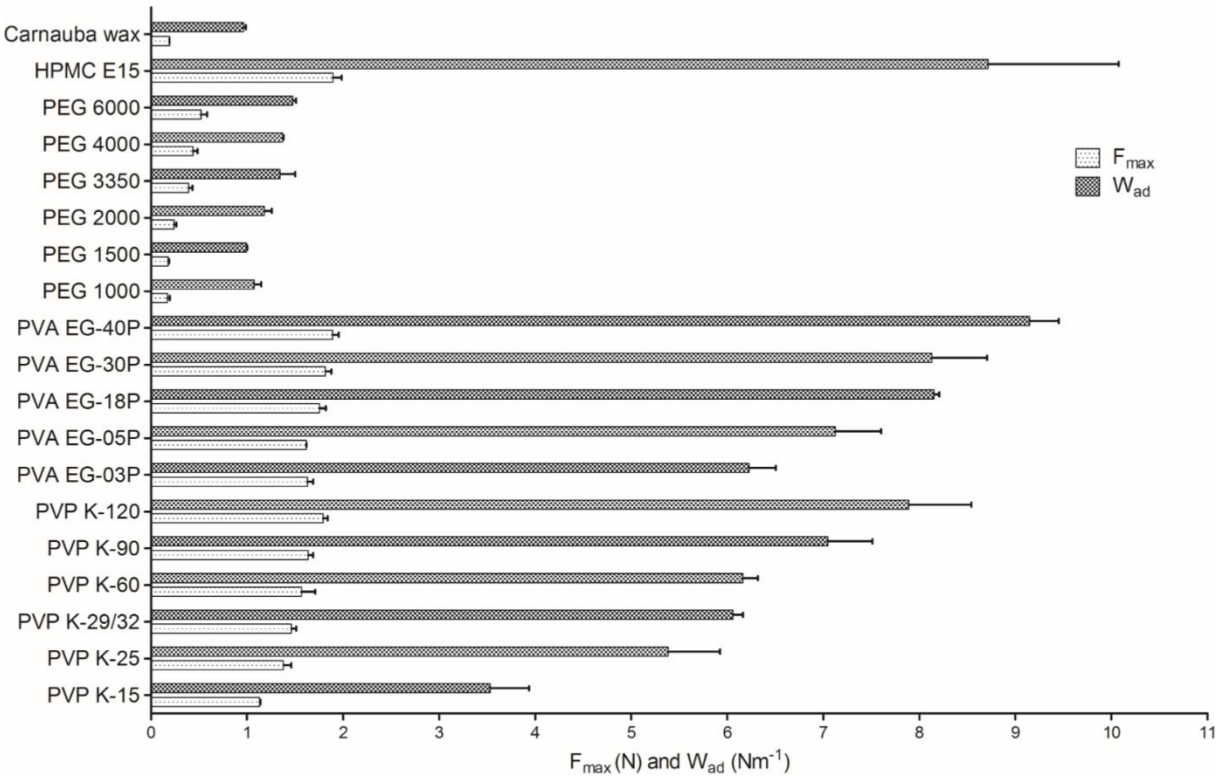

Figure 5. Maximum force of detachment (F_{max}) and work of adhesion (W_{ad}) obtained for the tested polymers with texture analyzer measurements.

3.3. Measurements with tensile tester

The L_{max} required to rupture the adhesive bond between the polymer film and the mucin disc was significant for PVA and PVP grades, with a positive correlation being related to the molecular grade tested. Reduced load forces were obtained for PEG grades, which once again demonstrates the poor mucoadhesive capacity of this polymer. Carnauba wax also displayed weak interactions with the mucin disc. On the other hand, HPMC scored in general the highest detachment loads when using the tensile tester method (Fig. 7).

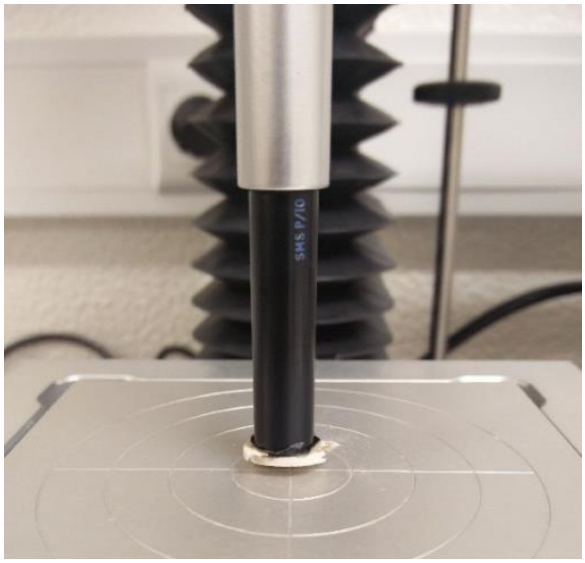

Figure 6. Attachment of the HPMC film and breakage of the mucin disc upon separation.

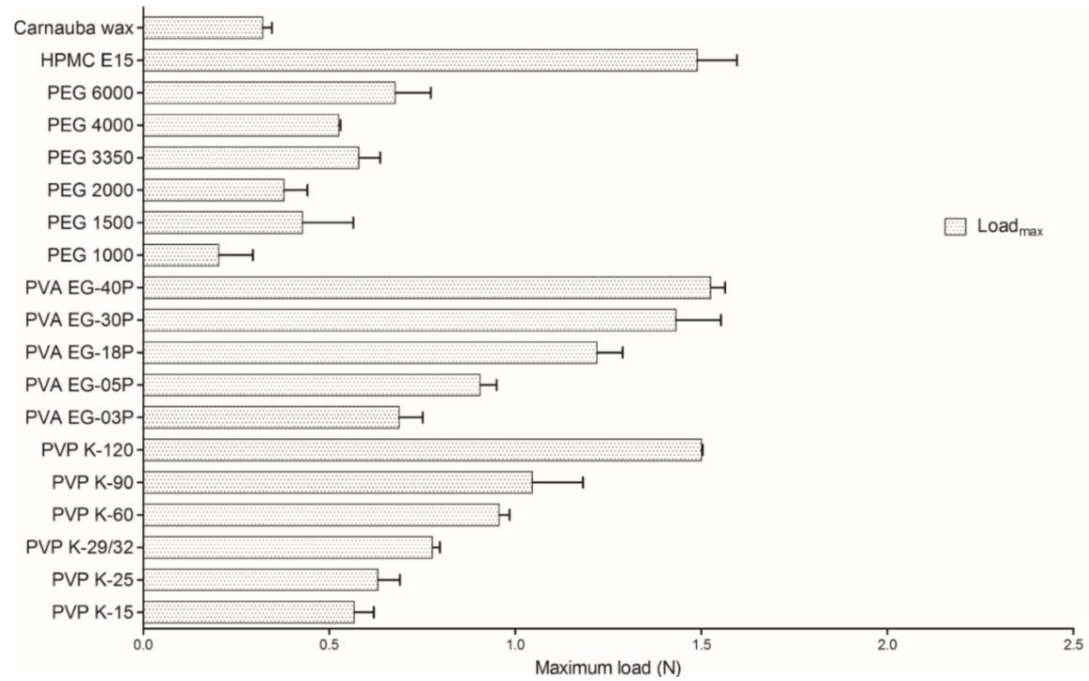

Figure 7. Maximum load of detachment (L_{max}) obtained for tensile tester measurements.

3.4. Mechanical force methods evaluation

3.4.1. Sensitivity of mechanical force methods to measure low levels of mucoadhesion

With the aim to investigate the sensitivity of mechanical force methods in measuring reduced mucoadhesion, the results were normalized according to the method used and a theoretical range of poor adhesive potential was established for the lower limit of normalization (0-10%). The obtained values (in percentage) can be visualized in table 1.

Table 1. Normalization of polymer results according to the mechanical force method.

	Mechanical force methods		
Polymer grade	**Force tensiometer measurements**	**Texture analyzer measurements**	**Tensile tester measurements**
PVP K-15	36.40	55.69	30.91
PVP K-25	36.71	70.06	35.49
PVP K-29/32	44.81	74.76	46.06
PVP K-60	52.20	80.92	58.99
PVP K-90	62.67	85.05	65.41
PVP K-120	94.25	94.02	98.24
PVA EG-03P	67.87	84.44	39.58
PVA EG-05P	73.07	83.89	55.31
PVA EG-18P	85.31	91.77	77.98
PVA EG-30P	90.73	95.40	93.28
PVA EG-40P	95.13	99.77	100.0
PEG 1000	4.07	0.00	0.00
PEG 1500	6.24	0.45	20.87
PEG 2000	0.00	4.00	17.31
PEG 3350	7.32	12.95	31.81
PEG 4000	7.23	15.40	27.89
PEG 6000	18.13	20.41	38.82
HPMC E15	100.0	100.0	97.40
Carnauba wax	6.09	1.27	13.14

The tensile tester measurements showed poor sensitivity in measuring low adhesive potential, as the normalized values are all above the theoretical upper limit of 10%. A higher degree of differentiation for lower levels of mucoadhesion could be obtained with the force tensiometer and texture analyzer methods. Between these two methods, the force tensiometer measurements exhibited a slightly higher sensitivity, especially when analyzing PEG grades. All the methods showed potential to discriminate the adhesive

strength of the different grades within the same polymer specie and predicted an equal raking of polymer mucoadhesive potential. By direct comparison of the normalized results obtained in this work with the results obtained for particle interaction methods, a higher level of accuracy in measuring low mucoadhesion is suggested for the rheological method as compared to force tensiometer measurements.

3.4.2. Method comparison studies – Bland Altman plots

An analysis based on Bland Altman plots was applied to obtain general information on the degree of agreement for mucoadhesive measurements using mechanical force methods (Giavarina, 2015; Hanneman, 2010). As no standard method for *in vitro* mucoadhesive evaluation when using mechanical force methods has been yet defined in the available literature, all methods were compared with one another. Information on the correct interpretation of Bland Altman plots has been already addressed previously when evaluating the degree of agreement for mucoadhesive measurements when using particle interaction methods (Chapter 5, Part 1). The obtained results for mechanical force methods can be visualized on Table 2.

Table 2. Mechanical force method-comparisons using Bland Altman plots.

Methods-comparison	Limits of agreement	Bias	No. of outliers
Force tensiometer vs. Texture analyzer (A)	-33.28 to 14.12	-9.58	1
Force tensiometer vs. Tensile tester (B)	-29.11 to 22.76	-3.17	1
Texture analyzer vs. Tensile tester (C)	-33.20 to 46.02	6.40	0

The force tensiometer method measured lower mucoadhesive potential when compared to both texture analyzer and tensile tester methods (comparisons A and B), while the texture analyzer method measured higher mucoadhesion with relation to the tensile tester method. This outcome for the force tensiometer measurements might be associated to its higher sensitivity for measuring lower mucoadhesion as compared to the other methods. The level of bias between mechanical force methods is relatively lower as compared to particle interaction methods. Comparison B showed the lowest bias, which indicates that both force tensiometer and tensile tester methods were closer during measurements. Comparisons A and B presented one data point outside of the limits of agreement (outlier).

4. Discussion

In this work, polymeric excipients commonly used in coating technologies were assessed to predict their low adhesive properties, as these are assumed to impact on smooth and safe swallowing of SODF. The measurements were performed with *in vitro* methods based on mechanical forces and were used to complement previous results obtained with a different *in vitro* setup based on particle interaction methods. The forces measured for the different polymers are in accordance with the distinct methods used, with lower adhesive forces being estimated for carnauba wax and PEG grades, followed by PVP grades, PVA grades and HPMC. The influence of the molecular grade was also significant, with greater molecular weights leading to higher forces required to break the adhesive bond between polymer film and mucin disc. This effect was not linear considering PEG grades, as it was already seen before when using particle interaction methods. Based on the detachment forces measured, the mechanical force methods correlate when considering a polymer raking of mucoadhesive potential. Therefore, PEG grades and carnauba wax emerge as strong candidates for further research towards the development of safe-to-swallow technologies.

The obtainment of animal tissue for *in vitro* experimentation is currently emerging into a difficult and time-consuming task due to regulatory and control procedures. This situation has lead researchers to search for easier and accessible sources when investigating the mucoadhesive potential of polymers and/or drug delivery systems. Built on previous studies, mucin discs (hydrated with simulated saliva) were used as mucous/mucosa-mimic substrate during the assessments (Baloglu et al., 2011; Bruschi et al., 2007). The usage of mucin discs appears to be a possible alternative to animal tissues in preliminary testing, as the results obtained in this work are in agreement with the ones obtained by Smart et al., where porcine esophageal tissue was used during force-measurement experiments (Smart et al., 2015, 2013). In these studies, low adhesive profiles were obtained for PEG grades, while PVA and HPMC showed increased adhesion following the same order. Moreover, the adhesive profile of PEG was not correlated to its molecular grade (Smart et al., 2015). Following the same methodology and for feasibility purposes, PEG grades were also prepared by melting since it was showed that the preparation method does not influence the polymer's adhesive profile (Smart et al., 2015).

The maintenance of the same experimental conditions during assessments with the different mechanical force methods (e.g., applied temperature, polymers, mucin, etc.) allowed their direct comparison based on the normalization of the results obtained for the mucoadhesive potential of the tested polymers. The analysis revealed that force tensiometer measurements present a higher sensitivity in measuring lower levels of

mucoadhesion when compared to the texture analyzer measurements. Considering the tensile tester measurements, the level of differentiation was very poor and it is in accordance with previous works (Mccargar et al., 2001). All the methods were capable of differentiating the adhesive potential for polymer grades within the same species. An evaluation of the capacity for particle interaction methods and mechanical force methods to measure reduced mucoadhesion revealed that a higher degree of differentiation could be obtained with rheological measurements. Nevertheless, based on both method comparisons, it was noticed that particle interaction methods present high variability when measuring mucoadhesion, while this effect was not so pronounced for mechanical force methods.

Some limitations in the methodology applied in this work can be pointed out. As example, the particle interaction methods are only applicable to water soluble polymers. On the other hand, even though the experimental setup within mechanical force methods is more similar to the *in vivo* conditions, the sensitivity of the force tensiometer to detect reduced mucoadhesion was limited when related to the rheological measurements. Nevertheless, based on the outcome from both method comparison evaluations, it is suggested to give preference to mechanical force methods rather than particle interaction methods. This also explains why mechanical force methods are being used more frequently in studies available literature that have addressed mucoadhesion. The combination of rheological and force tensiometer measurements can be an option to generate data when studying polymers coatings to improve swallowing safety of SODF. The investigation of the accuracy of different mechanical force methods to detect reduced mucoadhesion should be seen as the main strength of this work, although the usage of a single type of mucin should be pointed out as main limitation.

5. Conclusion

The increasing age of the population and its incidence of swallowing problems are alarming healthcare professionals for potential issues related to the management and administration of therapies based on conventional SODF. To properly address these problems, new easy-to-swallow technologies that can be applied to SODF and contribute to a smooth and safe intake of oral medications are still required. The results obtained in this work are in alignment with previous assessments, where optimal properties were predicted for PEG grades regarding the development of surface conditions that can enhance swallowing safety and oro-esophageal transit. In addition, carnauba wax is highly suggested for the same purpose. The combination of rheological and force tensiometer measurements emerge as a predictable tool for the design of polymer coatings that can contribute for increased safety when administering SODF.

Furthermore, based on the findings from the method comparison studies, preference should be given to mechanical force methods rather than particle interaction methods when measuring mucoadhesion.

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Polymer adhesion predictions for oral dosage forms to enhance drug administration safety.

Part 3: Review of *in vitro* and *in vivo* methods used to predict esophageal adhesion and transit time

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Nélio Drumond (N.D.), Sven Stegemann (S.S.); All authors have read and agreed to the published version of the manuscript.

Abstract

The oral cavity is frequently used to administer pharmaceutical drug products. This route of administration is seen as the most accessible for the majority of patients and supports an independent therapy management. For current oral dosage forms under development, the prediction of their unintended mucoadhesive properties and esophageal transit profiles would contribute for future administration safety, as concerns regarding unintended adhesion of solid oral dosage forms (SODF) during oro-esophageal transit still remain. Different *in vitro* methods that access mucoadhesion of polymers and pharmaceutical preparations have been proposed over the years. The same methods might be used to test non-adhesive systems and contribute for developing safe-to-swallow technologies. Previous works have already investigated the suitability of non-animal derived *in vitro* methods to assess such properties. The aim of this work was to review the *in vitro* methodology available in the scientific literature that used animal esophageal tissue to evaluate mucoadhesion and esophageal transit of pharmaceutical preparations. Furthermore, *in vivo* methodology is also discussed. Since none of the *in vitro* methods developed are able to mimic the complex swallowing process and oro-esophageal transit, *in vivo* studies in humans remain as the gold standard.

Keywords: esophageal mucoadhesion, esophageal transit, *in vitro* methods, *in vivo* methods, oral dosage forms, safe swallowing, unintended mucoadhesion

1. Introduction

Pharmaceutical drug therapy is one of the leading interventions in the treatment of acute and chronic diseases. The majority of pharmaceutical drug products are administered through the oral route as a non-invasive and patient self-managed therapy. Oral drug products are mainly solid dosage forms (SODF) such as tablets or capsules that are swallowed and move across the esophagus to release the drug content in the digestive system (Smart et al., 2015). The adhesion of the oral dosage form to the esophageal tissue might be intended for mucoadhesive vehicles that were developed to adhere to a specific mucosal surface area and release the drug (Makó et al., 2009; Zhang and Batchelor, 2004), or unintended and lead to cases of drug-induced injury that should be avoided (Palmer et al., 2000). Therefore, when considering SODF under development, the prediction of their unintended mucoadhesion to esophageal tissue (slower transit time) is an important aspect to consider for future administration safety and performance.

Over the years, different methods have been proposed to evaluate mucoadhesion and esophageal transit of pharmaceutical preparations for different applications. The available *in vitro* methods were mainly used with the purpose to develop mucoadhesive drug delivery systems. Nevertheless, these might also be used to test non-adhesive delivery systems and contribute for the development of SODF that can be safely swallowed (Smart et al., 2015, 2013). Based on this assumption, previous works have already investigated the suitability of non-animal derived *in vitro* methods to assess the non-adhesive properties of polymer coatings (Part 1 and Part 2).

The aim of this third part was to review the *in vitro* (using animal derived esophageal tissue) and *in vivo* methodology available in the scientific literature that was used to evaluate mucoadhesion and esophageal transit of oral dosage forms. Potential limitations and points to consider for further developments are also suggested.

2. *In vitro* methods assessing mucoadhesion of oral dosage forms to esophageal tissue

The *in vitro* methods developed to investigate the adhesion of oral dosage forms to the esophagus were based either on detachment force determinations or in retention systems. The first investigates the mechanical force required to break an adhesive bond between the dosage form and the esophageal tissue (direct method), while the latter measures the amount of dosage form retained on the esophageal tissue after being rinsed with medium (e.g., artificial saliva, indirect method) (Woertz et al., 2013).

2.1. Methods based on mechanical force determinations

The first *in vitro* method to study the mucoadhesive performance of drug delivery systems was developed by Marvola et al. (1982) and focused on measuring the adherence of SODF to the esophagus. Segments of freshly slaughtered porcine esophageal mucosa (6 to 7 cm) were cut and mounted into an organ bath containing 60 ml of Tyrode's solution at 37 °C. The lower end of the esophageal segment was fixed to the bottom of the glass tube while the upper end was attached around the opening. For the mucoadhesive measurements, the testing products were attached to a copper wire and put in contact with the tissue for a fixed amount of time (2 min for hard gelatin capsules and 3 min for tablets). The force required to pull the dosage form (tablets and capsules) from the esophageal strip was measured using a modified prescription balance, and this parameter was used as a predictor of adhesion (Fig. 1). The obtained results showed no correlation between contact time and detachment force, however, a

positive relation was observed for the surface area of the tested product (Marvola et al., 1982).

One year later, the same researchers investigated the impact of specific formulation designs on the adherence of drug products to the esophagus. With exception for the contact times (1 min for gelatin capsules and 2 min for other SODF), the experimental settings were kept the same. A higher tendency to stick in the esophageal tissue was noticed for flat tablets, hard gelatin capsules, soft gelatin capsules and tablets coated with hydroxypropyl methylcellulose (HPMC). Oblong tablets required lower forces to detach from the mucosa (Marvola et al., 1983).

The same methodology was later adapted by Swisher et al. to test the adhesion of different SODF to the esophageal tissue. Strips from dog and porcine esophagus (6 to 8 cm) were fixed into an organ bath containing oxygenated Tyrode's solution that was maintained at 37 °C through a water circulating system. The lumen of the esophagus was hydrated with artificial saliva (1 ml/min) and kept closed to avoid contact with the solution. The organ bath was mounted on a lab jack with vertical movement and the dosage form was attached to a wire that was connected to a force-displacement transducer by the other end. After placed in contact with the membrane for a specific amount of time, the dosage form was detached from the esophagus by lowering the jack at a constant rate of 1 cm/s. The results showed higher detachment forces for hard gelatin capsules, intermediate detachment forces for HPMC film-coated tablets and low detachment forces for sugar-coated tablets and some uncoated tablets. Identical results were obtained when measuring with either dog or porcine esophagus. The usage of artificial saliva allowed preserving the integrity of the mucosa for longer periods of time (Swisher et al., 1984).

Due to increasing reports in the scientific literature concerning the lodging and impaired transit of oral dosage forms in the esophagus, Gibson et al. used a similar *in vitro* testing system to examine the esophageal adhesion of commercially available risedronate and alendronate dosage forms. Porcine esophageal tissue was placed vertically into an organ bath containing Tyrode's solution at 37 °C. The dosage forms to be tested were attached to steel wires and connected to a motor strain gauge. Subsequently, the testing products were fixed to the esophageal membrane for either 10 or 30 s, and the detachment force required to pull the strain gauge was measured. Gelatin capsules exhibited higher degree of adhesion, followed by HPMC film-coated risedronate tablets (5 mg). Uncoated placebo tablets and wax-polished risedronate tablets (10 mg) exhibited a poor adhesive bond to the esophagus (Gibson et al., 2000).

A complementary version of the Tyrode's *in vitro* organ bath was also adapted by other researchers to investigate the performance of risedronate tablets in the esophagus.

The tablets were drilled in the center to produce a 1 mm hole. Subsequently, one end of a copper wire was inserted and fixed to the tablet with adhesive tape while the other end was clamped to the crosshead of an Instron testing machine. The crosshead was programmed to slowly move upwards, and the equipment measured the force required to detach the tablet from the mucosal surface. No differences were observed between round and oval uncoated tablets. However, HPMC film-coated oval tablets showed higher adhesive forces when compared to both uncoated forms (Mccargar et al., 2001).

An experimental setup to investigate the esophageal transit and mucoadhesive duration of polymeric microspheres was used by Kockisch et al. (Kockisch et al., 2003). The apparatus was an adaptation of that first described by Mortazavi and Smart, which had previously developed the method to assess the duration of mucoadhesion for different polymeric materials (discs) on rat intestinal tissue (Mortazavi and Smart, 1994; Smart, 1991). A segment of porcine esophageal tissue was fixed to the lower platform of the apparatus with a clamp. Subsequently, a weight coated with microparticles and suspended onto a sensor was placed in contact with the mucosal tissue for 2 min (Fig. 2). Afterwards, the surface of the weight was withdrawn from the tissue with constant force and the time elapsed until breakage of the adhesive bond was recorded. The experiments were performed in an environmentally controlled chamber (37 °C, 90% RH) to keep the integrity of the mucosal tissue. Chitosan microparticles exhibited a lower duration of adhesion to the mucosal tissue when compared to Carbopol® and Polycarbophil microparticles (Kockisch et al., 2003).

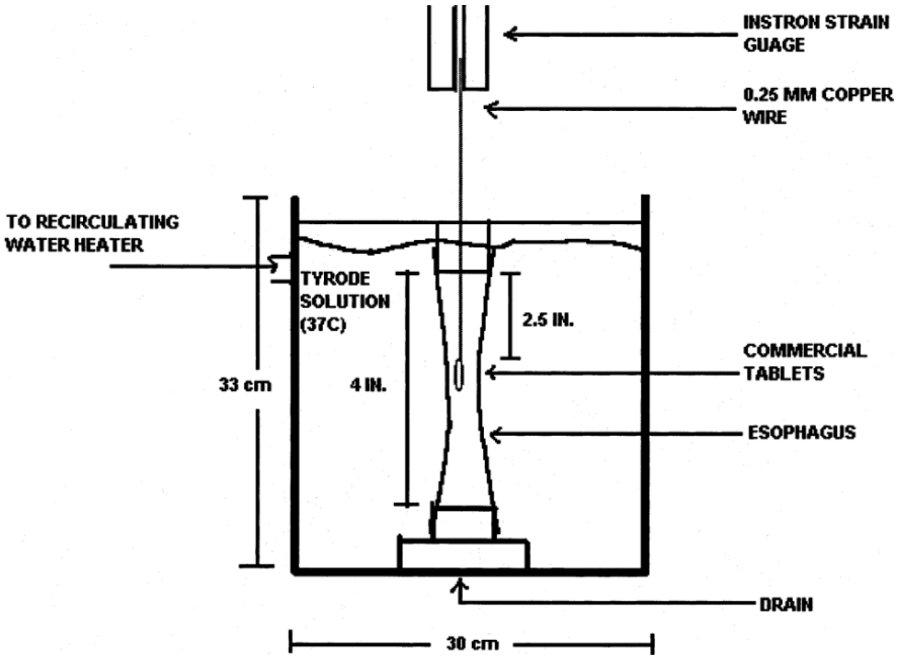

Figure 1. Setup applied by *McCargar* using an organ bath with Tyrode solution to investigate the adhesive properties of risedronate tablets to esophageal tissue.

Al-Dujaili et al. proposed an alternative *in vitro* system to assess the adhesiveness of SODF (tablets and capsules) to esophageal tissue. The measurements were based on the forces required to separate two parallel surfaces, which excluded the contribution of adhesive and friction forces that were considered in Marvola's method. A modified electronic balance was used to measure the force required to detach the SODF from the esophageal tissue. The balance pan was fixed to a plastic stub onto which a segment of fresh porcine esophagus was attached with histoacryl glue. The dosage form was secured to the bottom of an adjustable screw and lowered until contact with the tissue. After a contact time of 1 min, the screw was raised and the electronic balance recorded the force of detachment. Sugar-coated tablets and uncoated tablets (0.5-2.5 mN) exhibited lower forces as compared to gelatin capsules (25-88 mN). Furthermore, the esophageal adhesion of HPMC film-coated tablets contributed for the highest detachment forces measured (Al-Dujaili et al., 1986a). In the year after, the same methodology was used by the researchers to investigate the adhesiveness of hydroxypropyl cellulose (HPC) and HPMC film-coated tablets. The tested tablets proved to be highly adhesive to the esophageal mucosa, with this effect being reduced by the addition of polyethylene glycol (PEG) (Al-Dujaili et al., 1986b).

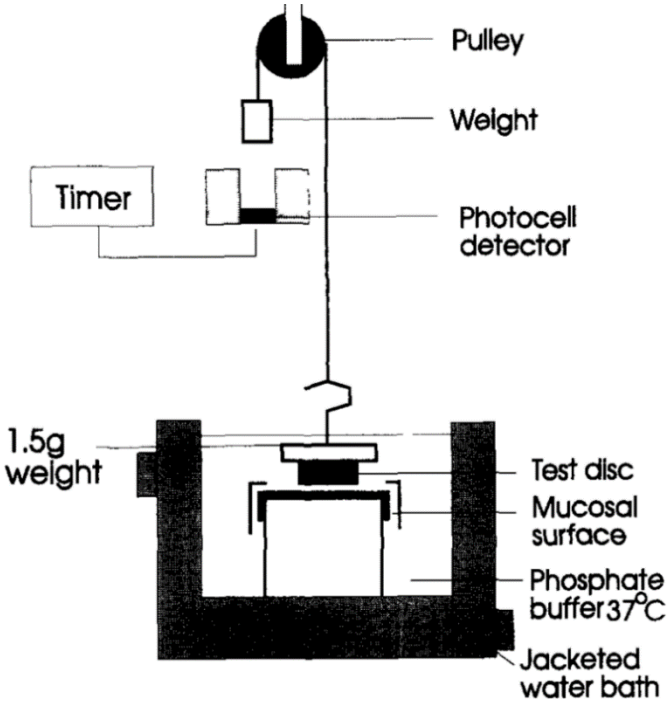

Figure 2. Setup applied by *Kockisch* et al. to measure the duration of adhesion of polymeric microspheres to esophageal tissue.

A modified tensile system was also used by Kockisch et al. to access the mucoadhesive potential of polymeric microspheres. Fresh segments of esophageal

mucosa were attached to a plastic support with cyanoacrylate glue. The plastic supports were later fixed to the moving platform of a tensiometer apparatus. The lower surface of a hooked weight was coated with 5 mg of microparticles and attached to a top pan balance with a nylon cord. The platform was then raised until the mucosal tissue pressured the sample with a force of 1 g. After a contact time of 2 min, the platform was lowered at 1 mm/min and the balance recorded the force required to separate both surfaces. The total work of adhesion (W_{ad}) and maximum detachment forces (F_{max}) were retrieved from the obtained force *vs* distance plots. Negligible results were obtained for tristearin microspheres (negative control) whereas the same parameters were significantly greater for Carbopol®, Chitosan and Polycarbophil microparticles (Kockisch et al., 2003).

The same concept was later applied by Bonacucina et al. to measure the mucoadhesive properties of Carbopol® gels. An Instron tensile tester was used to determine the F_{max} and W_{ad} required to separate Carbopol® gels from freshly excised bovine esophageal mucosa. The tissue was cut into discs of 2 cm that were later fixed with cyanoacrylate glue to the stationary platform of the equipment. Electrophoresis foils (1.5 cm) were coated with a thin layer of the Carbopol® gels and attached to the upper metal probe. The measurements were performed by applying a pre-load of 10 N during 5 min, after which the probe was withdrawn at 5 mm/min. An increase in the F_{max} was observed for Carbopol® species with gel-like characteristics (Bonacucina et al., 2006, 2004).

Shakweh et al. used a texture analyzer to predict the risk for esophageal adhesion of different alendronate formulations based on their detachment forces from esophageal tissue. The tablets to be tested were attached to the superior cross-sectional bar with cyanoacrylate glue while the porcine esophageal tissue was fixed to the lower support of the apparatus (Fig. 3). Subsequently, the mucosal surface was moistened with a small amount of distilled water (15 µl) and the tablet was brought into contact with an applied force of 0.5 N. After contact times of 1 or 2 min, the tensile measurement was initiated at 0.1 mm/s. The force was recorded as function of elongation until the break point, with the F_{max} and W_{ad} being extrapolated from the generated plots. The results showed differences in adhesion for the tested alendronate tablets, indicating that the method is able to predict undesirable mucoadhesion to the esophagus (Shakweh et al., 2007).

2.1.1. General remarks on mechanical force methods

Based on the results obtained from the different experimental works discussed, the adhesion to esophageal mucosa was impacted by the shape and the surface properties (coating) of the dosage form tested. In a general manner, higher mucoadhesion was

measured for HPMC-coated tablets and gelatin capsules. The mucoadhesive potential of celluloses is well established and several derivatives are widely used for developing of drug delivery systems with said properties (El-Samaligy et al., 2004; Ìkinci et al., 2004; Jug and Bećirević-Laćan, 2004; Minghetti et al., 1998; Nair et al., 2013; Perioli et al., 2004; Perioli and Pagano, 2013; Yehia et al., 2008). As a neutral cellulose (non-ionic), HPMC is known to have moderate to strong mucoadhesive properties (Russo et al., 2016). Moreover, the usage of gelatin in mucoadhesive formulations is also well recognized (Abruzzo et al., 2015, 2012; Liu et al., 2014; Ofokansi et al., 2007; Parodi et al., 1999, 1996). Therefore, the higher adhesion obtained for HPMC tablet coatings and gelatin capsules is expected. On the other hand, poor esophageal mucoadhesion was obtained for wax and sugar coatings, which is again in accordance with different reports available in the literature (Smart et al., 2015, 2013). This is also confirmed by the work developed by Al-Dujaili et al., where the addition of a waxy polymer (PEG) to cellulose coatings has reduced their level of mucoadhesion to esophageal tissue (Al-Dujaili et al., 1986b). Considering polymeric microspheres, greater adhesive efficiency was obtained for microparticles coated with Carbopol® and Polycarbophil. These are positively charged polyacrylates polymers with high crosslinking and swelling capacities, which makes them important tools for the development of mucoadhesive platforms for drug delivery. Subsequently, their performance is also according to several reports (Boyapally et al., 2010; Caviglioli et al., 2013; Ceschel et al., 2001; Goel et al., 2008; Shin and Kim, 2000; Singla et al., 2017; Takeuchi et al., 2003; Zeng et al., 2014). Lastly, with relation to shape, superior mucoadhesion was observed for flat tablets. Studies have shown that the tendency of a dosage form to adhere to the esophagus is highly dependent on its surface area, which confirms the increased adhesion observed for flat tablets (higher contact area) as compared to oval and oblong forms (Channer and Virjee, 1985; Overgaard et al., 2001).

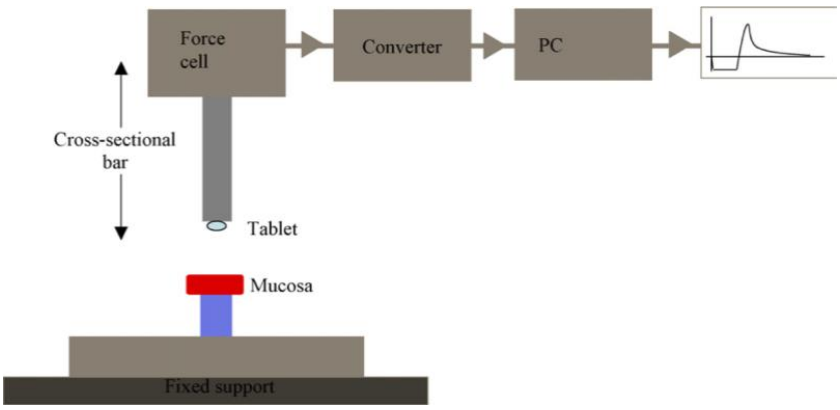

Figure 3. Setup applied by *Shakweh* using a tensile testing system.

Although several setups were developed and used, they all rely on the same principle of measuring the force involved in the breakage of an adhesive bond between dosage form and esophageal tissue. Kockisch et al. adopted an alternative measurement based on the duration of adhesion (time required to separate both surfaces). Nevertheless, the measurement is highly dependent on the applied force (and subsequently on adhesive bond strength) and does not bring any benefit when compared to the direct measurement of the detachment force. The different setups varied mostly on the experimental conditions adopted and on the measuring equipment (e.g., balance, texture analyzer, Instron). Although the setup using an organ bath with Tyrode solution is expected to better mimic the physiological conditions, systematic comparisons with *in vivo* data are still required.

2.2. Methods based on retention systems

Dobrozsi et al. developed an *in vitro* mucoadhesion method based on a dissolution testing system. Following previous works (Sakr et al., 1994), the authors created a rat esophagus model to study the adhesive characteristics of ^{51}Cr-labelled sucralfate suspensions. The esophageal segments were everted and placed onto a glass rod that had a ball tip to hold the tissue. The tissues were equilibrated in medium at 37 °C for 2 min, and later immersed in the testing formulation. Subsequently, the coated mucosal surfaces were rinsed in a custom apparatus using a vertical immersion technique to mimic the peristaltic movements in the esophagus, or by immersion and rotation using a type I/II dissolution tester (Fig. 4A). After removal, the mucosal strips were rinsed again with medium (simulated saliva or gastric fluid) and the formulation retained in the tissue was measured by γ-scintillation. Higher shear forces were provided with vertical immersions when compared to the rotation method. In addition, rinse conditions such as pH and mucin type influenced the mucoretention of *in-situ* gelling formulations. Gel-like sucralfate suspensions showed higher retention levels on esophageal mucosa as compared to non-gel suspensions (Dobrozsi et al., 1999).

Another *in vitro* apparatus to access the mucoadhesive potential of pharmaceutical preparations was developed by Young and Smart. The porcine esophageal mucoadhesion test system comprised a test cell into which an esophageal mucosa was clamped and inclined at 30°. Surface desiccation was prevented with humidified air (37 °C) and artificial saliva, which was eluted from the top of the test cell and recovered in the lower section using a fraction collector (Fig. 4B). After equilibration, 1 g of gel formulations labelled with soluble and insoluble fluorescent markers were released at the top of the teste cell. The eluted fractions were recovered and measured by fluorescence to determine the amount of formulation that was retained in the esophageal tissue

(Young and Smart, 1998). Based on the results, the method presented capabilities to differentiate the duration of adhesion for Carbopol® and Polycarbophil formulations. The method was also applied later to investigate the oral behavior of polymeric microspheres and the esophageal adhesion of polyacrylic acid dispersions (Kockisch et al., 2003; Smart et al., 2003).

An enhanced version of the porcine esophageal mucoadhesion system was used to investigate the surface retention of drug-loaded microspheres under dynamic test conditions (Kockisch et al., 2004). The traditional test cell was adapted by the application of two inserts on each side, which created a reduced surface area to support a constant flow of artificial saliva in the center of the tissue. After fixation of the mucosal tissue on the test cell at 30°, vacuum was applied from the bottom to maintain the membrane flat. A transparent jacket was placed on top of the cell to maintain an *in vivo* environment (37 °C and 90% RH). Additionally, a flow of artificial saliva (pH 7) circulated over the tissue (1 ml/min) and the system was allowed to equilibrate for 1 h. Before the assessments, the test cell was set back to a horizontal position and the flow of artificial saliva was interrupted. Subsequently, the fluorescent-labelled microspheres (1 mg) were applied on the center of the mucosa, and after 1 min contact time the system was brought back to 30° with simultaneous restoration of the artificial salivary flow. The retention of sodium fluorescein at the point of application was assessed by means of a digital video camera that was positioned above the testing system. The particles were recorded under visible and UV light to measure the distribution and concentration of the marker, respectively, at different time points over a 2 h period. The tissue section, magnification (20x) and light source position were not altered during the recordings to allow direct comparisons between the formulations. Using appropriate software, the images were analyzed to measure the area of tissue covered by polymer particles and the intensity of sodium fluorescein. The integration of both parameters provided an overtime image of the microspheres elution across the tissue.

Batchelor et al. developed a simplified version of the porcine esophageal mucoadhesion test system using a polymethylmethacrylate plate with a central groove to which the porcine esophageal tissue was fixed (Batchelor et al., 2002). The testing system was later placed within a cabinet with controlled temperature and humidity (37 °C, 90% RH) with different slopes. A peristaltic pump supplied an evenly distributed flow of washing medium across the entire tissue section, with the washed material being later collected into glass vials. During testing, the plate was retained in horizontal position and a known dose of fluorescently labelled alginate was distributed over the surface of the esophageal tissue. After a set period of time (30 min), the system was allowed to return to a designated descending angle position and the tissue was rinsed with washing media

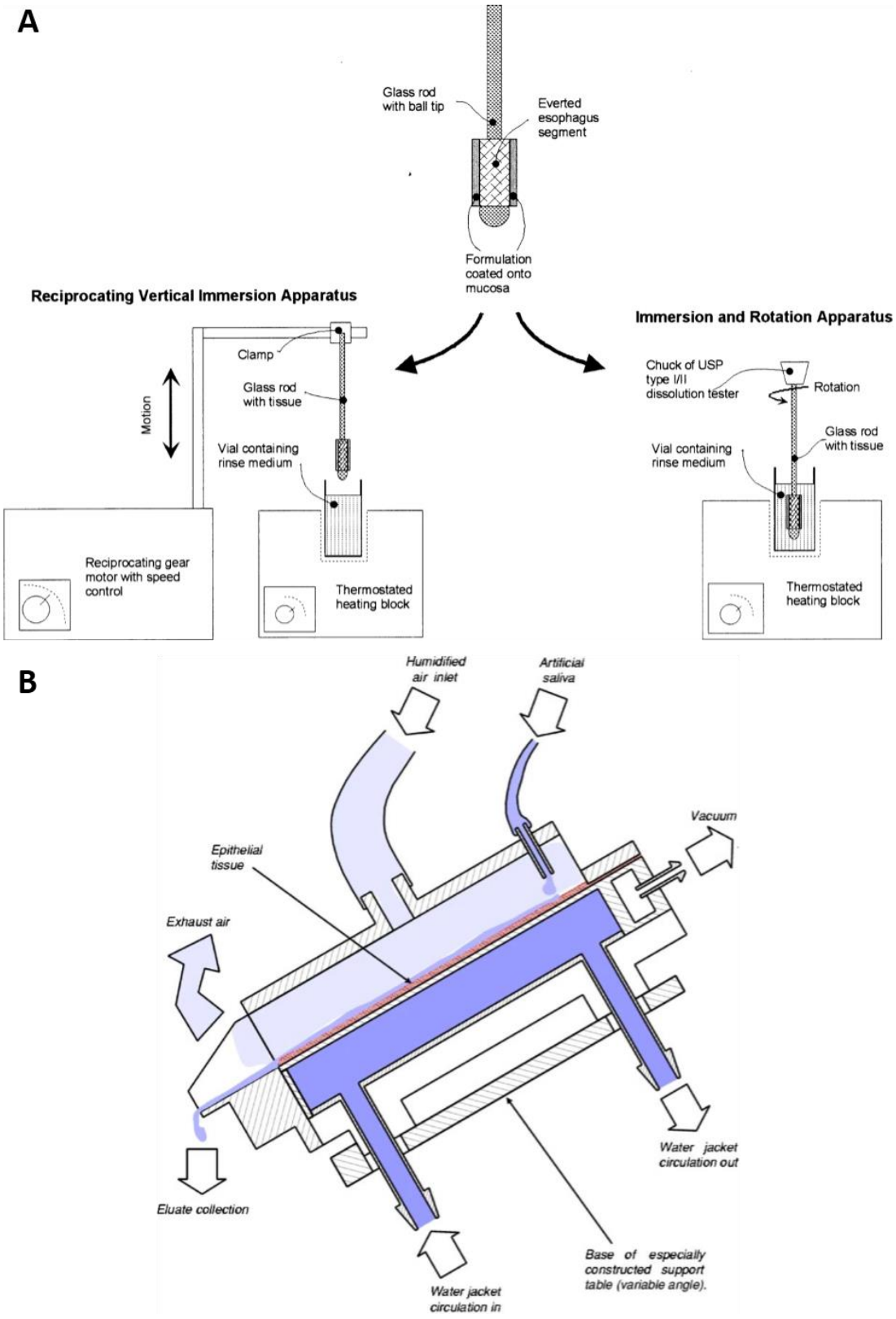

Figure 4. *In vitro* methods based on retention systems. A: dissolution apparatus used by *Dobrozsi et al.*, B: porcine esophageal mucoadhesion test developed by *Young & Smart*.

at a flow rate of 1ml/min. Fluorimetric analysis of the eluted material was used to calculate the alginate retained on the tissue. Four washing media were tested: deionized water, two artificial saliva formulations (Embleton et al., 1998; Letner, 1981) and human saliva (previously collected from healthy volunteers). Based on the results obtained, the authors suggested the use of an equilibration period of 60 s and a descending angle of 60°, since these parameters gave reproducible results and were suggested to be closer to the physiological condition (Batchelor et al., 2002). The porcine esophageal mucoadhesion system was later modified to investigate adhesion of solid oral dosage forms to the esophagus. Uncoated (control) and polymer-coated glass discs (2 g) were attached to a nylon cord that was mounted to pass through a small wheel and connected to the base of a top-pan balance linked to data collector. The mucosal tissue was allowed to equilibrate with a constant flow of simulated saliva (1 ml/min) for 30 min, at a 10° angle. The glass discs were placed on a polytetrafluoroethylene (PTFE) surface launch that could be pulled up along the 10° incline. With the application of a shear force, the platform was lowered at a rate of 0.2 mm/s until the cord was fully taut, and the FTPE surface was carefully removed allowing the test disc to contact directly with the mucosa. Subsequently, the F_{max} required to initiate motion and the W_{ad} needed to move the glass disc across the surface of the tissue (59.5 mm, 290 s) were recorded. Based on the two variables, the relative adhesive performance was determined for the tested polymers. In addition, for cases in which fluorescein was incorporated into the coating, a UV-lamp was used to examine the presence of a fluorescent track along the tissue. Greater resistance to movement was observed for discs coated with sodium alginate whereas low resistance was seen for discs coated with paraffin wax. Furthermore, a long fluorescent trail in the mucosa was detected for Pluronic™ F_{127} while no traces were identified for PEG (Smart et al., 2013).

Two years later, Smart et al. used the same modification to evaluate the adhesive potential of polymers commonly used in coating applications (Fig. 5). Different materials such as Pluronic™ copolymers (e.g., F38, F98, F127), hydrophobic polymers (e.g., ethylcellulose, paraffin wax, sorbitan monopalmitate), polyoxyethylene polymers (e.g., PolyOx™, PEG 1450, PEG 6000) and other coatings (HPMC, sodium alginate, polyvinyl alcohol (PVA), gelatin, LustreClear™) were assessed for their adhesive properties. Additional polymer blends were also tested for their mucoadhesive properties (HPMC/triacetin, HPMC/PEG 200, HPMC/triacetin/F127). Pluronic™ are triblock copolymers constituted of a central hydrophobic chain of polypropylene oxide (PPO) flanked by two hydrophilic chains of polyethylene oxide (PEO).Their coding starts with a letter to define the physical state (F = flake, solid), followed by two or three digits to define the molecular mass of the PPO core and the percentage of PEO content. PolyOx™ is a PEO

with an average molecular weight (MW) of 100000, whereas LustreClear™ is a microcrystalline cellulose/carrageenan/PEO-based coating. In order to account possible tissue variabilities, measurements were first taken with an uncoated control disc and followed by the coated testing discs. For cases where similar results were obtained between testing discs and controls, the measured forces were considered as being frictional forces (required to pull the disc) and not as adhesive forces. Sodium alginate and HPMC exhibited a greater resistance to movement whereas PVA, gelatin and Lustraclear™ displayed lower adhesive properties. Regarding polyoxyethylene polymers, higher MWs increased the resistance to movement in comparison to the low molecular grades. Poor resistance to movement was seen for ethylcellulose and sorbitan monopalmitate. Additionally, the mixture of HMPC with other materials did not improved its mucoadhesive potential. The method of coating (solution or melt) showed no influence on the performance of the polymers (Smart et al., 2015).

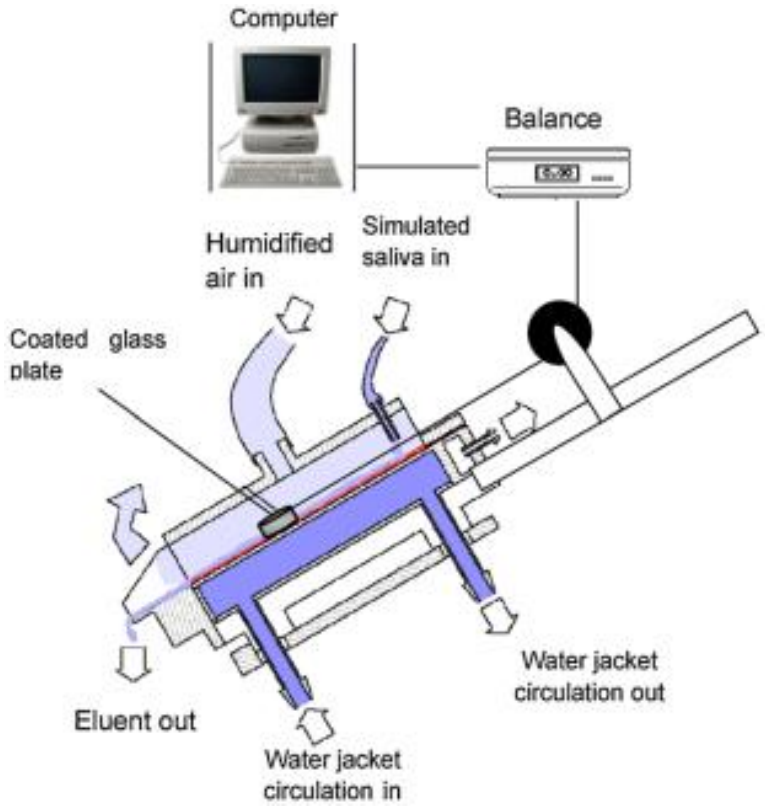

Figure 5. Modification of the porcine esophageal mucoadhesion system by *Smart et al.* to assess the mucoadhesion of different solid oral dosage form coatings.

2.2.1. General remarks on methods based on retention systems

Different setups have been developed to investigate the retention of various formulations in the esophageal mucosa. The majority of studies available in the literature have used the porcine esophageal mucoadhesion test developed by Smart et al. (Young

and Smart, 1998). When compared to the setups developed by Dobrozsi and Batchelor (Batchelor et al., 2002; Dobrozsi et al., 1999), the porcine esophageal mucoadhesion test appears to be the most up-to-date method, as it is expected to better mimic the conditions within the human esophagus. In addition, several optimizations were performed over the years, allowing the assessment of the majority of dosage forms used in oral drug delivery. Depending on the type of dosage form tested, the measuring principle is versatile and can be based on fluorescent emissions (for liquid and semi-solid formulations) or on force determinations (for SODF). Therefore, the increased usage of this setup by the scientific community to examine the mucoadhesive properties of oral dosage forms is very appropriate.

During assessments for the retention of microparticles in the esophageal mucosa, improved outcomes were obtained for microparticles coated with Carbopol®, Polycarbophil, polyacrylic acid and chitosan. Considering Carbopol® and Polycarbophil, their mucoadhesive potential has already been validated previously. With regard to the other tested polymers, polyacrylic acid is a high MW polymer with the ability to retain water and swell (Craig et al., 1994; Park and Robinson, 1987; Zhuang et al., 2013), while chitosan is a biodegradable amino polysaccharide with hydrogen bonding capacity (Andersen et al., 2015; Sogias et al., 2008). As these are important mechanisms involved in the formation of mucoadhesive bindings (Chatterjee et al., 2017; Mansuri et al., 2016; Shaikh et al., 2011; Smart, 2005), the positive results obtained for these polymers are expected. Furthermore, several other experimental works have used these polymers in successful development of mucoadhesive delivery systems (Andersen et al., 2015; Carvalho et al., 2010; Cilurzo et al., 2013; Minghetti et al., 1998; Roy et al., 2009; Silva et al., 2017; Takeuchi et al., 2001). With regard to coatings applied to SODF, higher adhesive forces were measured for sodium alginate while the opposite effect was estimated for paraffin wax and ethylcellulose. The poor mucoadhesive properties of paraffin wax and ethylcellulose are well established due to their water-repelling (hydrophobic) properties (Ali et al., 2014; Khobragade et al., 2015; Martin-Polo et al., 1992; Smart et al., 2015). In addition, the findings obtained for sodium alginate are also in compliance to the literature, since this polymer has been repeatedly used in the production of mucoadhesive delivery systems (Boateng and Areago, 2014; Kesavan et al., 2010; Pal et al., 2011; Shaikh et al., 2012). Regardless of the fact that the generated results appear to be according to the available literature, the used *in vitro* setups still require a proper correlation to *in vivo* measurements.

A resume of the *in vitro* methods identified and discussed in this section is given in table 1.

Table 1. Resume of *in vitro* methods used to assess esophageal adhesion of pharmaceutical preparations.

Method	Assessment(s)	Formulation(s)	Author(s), year
Mechanical force determinations	Modified prescription balance Force-displacement transducer Motor strain gauge Instron tensile tester	Hard gelatin capsules Soft gelatin capsules Uncoated tablets Sugar-coated tablets Film-coated tablets	Marvola et al. 1982, 1983 Swisher et al. 1984 Gibson et al. 2000 McCargar et al. 2001
	Pulley mechanism with time recorder	Polymeric microspheres	Kockisch et al. 2003
	Modified electronic balance Top pan balance Instron tensile tester Texture analyzer	Gelatin capsules Uncoated tablets Sugar-coated tablets Film-coated tablets Polymeric microspheres Semisolid systems (gels)	Al-Dujaili et al. 1986a,b Kockisch et al. 2003 Bonacucina et al. 2004, 2006 Shakweh et al. 2007
Retention systems	Dissolution tester Perspex® block Porcine esophageal mucoadhesion system	Viscous liquids Solutions Gels Microparticles Microspheres SODF coatings	Dobrozsi et al. 1999 Batchelor et al. 2002 Young and Smart, 1998 Kockisch et al. 2003, 2004 Smart et al. 2003, 2013, 2015

3. *In vivo* methods assessing swallowing safety and transit times of oral dosage forms in the esophagus

The *in vivo* methods that are currently used to investigate the mucoadhesive properties of oral dosage forms in the esophagus measure the time required for the dosage form to reach the stomach after being swallowed (esophageal transit time). Subsequently, longer times are indicative of mucoadhesive dosage forms that were retained in a specific portion of the esophageal tract during transit. On the other hand, dosage forms with poor mucoadhesive properties (optimal gliding) are expected to reach the stomach very quickly. All methods are based on monitoring techniques that are capable of tracking the dosage form during swallowing and transit time in the esophagus.

3.1. Video endoscopy

Video endoscopy is an established medical procedure that uses a video camera in the tip of an endoscope to diagnose gastrointestinal diseases. Later, the same procedure was also applied to evaluate the oro-esophageal transport of SODF. The safety and swallowing performance of conventional and orodispersible tablets (ODT) was investigated in 36 patients with swallowing impairments (dysphagia) (G Carnaby-Mann

and Crary, 2005). Both tablets had similar physical characteristics (average weight and thickness) and were colored in blue to allow visualization during assessments. Patients were asked to place the tablet in their tongue and to swallow it completely whenever ready. All assessments were conducted using a computer-integrated system for swallowing measurements (Kay Digital Swallowing Workstation and Swallowing Signals Laboratory, model No. 7100) that integrates video endoscopy, surface electromyography (sEMG) and respiratory monitoring. The nasopharyngeal endoscopic video was used to evaluate the global success of the swallowing performance, including route of clearance (pathway taken by the bolus), safety (tablet remains left in the laryngeal vestibule/proximal trachea), number of swallows (to remove the tablet from the oropharynx), and extent of bolus clearance (time taken to clear the bolus). Information obtained from sEMG was used to calculate the muscular activity associated with swallowing whereas respiratory monitoring provided the apneic duration of swallowing for each preparation. The ODT formulation reduced the effort and physiological stress associated with tablet swallowing regarding dysphagic patients. Furthermore, these patients showed preference for the ODT formulation as compared to the conventional tablet.

Schiele et al. also applied video endoscopy to evaluate the swallowing outcome of different SODF in patients with stroke-induced dysphagia (Schiele et al., 2015). During laryngoscopy examinations, 52 patients were asked to swallow four different placebo formulations twice (capsules and round, oval and oblong tablets). One administration was assisted with milk and the other with texture-modified water (pudding consistency). The swallowing performance was evaluated according to a 8-point Penetration Aspiration Scale (PAS) (Rosenbek et al., 1996), which is determined by rating the depth of bolus entry into the airways and whether it is expelled or not. Patients were allowed to swallow the SODF with the administration aids if they had previously yielded a PAS < 5 for the administration aids alone. The four placebos were delivered on a teaspoon with 3 ml of TMW and the same procedure was repeated after with 3 ml of milk. Food coloring was used to dye both products and enhance visualization during assessments. The findings obtained from this work suggest an increased risk of penetration and aspiration for a substantial fraction of patients with stroke-induced dysphagia. Differences in the type and shape of the SODF did not modulated this risk. The video endoscopy was crucial to identify swallowing issues during administration of tablets (Fig. 6A) and capsules (Fig. 6B). For this reason, the authors suggested using this procedure when evaluating the administration safety of SODF among critical patient populations (Schiele et al., 2015).

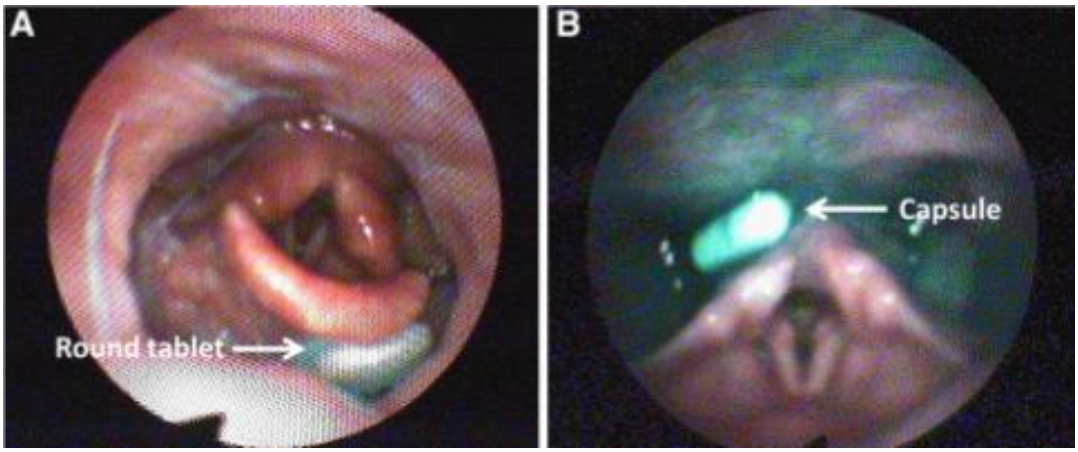

Figure 6. Video endoscopy procedure to assess SODF swallowing safety (*Schiele et al.*). A: lodging of a tablet in the left vallecula, B: capsule lodging in the pyriform sinus.

3.2. Video fluoroscopy

Video fluoroscopy is a monitoring technology that uses a tracer (e.g., barium sulfate tablets) and an x-ray video camera. The procedure was first used in 1982 to investigate the esophageal transit of tablets and capsules in healthy volunteers (Hey et al., 1982). The subject's position (supine or upright) and the amount of water taken (25 or 100 ml) were also assessed for their influence on the SODF transit profile. Different designs were tested, from oval and round tablets (large and small sizes) to capsules with high or low densities. A Siregraph E universal-couch with monitor and fluoroscopy was used to evaluate the velocity and route of the SODF across the esophagus. The obtained results suggested faster transit times for oval tablets and high-density capsules when administered in upright position with 100 ml of water. The same methodology was later applied by other researcher to investigate the transit times of different SODF (Channer and Virjee, 1986, 1985), as well as for the evaluation of oral film formulations (Okabe et al., 2008).

3.3. Gamma scintigraphy

A procedure based on gamma scintigraphy was used to study the esophageal transit times of SODF in a population of elderly patients aged 50 years or older (Perkins et al., 1994). During assessments, the subjects were seated facing the scintigraphy camera and instructed to swallow the SODF (marked with ^{99m}Tc) with 50 ml of water. Images were recorded during 10 min and analyzed later by computer. The collected frames were used to determine the time in which oropharynx activity started and the arrival time of the dosage form in the stomach. The assessments revealed that gamma scintigraphy could be adopted to identify differences in the transit times of distinct SODF (Perkins et al., 1999).

Other researchers used gamma scintigraphy studies to investigate the esophageal transit of SODF in overnight fasted subjects. Patients were instructed to swallow the SODF in upright position with assistance of water (235 ml, using a straw). The scintigraphy camera collected images at 1 sec/frame and the esophageal transit times were calculated based on selected regions of interest (proximal, distal and lower esophagus). The results showed that wax-polished alendronate tablets moved very quickly across the esophagus, taking less than 6 s to reach the stomach (Drake et al., 2002).

Gamma scintigraphy was also applied to investigate the gastro-retentive properties of ^{152}Sm-activated chitosan multiparticulates dispensed in gelatin capsules. During the course of the study, one patient was excluded due to the strong adhesion of the formulation to the esophagus. The subject reported was a 22-year-old healthy male that administered the capsule with 180 ml of water while seated. Subsequently, further scintigraphy examinations were conducted to better understand the adhesive properties of the formulation across the esophagus. Images of 1 min duration were recorded during defined periods and a gamma counter was used to measure the emitted radiation. The collected images showed that the capsule was still adhered to the esophageal mucosa after 5 min (Säkkinen et al., 2004).

Perkins et al. used gamma-scintigraphy to investigate the esophageal transit time and gastric emptying of SODF in osteoporotic patients with Kyphosis. The combination of postural problems and oral bisphosphonate therapy lead the researchers to evaluate the incidence of drug-induced esophageal injuries experienced by these patients. During the measurements, the patients were seated in front of a gamma camera and administered a radiolabeled-film-coated risedronate tablet with either 50 or 120 ml of water. Using appropriate software, the esophageal transit time and gastric emptying calculated based on the collected images. No correlation was found between esophageal transit time and the amount of water ingested with the SODF. Moreover, the transit times were not influenced by the patient's degree of kyphotic curvature (Perkins et al., 2006).

3.4. Magnetic Marker Monitoring

Magnetic Marker Monitoring (MMM) is a real time procedure that measures magnetic components using a superconducting quantum Interference device (SQUID) (Andrä et al., 2000; Biller et al., n.d.). The markers consist of pure magnetized magnetite and the technique has been applied to explore the gastrointestinal transit of SODF (Weitschies et al., 2010, 2005; Weitschies and Wilson, 2011) and the dissolution behavior of disintegrating capsules (Weitschies et al., 2001). In 2004, Osmanoglou et al. specifically used MMM to investigate the esophageal transit time of magnetically marked

capsules in healthy volunteers, depending on their body posture (upright or supine) and volume of liquid ingested (5, 25 and 50 ml). The rate of esophageal retention was seen as being highly dependent on the body position, swallowing volume and pharyngeal propulsion velocity. Results showed that higher esophageal transit velocities could be obtained in upright body position with at least 50 mL of water, in order to minimize the capsule entrapment in the esophagus. (Osmanoglou et al., 2004).

3.5. General remarks on *in vivo* methodology

A common characteristic related to *in vivo* methods is their dependence on imaging techniques to monitor the SODF throughout the oro-esophageal system. Different imaging tools can be adopted such as video endoscopy, video fluoroscopy, gamma scintigraphy and MMM.

Video endoscopy is a real time technique that provides information about patients' swallowing function, making it useful for assessing their swallowing capabilities during SODF administration (G Carnaby-Mann and Crary, 2005; Schiele et al., 2015). This is extremely important considering patients with swallowing impairments (dysphagia), as it can contribute for increased swallowing safety and compliance to oral drug regimens (Stegemann et al., 2012). Video fluoroscopy, gamma scintigraphy and MMM are techniques that rely on x-ray, scintigraphy and SQUID devices to allow real time monitoring of the SODF, respectively (Channer and Virjee, 1986; Hey et al., 1982; Perkins et al., 2006; Weitschies and Wilson, 2011). In order to be visible during the assessments, the dosage for has to marked with an adequate tracer. These methods are non-evasive, comfortable for the patient, involve little radiation exposure and provide quick evaluation of the transit time of the dosage form throughout the esophagus. Notwithstanding, one major disadvantage of scintigraphy assessments is related to the low sampling rate and prolonged washout time for radioactivity from the gastrointestinal tract (Osmanoglou et al., 2004).

There is no major preference for a specific methodology since all are generally accepted and can be easily applicable. In addition, no relevant information is available about which type of assessment can be more accurate or provide better results. As such, their applicability will be highly dependent on the instrumentation available for testing. Despite seen as ideal methodologies to be applied when investigating the swallowability and transit time of SODF, their dependence on human volunteers and ethical committee approvals makes them difficult be to establish and are seen as major research challenges.

A resume of the different *in vivo* methods identified and discussed in this section is given in table 2.

Table 2. Resume of *in vivo* methods to assess oral transit of drug pharmaceutical forms.

Method	Assessment(s)	Formulation(s)	Author(s), year
Video endoscopy	Nasopharyngeal endoscopy assisted with sEMG and respiratory monitoring Laryngoscopy examination and evaluation with PAS scale	ODT tablets Conventional tablets Round, oval and oblong tablets Capsules	Carnaby-Mann et al. 2005 Schiele et al. 2015
Video fluoroscopy	Esophageal transit time based on body position and amount of water taken	Oval and round tablets (small/large sizes) Capsules (high/low density) Film-coated tablets	Hey et al. 1982 Channer et al. 1985, 1986 Okabe et al. 2008
Gamma scintigraphy	Esophageal transit time in elderly and Kyphosis patients	Capsules Enteric-coated tablets Wax-polished tablets Film-coated tablets	Perkins et al. 1994 Drake et al. 2002 Perkins et al. 2006
Magnetic Marker Monitoring	Esophageal transit time in health young adults	Hard gelatin capsules	Osmanoglou et al. 2004

4. Discussion

The development of new pharmaceutical drug products for human use requires a variety of predictive *in vitro* methods to compare the performance of potential formulations, dosage forms or drug product concepts. For solid oral dosage forms, the esophageal transit behavior is an important aspect to assure safe swallowing. Based on the increasing number of cases reporting unintended drug-induced esophageal injuries in the early 1980's, the first *in vitro* methods to evaluate mucoadhesion were developed by this time (Kikendall et al., 1983; Teplick et al., 1980).

The developed *in vitro* methods focused on the interaction of the dosage form with the mucosal tissue using mechanical force measurements (detachment forces) or quantified the amount of formulation remaining on the mucosal tissue (Al-Dujaili et al., 1986a; Marvola et al., 1982; Young and Smart, 1998). These methods were further adapted to better mimic the *in vivo* conditions. The strength of mucoadhesion was determined through comparison of mucoadhesive forces between different dosage forms, formulations or polymers. The obtained data on mucoadhesion and transit times with the different methods did not provide consistent results with regard to the different dosage forms tested (mainly tablets, capsules and microparticles). Such disparities might be related to differences in SODF designs such as coating, shape, size,

formulation and polymers investigated in the different methods. Furthermore, the results from the different methods cannot be compared directly due to their individual focus on specific research questions (e.g., bioadhesion to the buccal area, esophageal transit properties, etc.) and to the distinct experimental settings applied during measurements (e.g., probe hydration prior measurement, contact time, temperature, contact area, type of tissue, type of buffer, etc.).

In parallel, *in vivo* methods have been developed to investigate the gastrointestinal transit of SODF, with the purpose of understanding the *in vivo* drug release from the dosage form and its relation to drug absorption and plasma profiles. Gamma scintigraphy uses short half-life radiotracers to monitor dosage forms or formulations throughout the GI tract. For oro-esophageal transport studies, gamma scintigraphy is limited by its temporal resolution. The recently introduced methods capable of tracking magnetic materials allow a real time temporal resolution better suited for the short oro-esophageal transit times (Weitschies and Wilson, 2011). Video endoscopy is an *in vivo* technology using a video camera to visualize the oro-esophageal system during the swallowing process. While video endoscopy provides direct information on the localization and mucoadhesion of a dosage form, the endoscopic tube might affect the patient's swallowing efficacy. In contrast to this, video fluoroscopy visualizes the swallowing process and dosage form route from outside the body but requires a radiotracer, as it happens for gamma scintigraphy.

Since swallowing is a complex physiological mechanism involving volitional and reflexive activities, as well as synchronized neuronal and muscular activation, the *in vivo* interaction between the surface of the dosage form and the mucous layer is influenced by several additional factors such as peristaltic movements, pressure gradients, liquid intake and other conditions that are not considered during *in vitro* testing. Maybe for this reason, the predictivity of *in vitro* methods and their correlation to the *in vivo* performance have not been established until today. McCargar et al. correlated their *in vitro* adhesion results (Mccargar et al., 2001) with the data obtained from the *in vivo* scintigraphy study developed by Perkins (Perkins et al., 1999). The esophageal transit time of the film-coated risedronate tablet was lower when compared to an uncoated round tablet during the *in vivo* studies, which was not the case for the *in vitro* study. These findings point out that current *in vitro* methods based on the retention or measurement of the detachment force between SODF and ex vivo esophageal mucosa do not give a real prediction of their *in vivo* esophageal transit. Over the years, the constant improvements in the setups used for *in vitro* assessment to better mimic the physiological conditions show the importance of this research topic within the medical sciences. However, the measuring principles behind the developed setups are still the same as used in the 1980's. As such,

proper *in vitro* methods that can better predict the transport properties (e.g., kinetic forces, resistance to movement) of different SODF on ex vivo esophageal tissue to better correlate with *in vivo* esophageal transit are still required.

To summarize, *in vitro* methods using animal tissue can provide useful information on the general tendency and relative interaction of polymers to adhere to mucosal tissue. Since none of the *in vitro* methods developed until today are able to mimic the complex swallowing process and oro-esophageal transit, nor do suitable animal models exist, *in vivo* studies in humans using video endoscopy, video fluoroscopy, gamma scintigraphy or MMM are still the gold standard (Osmanoglou et al., 2004; Weitschies et al., 2010).

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An evaluation of the gliding performance of solid oral dosage form film coatings using an artificial mucous layer

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All authors have read and agreed to the published version of the manuscript.

Abstract

Oral drug delivery technology is mainly provided in the form of solid oral dosage forms (SODF) that have to be swallowed intact and move throughout the oro-esophageal system to release the drug content in the stomach or intestine. As there is growing evidence for an increasing prevalence of impaired swallowing functions in certain diseases, multimorbidity and advanced age, predictive *in vitro* methods for the oro-esophageal gliding behavior of SODF would be very useful. The gliding performance of different SODF polymer films was investigated across an artificial mucous layer using a versatile *in vitro* gliding system. In a first phase, the system measures the force required to move the polymer surface when placed in contact with the mucin layer and, in a second phase, the resistance behavior over a defined length. The obtained results showed that comprehensive gliding profiles could be obtained depending on the polymer film tested. The carnauba wax and PEG coatings required lower gliding peak forces and showed poor gliding resistance, which is indicative of free gliding capacity. In contrast, HPMC, PVP and gelatin coatings required higher gliding forces and exhibited greater resistance due to an adhesive interaction with the artificial mucous layer. The obtained profiles correlate with prior *in vitro* data during polymer gliding evaluations on mucosal membranes. Lastly, Principal Component Analysis (PCA) has proven to be a useful tool to identify trends between coating materials and output parameters retrieved from the gliding curves.

Keywords: artificial mucous layer, dynamic friction, gliding performance, *in vitro* methods, polymer film coatings, solid oral dosage forms, static friction, swallowing safety

1. Introduction

The oral cavity remains as the preferable route for drug administration in primary and secondary cares. Solid oral dosage forms (SODF), such as tablets and capsules, represent 70% of all available medicines and are commonly prescribed by physicians for therapy management (Heppner et al., 2006).

One major attribute required to achieve efficacy with SODF treatments and often not considered by healthcare professionals is the ability of patients to swallow (Schiele et al., 2013). Swallowing problems have shown a negative impact on the management and administration of SODF (Fusco et al., 2016), affecting the efficacy of prescribed treatments either by poor compliance or by drug modifications to improve swallowability (Kelly et al., 2010; Kirkevold and Engedal, 2010). As the major population of patients practicing polypharmacy are older adults (aged >65) with strong likelihood for swallowing

impairments, the successful and safe administration of SODF by these patients is rather questionable (Bhattacharyya, 2014; Charlesworth et al., 2015). Subsequently, in order to be safely swallowed by the majority of patients, the SODF should be non-adhesive to mucosal tissue and slide easily throughout the oro-esophageal system along with the peristaltic movements (Domb and Khan, 2014; Helliwell and Taylor, 1993).

In general, the currently available *in vitro* methods were developed to target the investigation of mucoadhesive drug delivery systems in the gastrointestinal tract. They usually rely on the measurement of the tensile force needed to detach the dosage form from an mucosal-mimicking membrane (e.g., esophageal mucosa) (Al-Dujaili et al., 1986; Marvola et al., 1982; Shakweh et al., 2007; Swisher et al., 1984). Recently, other methods also included the determination of the shear stress (resistance) required to overcome the adhesive interactions during the gliding of polymer-coated discs. Nevertheless, having in consideration the physiological length of a human esophagus (± 23 cm), the sliding length (5.95 cm) adopted in these studies may not be sufficient to generate comprehensive gliding profiles for the tested coatings (Smart et al., 2015, 2013). Therefore, although different methods have been suggested throughout the years, their contribution for a deep understanding of the gliding performance of different coating surfaces throughout an extended mucosal length is still limited (Mccargar et al., 2001).

The aim of this work was to evaluate and characterize the gliding behavior of different polymer coating surfaces throughout an extended mucous length. To confirm the applicability of the *in vitro* method, the gliding performance of different polymers was investigated on an artificial mucous layer. The selected polymers were investigated due to their extended applicability for developing SODF coating formulations. Furthermore, Pearson's correlation and Principal Component Analysis (PCA) were applied to identify positive trends between gliding parameters and film coating materials.

2. Materials and Methods

2.1. Materials

PVA grades (EG-03P, EG-18P, EG-40P) were a kind gift from Nippon Gohsei (Uto, Japan). HPMC E15 and PVP K-90 were donated by IMCD (Wien, Austria). PEG 1500 and carnauba wax were purchased from Alfa Aesar (Lancashire, UK). PEG 3350 and lyophilized mucin from porcine stomach were purchased to Sigma-Aldrich (Munich, Germany). PEG 6000 was obtained from Baxter (Vienna, Austria) and polymer strips of HPMC and hard gelatin (used in the production of capsule shells) were supplied by Capsugel (Colmar, France). Double-sided carbon tape was purchased from Science

Services (Munich, Germany) and Universal double-sided adhesive tape was obtained from Tesa SE (Norderstedt, Germany). The water used was purified through a Milli-Q system (Merck Millipore, Darmstadt, Germany).

2.2. Preparation of polymer-coated discs

Aqueous solutions of 10% (w/v) were prepared at room temperature for HPMC E15, PVP and PVA grades. For each polymer, the appropriate amount was added to a beaker containing stirring water (using a magnetic stirrer) and left under agitation until complete dissolution. The films were produced from the aqueous polymer solutions using previously described solvent casting techniques (drying overnight in a vacuum oven at 50 °C) (Hossain et al., 2018; Siemann, 2005). The generated polymer films were later cut (using a scalpel) and fixed into the surface of the testing discs using universal double-sided adhesive tape (surface area: 7.065 cm2). The thickness of the applied polymer film coatings was approximately 200 µm, which relates to standard coating thicknesses usually applied to pharmaceutical SODF.

2.3. Preparation of PEG and carnauba wax-coated discs

Carnauba wax and PEG grades were melted over a beaker of boiling water. Subsequently, the testing discs (same surface area) were dipped into the molten (using tweezers) and the coating was allowed to solidify at room temperature (Smart et al., 2013). If required, the procedure was repeated until a coating thickness of 200 µm could be achieved.

2.4. Experimental Setup

2.4.1. Pre-treatment of lyophilized mucin

The mucin used during the experiments was subjected to a sieving process in order to reduce of the particle size distribution (sieve size: 1250 µm) and increase sample homogeneity.

2.4.2. Description of the apparatus

The *in vitro* apparatus consisted of an Instron Universal Testing Machine (Fig. 1), model 5942, with a speed range of 0.05 - 2500 mm/min (High Wycombe, UK), equipped with a horizontal platform containing a defined gliding region (Fig. 1C, 20 x 4 cm). The testing disc (high-density polyethylene plastic material, 12 grams, 2 x 1 cm) contained a small metal hook (Fig. 1A) that was connected to the load cell via a nylon cord (non-elastic monofilament, diameter: 0.56 mm). The nylon cord (Fig. 1D) passed through a metal wheel (Fig. 1E) inserted in a height-adjustable column that was vertically aligned

to a 10 N load cell (Fig. 1F). The integration of a position stopper on the metal wheel (using a stable screw mechanism) allowed the nylon cord to be maintained horizontal at a 90° measuring angle.

Figure 1. Schematic illustration of the *in vitro* gliding system developed in this work: (A) testing disc, (B) weight, (C) gliding region, (D) nylon cord connecting the disc to the load cell, (E) height-adjustable wheel with position stopper, (F) load cell, (G) software dysplay.

2.4.3. Preparation of the artificial mucous layer

A schematic representation of the steps involved in the preparation of the artificial mucous layer can be visualized in Fig. 2. A rectangular aluminum frame containing the same dimensions of the gliding region (20 x 4 cm) and having a PTFE-coated removable base through a sliding system was used for the assembly (Fig. 2A). In a first step, the

mucin (350 mg per surface prepared) was evenly distributed inside the frame area (Fig. 2B). An equally sized PTFE-coated press was inserted in the frame to uniformly compress the mucin power (Fig. 2C). After a compression time of 30 s, the press was withdrawn from the frame and the homogeneous mucin surface generated from the process was retained in the lower base of the frame (Fig. 2D). A strip of double-sided adhesive carbon tape (carbon-filled acrylic, 20×4 x 0.016 cm) was fixed to the defined gliding region on the platform (Fig. 1C) by its lower adhesive side. Subsequently, the frame was aligned over the adhesive tape and the sliding base was carefully moved to precisely distribute the homogeneous mucin surface across its upper adhesive side (Fig. 2E). After complete distribution, the PTFE-coated press was again inserted to push the mucin against the adhesive tape (for 5 s) and fix the artificial layer to the platform. The frame was later removed from the platform and the final preparation step involved the humidification of the mucin layer to provide a moistened mucous surface for the gliding measurements. This was achieved by spraying 0.5 ml of water at room temperature (spraying distance: 5 cm) to each of six central positions defined across the total length of the gliding region (Fig. 2F).

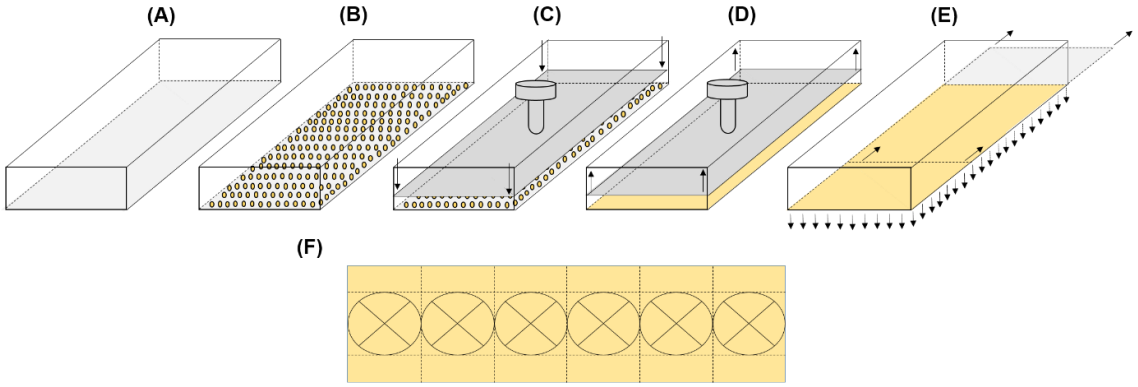

Figure 2. Schematic illustration of the steps involved in the preparation of the artificial mucous layer: (A) frame with PTFE-coated sliding base, (B) distribution of the mucin powder in the frame, (C) compression of the mucin power with a PTFE-coated press, (D) press withdrawal and retention of the homogeneous mucous layer in the lower base of the frame, (E) base sliding with distribution of the mucin surface in the carbon adhesive tape, (F) moistening of the artificial mucous layer by spraying water to six specific central positions in the gliding region.

2.4.4. Gliding performance measurements

All evaluations were performed at room temperature and an artificial mucous layer was prepared for each polymer gliding performance. Immediately after the humidification of the artificial mucous layer, the coated testing disc containing on top a 50-g weight (Fig.

1B) was directed to the left end of the gliding region and the measurement was promptly initiated after contact of the coating with the mucous layer (no wetting time), in tension mode. The force (resistance) required to glide the coated disc at a constant speed of 2.6 cm/s through a gliding distance of 16.5 cm was measured with the load cell and automatically recorded with the equipment's Bluehill® software (Fig. 1G). Five replicates were performed for each polymer specie.

2.4.5. Evaluation of the experimental setup

Testing discs coated with HPMC polymer strips were used to evaluate the selected experimental conditions for the gliding performance and investigate the reproducibility of the produced moistened artificial mucous layer. Four replicates were evaluated and the overall reproducibility of the method was analyzed.

2.5. Statistical analysis

Pearson's correlation was applied to measure the linear correlation between the different variables retrieved from the gliding curves obtained with the *in vitro* gliding system. Furthermore, multivariate analysis based on Principal Component Analysis (PCA) was used to dimensionality-reduce the different gliding variables into a small set of data, but still containing the majority of the information in the large set, with the aim of identifying which polymer films are contributing strongly for each of the parameters measured (Otsuka et al., 2011, Van Snick et al. 2018). The gliding output selected for the analysis was the Dynamic friction (Dynamic F) as it is a good indicator of enhanced for enhanced gliding performance. Both analysis were performed using Minitab® 18 software (SquareCircle Global FZ LLC).

3. Results

3.1. Evaluation of the experimental setup

The experimental setup, including the prepared artificial mucous layer, showed good reproducibility and a low coefficient of variation (CV = 0.25), as the four HPMC-coated disc replicates presented similar gliding performances (Fig. 3).

3.2. Investigation into the gliding profile obtained for the different polymers

For a detailed interpretation of the gliding profiles obtained for the tested polymers, it is possible to divide the acquired curves in two distinct areas: a region A, which corresponds to the maximum load (ML) required to overcome the initial static friction and start gliding the coated substrate, followed by a targeted extended region B, that relates to the dynamic friction of the same coating in the artificial mucous layer (Fig. 4).

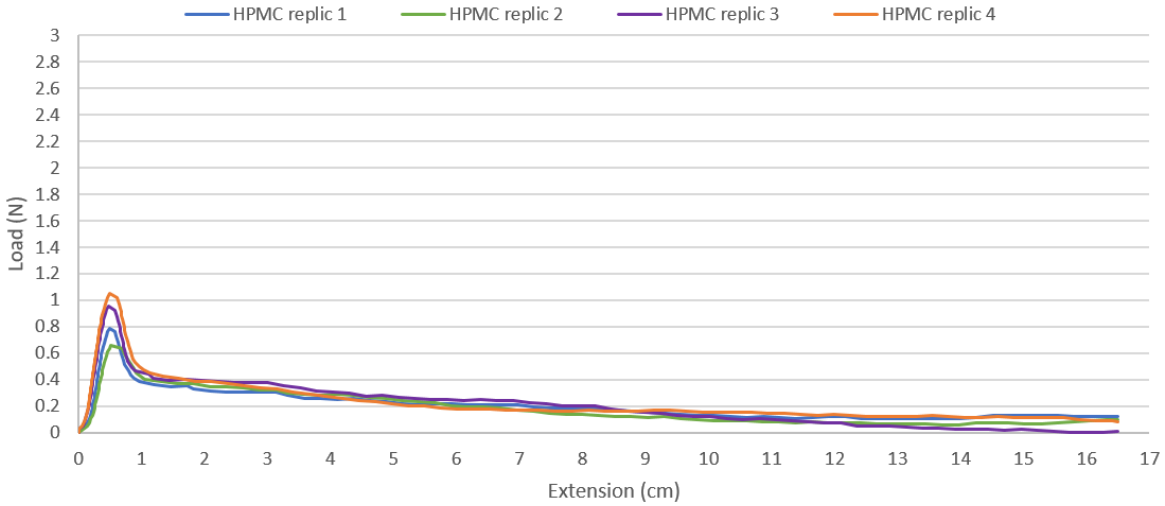

Figure 3. Evaluation of the experimental conditions and the reproducibility of the prepared artificial mucous layer using HPMC-coated discs (n = 4).

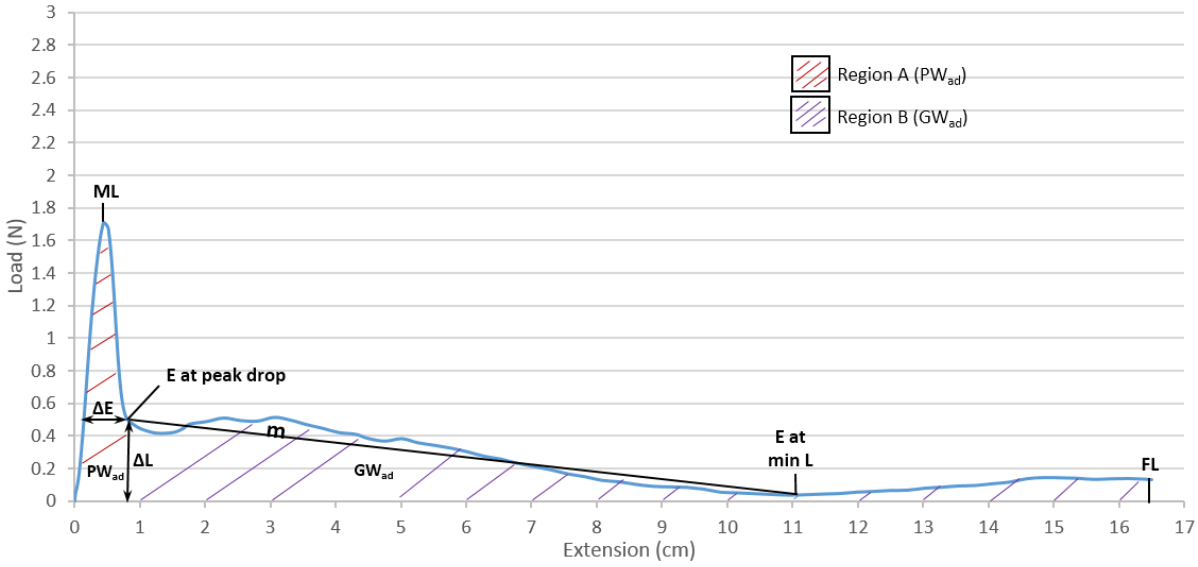

Figure 4. Curve interpretation for evaluation of the gliding performance: (PW_{ad}) peak region A, (GW_{ad}) gliding region B, (ML) maximum load, (ΔE) maximum peak extension, (ΔL) load at peak drop required to start GW_{ad}, (m) slope calculated between E at peak drop and E at min load, (FL) final load.

Within the total work of adhesion (TW_{ad}), it is thus possible to calculate the peak work of adhesion (PW_{ad}) and the gliding work of adhesion (GW_{ad}) from regions A and B, respectively. Furthermore, the evaluation of specific details along both regions might also provide valuable information on the adhesive and gliding behavior of the polymer. In region A, the analysis of the ML combined with the peak extension (ΔE) and load at peak drop (ΔL), can give an estimation of the mucoadhesive capacity of the polymer. As

example, polymers with combined increased in ML, ΔE and PW_{ad} are suggestive of significant adhesive bonds to the mucin layer, which is reflected by greater force and resistance to initiate the gliding movement, respectively. Moreover, the load at peak drop (ΔL) details the force required to start the film gliding (region B), so it is expected that polymers with optimal gliding performances should present lower values for ΔL.

Regarding the gliding region (B), the calculation of the slope (m) between the extension at peak drop (E at peak drop) and the extension at minimum load (E at min L) is a valuable predictor of the polymer gliding performance. Slopes with values closer to zero are excellent indicators of polymers with optimal gliding properties on mucous layers. In addition, the load measured at the final extension (FL) is indicative of the force required to maintain a continuous gliding movement at later stages (gliding maintenance force), and it can also be a predictor of the stability of the gliding layer upon exposure to shear stress during the gliding phase. Therefore, polymers with free gliding properties will present lower values for m and FL. Lastly, a reliable and robust prediction for the polymer gliding behavior across mucous layers can be obtained through the integration of all variables.

3.2.1. Influence of the molecular weight grade

A positive correlation between the molecular weight (MW) and ML was observed for PVA polymers (Fig. 5A). Greater forces (2.058 N) were obtained when assessing discs coated with the highest molecular grade (EG-40P). All tested grades recorded higher forces to initiate movement in comparison to the uncoated disc (0.831 N), demonstrating higher bonding to the artificial mucous layer. Nevertheless, the ML obtained for the lowest molecular grade of PVA (EG-03P) was closer to the one obtained for the uncoated disc (1.047 N). PEG grades showed little dependence on MW and no related adhesion to the mucous layer, as the measured forces were negligible in comparison to the reference (Fig. 5B). The same assumptions can be taken based on the work of adhesion (Supplementary material, Appendix A) obtained for regions A (PW_{ad}) and B (GW_{ad}).

3.2.2. Polymer screening for gliding performance

With regard to the PVA and PEG grades tested, only PVA EG-18P and PEG 6000 were further selected for comparison with other polymer species. The gliding performance obtained for the tested polymers can be visualized in Fig. 6. Both kinetic (Fig. 7A) and dynamic friction (Fig. 7B) were calculated for each polymer coating. Further information concerning specific parameters for the obtained gliding curves can be visualized on Table 1. Higher static friction was observed for discs coated with HPMC E15 and PVP. The HPMC film strip showed values closer to the uncoated disc, whereas

carnauba wax and PEG-coated discs displayed minor dynamic friction, which is indicative of poor adhesive interactions with the artificial mucous layer and improved gliding properties.

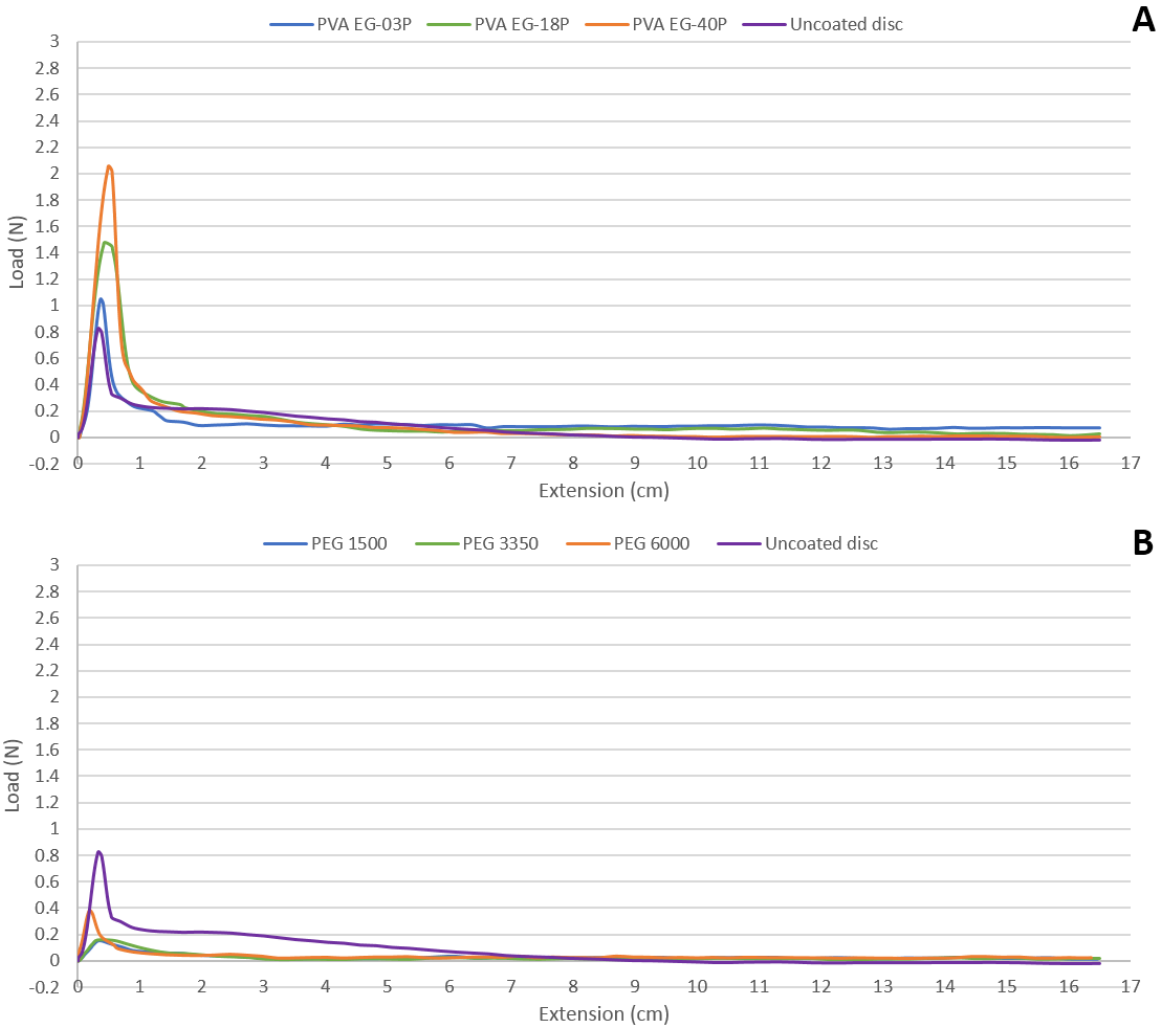

Figure 5. Influence of molecular weight on the gliding profile (n = 5): (A) PVA grades, (B) PEG grades.

A similar trend was observed with regard to the region B of the curves (gliding performance), as higher GW_{ad} were needed for discs coated with PVP and HPMC E15 (higher dynamic friction), while PEG- and carnauba wax-coated discs showed GW_{ad} inferior to the uncoated disc. The load measured at the starting point of region B (ΔL) was the lowest for PEG, PVA and carnauba wax. Furthermore, according to the obtained dynamic frictions and calculated slopes, optimal gliding performances are also expected for the same polymers. The total gliding work was higher for HPMC E15, followed by PVP and the hard gelatin film strip, whereas greater resistance at FL was noticed for PVP-coated discs.

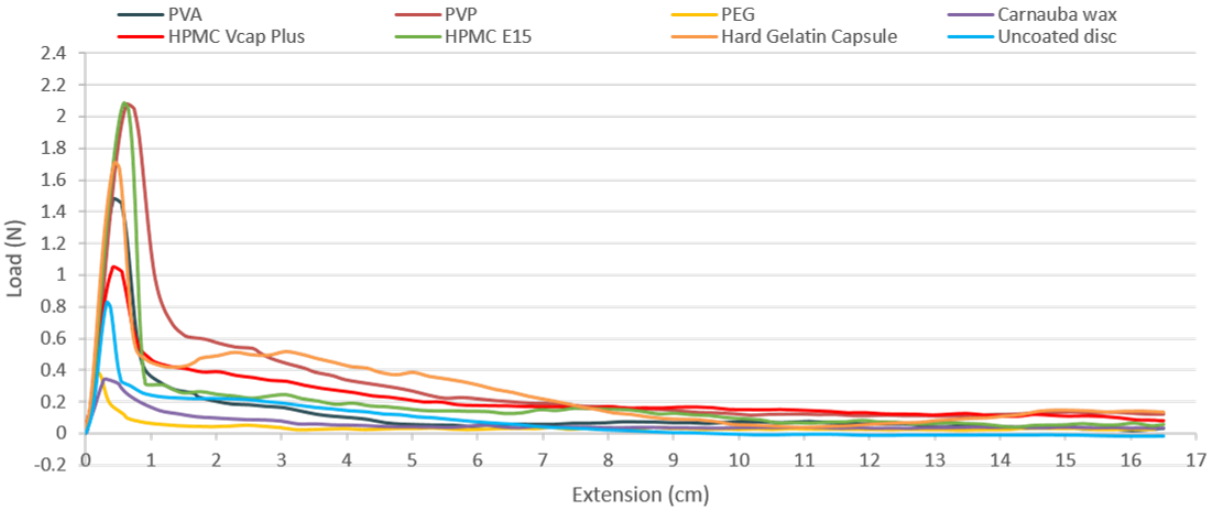

Figure 6. Gliding profiles obtained for the different tested polymers (n = 5).

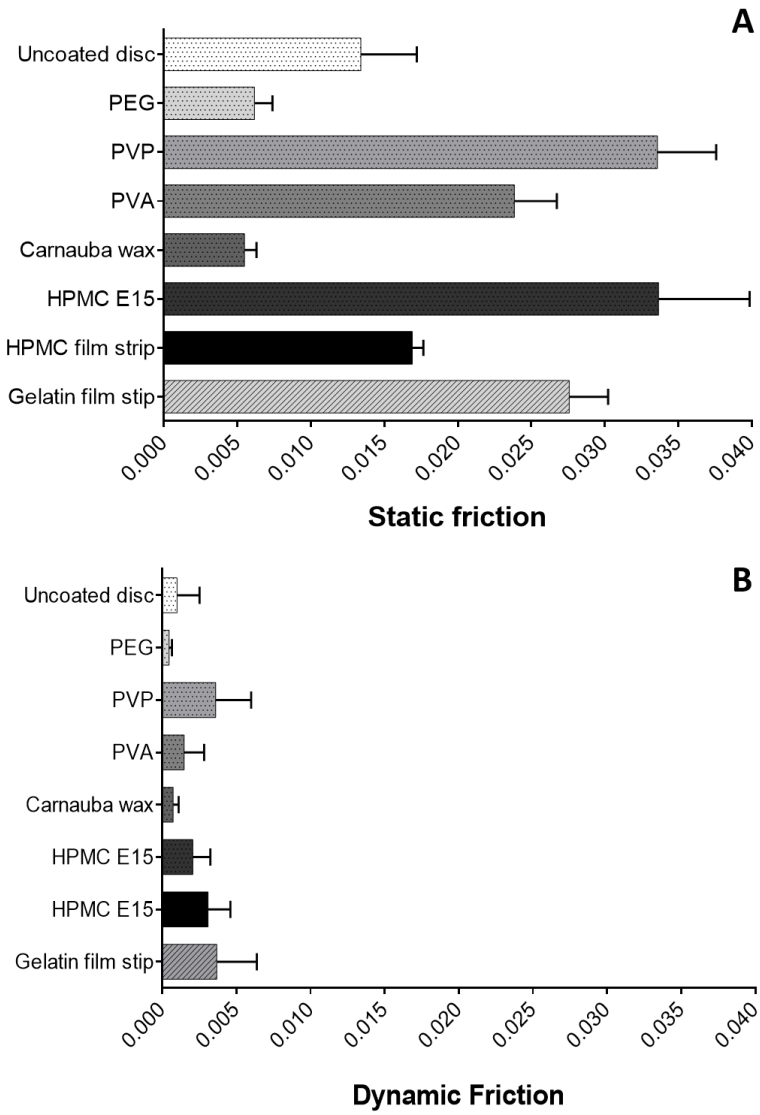

Figure 7. Coefficient of friction obtained for the polymer coatings (n = 5): (A) static friction; (B) dynamic friction.

Table 1. Gliding parameters obtained for the different polymers tested (n = 5).

Polymer	Gelatin	HPMC	HPMC E15	Wax	PVA	PVP	PEG	No coat
ML (N)	1.71 ± 0.16	1.05 ± 0.05	2.09 ± 0.38	0.34 ± 0.05	1.48 ± 0.18	2.08 ± 0.25	0.38 ± 0.08	0.83 ± 0.24
ΔE (cm)	0.45 ± 0.04	0.49 ± 0.06	0.59 ± 0.08	0.66 ± 0.06	0.43 ± 0.13	0.82 ± 0.03	0.33 ± 0.08	0.69 ± 0.03
PW_{ad} (mJ)	8.34 ± 2.37	6.46 ± 0.56	7.67 ± 3.32	3.76 ± 0.30	7.24 ± 2.26	18.93 ± 7.6	2.07 ± 0.65	4.02 ± 0.37
ΔL (N)	0.47 ± 0.05	0.45 ± 0.09	0.30 ± 0.08	0.14 ± 0.02	0.18 ± 0.02	0.61 ± 0.18	0.09 ± 0.07	0.30 ± 0.05
m	0.030 ± 0.04	0.018 ± 0.01	0.014 ± 0.02	0.004 ± 0.01	0.007 ± 0.01	0.028 ± 0.04	0.002 ± 0.01	0.019 ± 0.01
FL (N)	0.07 ± 0.05	0.04 ± 0.04	0.07 ± 0.01	0.03 ± 0.00	0.07 ± 0.04	0.12 ± 0.05	0.05 ± 0.04	0.00 ± 0.09
GW_{ad}(mJ)	25.43 ± 3.80	15.47 ± 0.40	38.70 ± 3.33	4.44 ± 0.97	25.92 ± 1.83	43.39 ± 5.39	3.52 ± 1.36	7.35 ± 0.26
TW_{ad} (mJ)	37.99 ± 3.49	21.93 ± 0.26	46.36 ± 4.54	8.202 ± 0.74	33.15 ± 3.08	43.50 ± 5.41	7.39 ± 2.56	11.37 ± 0.15
Static Friction	0.0276 ± 0.00	0.0169 ± 0.00	0.0337 ± 0.01	0.0055 ± 0.00	0.0236 ± 0.01	0.0336 ± 0.01	0.0062 ± 0.00	0.0134 ± 0.01
Dynamic friction	0.0037 ± 0.00	0.0031 ± 0.00	0.0021 ± 0.00	0.0007 ± 0.00	0.0015 ± 0.00	0.0036 ± 0.00	0.0005 ± 0.00	0.0010 ± 0.00

3.3. Statistical analysis

The coefficient of determination (R^2) for each pair of gliding parameters was calculated based on Pearson's correlation. Based on the obtained results (Table 2), high correlations were found between the following combination of parameters: GW_{ad} and ML (R^2 = 0.951), TW_{ad} and ML (R^2 = 0.976), Static friction and ML (R^2 = 1.00), Static friction and GW_{ad} (R^2 = 0.951), Static friction and TW_{ad} (R^2 = 0.976), *m* and ΔL (R^2 = 0.878), Dynamic friction and ΔL (R^2 = 0.867) and TW_{ad} and GW_{ad} (R^2 = 0.947). From the PCA analysis (Fig. 8), it can be seen that FL, TW_{ad}, GW_{ad} and Static friction (Satic F) parameters are being highly influenced by PVA and HPMC E15 gliding curves (purple circle), while PW_{ad}, Dynamic friction (Dynamic F), *m* and ΔL parameters are being affected by PVP, gelatin and HPMC film coatings (red circle). Moreover, ΔE trend seems to be most likely associated with the gliding curves obtained for the PVP film and the uncoated disc (light blue circle). Lastly, no linking trend for PEG and carnauba wax can be identified, which indicates that the gliding curves for both polymers are assumed to present little effect on all parameters measured.

4. Discussion

A practical experimental setup was developed with the aim to generate comprehensive gliding profiles and evaluate the gliding performance of different SODF polymer films coatings across an artificial mucous layer. The setup is very flexible, since it can be adapted to any equipment capable of performing measurements in tensile mode and enables the implementation of mucosal surfaces with different thicknesses (e.g., ex

vivo esophageal tissue) by adjusting the height of the metal wheel through which the nylon cord is pulled by the equipment, without affecting the measurement angle.

Table 2. Pearson's correlation and R^2 extrapolation for paired gliding parameters.

Sample 1	Sample 2	Correlation	ρ-value	R^2
ΔE	ML	0.286	0.493	-
PW_{ad}	ML	0.775	0.024	-
ΔL	ML	0.687	0.060	-
m	ML	0.670	0.069	-
FL	ML	0.744	0.034	-
GW_{ad}	ML	0.975	0.000	0.951
TW_{ad}	ML	0.988	0.000	0.976
Static F	ML	1.000	*	1.000
Dynamic F	ML	0.739	0.036	-
PW_{ad}	ΔE	0.582	0.130	-
ΔL	ΔE	0.481	0.228	-
m	ΔE	0.414	0.307	-
FL	ΔE	0.131	0.758	-
GW_{ad}	ΔE	0.356	0.387	-
TW_{ad}	ΔE	0.208	0.621	-
Static F	ΔE	0.286	0.493	-
Dynamic F	ΔE	0.220	0.600	-
ΔL	PW_{ad}	0.813	0.014	0.661
m	PW_{ad}	0.680	0.064	-
FL	PW_{ad}	0.837	0.010	0.701
GW_{ad}	PW_{ad}	0.845	0.008	0.714
TW_{ad}	PW_{ad}	0.746	0.034	-
Static F	PW_{ad}	0.775	0.024	-
Dynamic F	PW_{ad}	0.751	0.032	-
m	ΔL	0.937	0.001	0.878
FL	ΔL	0.537	0.170	-
GW_{ad}	ΔL	0.655	0.078	-
TW_{ad}	ΔL	0.629	0.095	-
Static F	ΔL	0.687	0.060	-
Dynamic F	ΔL	0.931	0.001	0.867
FL	*m*	0.412	0.311	-
GW_{ad}	*m*	0.577	0.134	-
TW_{ad}	*m*	0.600	0.116	-
Static F	*m*	0.670	0.069	-
Dynamic F	*m*	0.874	0.005	0.764
GW_{ad}	FL	0.827	0.011	0.684
TW_{ad}	FL	0.785	0.021	-
Static F	FL	0.744	0.034	-
Dynamic F	FL	0.647	0.083	
TW_{ad}	GW_{ad}	0.973	0.000	0.947
Static F	GW_{ad}	0.975	0.000	0.951
Dynamic F	GW_{ad}	0.697	0.055	-
Static F	TW_{ad}	0.988	0.000	0.976
Dynamic F	TW_{ad}	0.732	0.039	-
Dynamic F	Static F	0.739	0.036	-

In order to successfully meet the purpose of the work and generate meaningful information with regard to the gliding curves obtained for the film polymers tested, the different experimental conditions tested during the optimization of the setup were kept within parameters that can be found on the human esophagus. As such, the gliding velocities and applied weights were based on physiological values obtained on previous

clinical studies for esophageal motility and peristaltic pressure (converted to weight), respectively (Zhang et al., 2013).

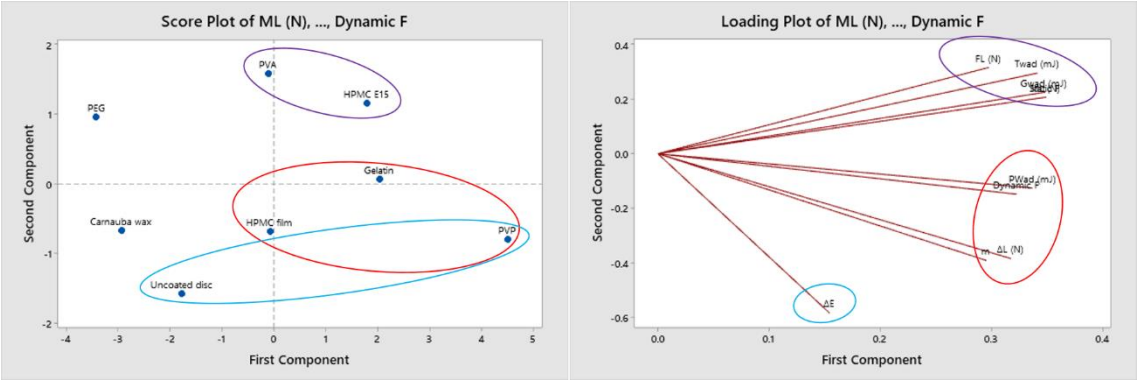

Fig. 8. Principal component analysis (PCA) correlating film coatings with gliding parameters.

Subsequently, the optimized experimental conditions were defined as having a gliding speed of 2.6 cm/s and a weight (pressure) of 62 g (12-g disc, 50-g weight), as these contributed for more detailed and comprehensive gliding profiles (supplementary material, Appendix B). Different polymer film thicknesses have shown no wear effect or influence on the obtained gliding profiles (Supplementary material, Appendix C). As such, a standard coating thickness of 150-200 µm was employed during the evaluations to ensure that all films based on pure polymer could support mechanical preparation for the gliding measurements. Furthermore, the immediate start of the measurement after placing the coated disc into contact with the artificial mucous layer (no wetting time) was purely based on the assumption of immediate swallowing during SODF administration and is expected to better reflect the gliding properties of the tested polymers.

It was defined that an artificial mucous layer length of 16.5 cm would be reasonable to generate comprehensive gliding profiles, something that was later confirmed built on the diversified gliding profiles obtained for the different coatings tested (Allen and Cameron, 2004; Wang, 1991). Previous studies have demonstrated the similarities between human salivary mucins and porcine gastric mucins and confirmed that human mucin can be modelled by porcine gastric mucin. As such, lyophilized mucin was used to develop the artificial mucous layer (Birgit J Teubl et al., 2013). Additionally, the usability of this mucin during development of buccal mucosa *in vitro* permeation systems or simulated saliva formulations (including simulated saliva fluid for dissolution testing) is well established in the literature and has been extensively tested by other researchers (Gittings, 2017; Marques et al., 2011; Park et al., 2007; Roblegg et al., 2012; Teubl et al., 2013).

Previous measurements have shown optimal adhesive properties for the double-sided carbon tape in the preparation of the artificial mucous layer when compared to universal double-sided adhesive tape. This was reflected by a lower coefficient of variation obtained for gliding measurements performed on artificial mucous layer prepared with double-sided carbon tape (Supplementary material, Appendix D). The measurements were also seen to destroy the integrity of the artificial mucous layer after gliding of the testing disc, which required freshly prepared artificial mucous layer for each gliding measurement (Supplementary material, Appendix E).

The resulted gliding curves are characterized by two main domains: a first region (A) related to the force (ML) required to overcome the initial static friction of a defined coated disc, followed by a second region (B) that represents the dynamic (kinetic) friction of that same surface during gliding on the artificial mucous layer. Hence, both static and dynamic friction are relevant parameters, as they will reflect the free gliding performance of the tested polymer coating surfaces. Depending on the type of polymer and its wetting capabilities, the subsequent level of adhesion to the artificial mucous layer will affect the values obtained for ML and ΔE. Moreover, the progressive hydration of the coating surface during gliding on the moistened artificial mucous layer will lead to changes in the dynamic friction and in the gliding force/resistance over time (later stages of gliding).

After a detailed analysis of the gliding performances obtained for the tested polymers, optimal gliding properties are expected for PEG grades, low MW PVA and carnauba wax, as these showed low dynamic friction and their slopes were closer to zero. The quick hydration capacity of PVA-based coatings by hydrogen bonding of its OH groups to water molecules in saliva leads to a moistened coating layer that glides easily by reducing friction. However, with higher MW, longer polymer chains are available to penetrate the mucin structure and generate bonds, increasing the mucoadhesive potential and the dynamic friction. In addition, PEG grades and carnauba wax exhibited lower ML and PW_{ad} (static friction) in comparison to the negative control (uncoated disc) indicating free gliding performance. The improved performance of carnauba wax is related to its hydrophobic nature, which interacts poorly with the artificial mucous layer and optimizes gliding throughout the mucous layer. On the other hand, the waxy composition and quick wettability of PEG grades also provide an optimal coating surface with improved slip. Contrarily, PVP, HPMC and gelatin showed stronger resistance to gliding (higher dynamic friction) and are suggested to gain significant adhesion to the artificial mucous layer. These are polymers are known for its extensive use in the development of mucoadhesive drug delivery systems due to their swelling and crosslinking capabilities (Tracton, 2006).

The applied statistical analysis using PCA proved to be useful to assist in the identification of positive trends between the tested film coatings and the parameters extrapolated from the gliding curves. Therefore, this tool can be very useful in the future to access the impact of individual formulation excipients and their applied concentrations when formulating film coating materials for enhanced gliding performance.

The results are in accordance with previous findings, where discs coated with high MW PVA and HPMC showed increased adhesion to ex vivo porcine esophageal tissue. Furthermore, lower adhesive profiles were obtained for water-insoluble coatings (carnauba wax) and PEG grades, with no correlation to its MW (Smart et al., 2015). Notwithstanding, the outcome of these studies were based on adhesion/detachment ratios retrieved from very small gliding distances, which may not provide enough detailed information about the specific gliding properties of the coatings. As such, this work was developed to provide an experimental setup that enables gliding measurements throughout an extensive mucous layer, contributing for the acquisition of comprehensive profiles that can better evaluate and distinguish the gliding performance of polymer coatings across mucosal surfaces. In addition, the similarity of the results indicate that the artificial mucous layer adopted in this work might potentially be useful for preliminary *in vitro* screening. Nevertheless, additional measurements using ex vivo mucosal tissue (e.g., porcine esophageal tissue) are still required.

The developed experimental setup proved to be suitable in measuring the gliding performance of polymer coating surfaces across artificial mucous layer. With this approach, the hydrodynamic interactions between the coating layer and the moistened mucous layer are taken into account. Therefore, the obtained profiles can be used for future development of new surface coatings that can improve the mucosal gliding properties of SODF and assist with SODF administration (swallowability) regarding special patient populations. Future work will investigate the *in vitro* gliding performance of new surface coating formulations using polymer species that demonstrated optimal gliding properties in this work (and their further combinations).

5. Conclusion

A practical experimental setup was developed in this work to allow the investigation and evaluation of the gliding performance of polymer coatings on an extended artificial mucous layer. The experimental setup can be adapted to any equipment capable of performing measurements in tension mode and the platform setup design supports the layering of mucosal surfaces with different thicknesses without affecting the measuring angle. PEG grades, carnauba wax and low MW PVA showed improved gliding performance as compared to PVP, HPMC and gelatin, which demonstrated both higher

static and dynamic friction. The proposed method generates comprehensive gliding profiles can be useful for future development of new functional surface coatings for SODF. In addition, PCA appears to be a useful tool to generate more information on specific coating excipients and their influence on individual parameters retrieved from the gliding curves.

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Supplementary material

Appendix A: *Influence of the molecular grade on the gliding parameters obtained for PVA and PEG polymers (n = 5).*

Specie	Grade	ML (N)	PW_{ad} (mJ)	*m*	GW_{ad} (mJ)	TW_{ad} (mJ)
PVA	EG-03P	1.047 ± 0.047	3.506 ± 0.642	0.0040 ± 0.008	8.148 ± 1.536	11.654 ± 2.778
	EG-18P	1.479 ± 0.179	7.235 ± 2.264	0.0067 ± 0.005	29.654 ± 3.798	37.990 ± 3.488
	EG-40P	2.058 ± 0.210	10.325 ± 6.332	0.0113 ± 0.025	29.038 ± 4.325	39.363 ± 6.342
PEG	1500	0.151 ± 0.053	1.096 ± 0.269	0.0003 ± 0.001	3.304 ± 0.542	4.400 ± 0.279
	3350	0.158 ± 0.146	1.487 ± 0.248	0.0008 ± 0.004	4.294 ± 0.501	5.782 ± 0.669
	6000	0.382 ± 0.076	2.070 ± 0.654	0.0015 ± 0.009	3.521 ± 1.363	7.391 ± 2.563
Uncoated disc		0.831 ± 0.236	4.015 ± 0.368	0.0188 ± 0.011	7.350 ± 0.262	11.365 ± 0.145

Appendix B: *Evaluation of optimal testing parameters for gliding performance.*

Three experimental variables were defined as being critical to generate curves that can better reflect the gliding properties of the tested polymers: 1) gliding speed; 2) gliding weight; 3) wetting time. Based on cited literature, center points were defined for these variables and tested against their upper and lower limits to identify optimal testing parameters that can provide comprehensive gliding curves. The obtained profiles were analyzed to investigate the sensitivity of each parameter in generating the overall gliding curve.

1) *Gliding speed (A, n = 1)*

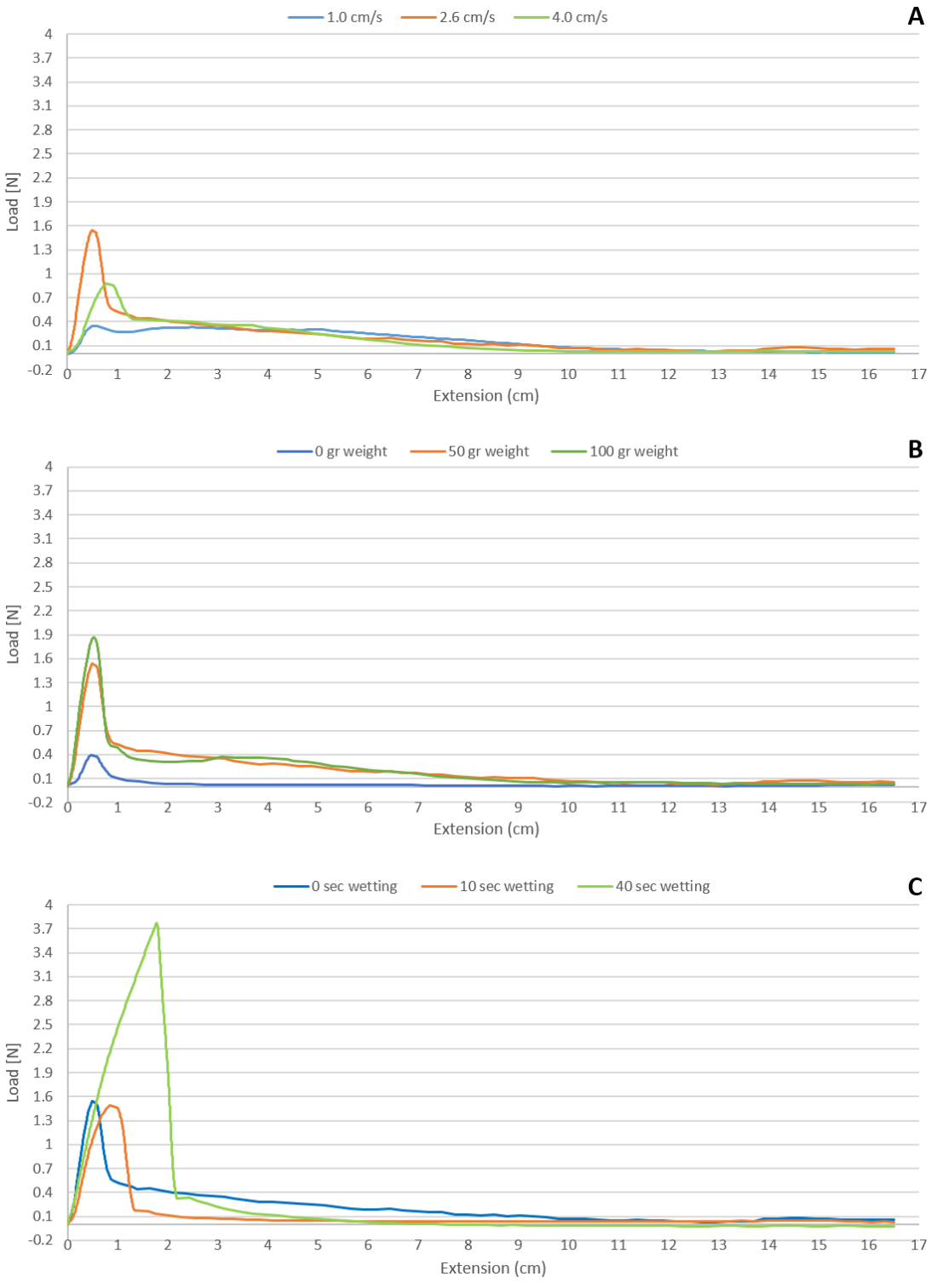
The influence of the tension mode speed on the gliding profile was evaluated using the following velocities: 1.0 cm/s, 2.6 cm/s and 4.0 cm/s.

2) *Gliding weight (B. n = 1)*

The mass applied on top of the gelatin-coated substrates was investigated by performing measurements with no weight, 50 grams and 100 grams.

3) *Wetting time (C, n = 1)*

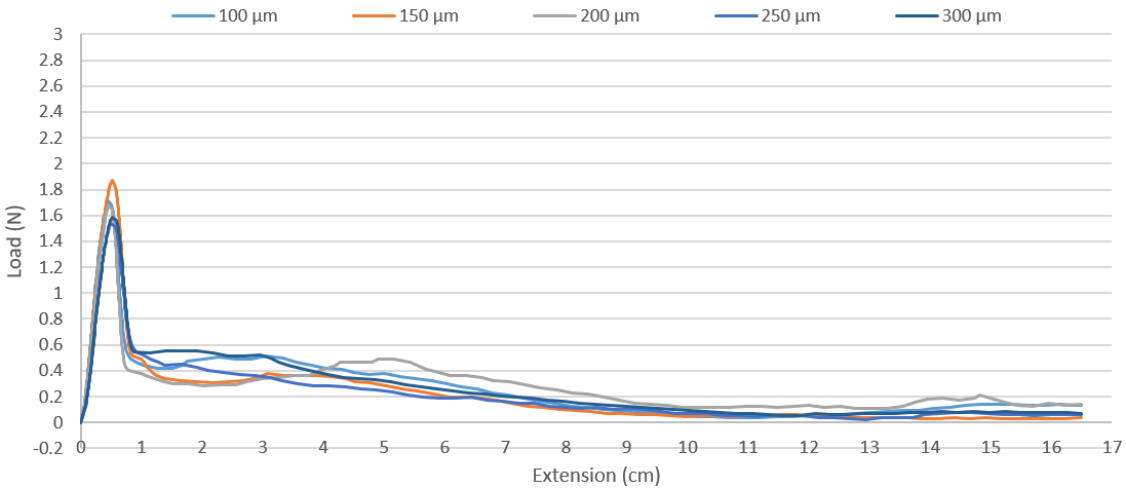
The time elapsed between the positioning of the coated disc on the mucin-coated layer and the beginning of the gliding measurement was tested at 0 s, 10 s and 40 s, respectively.



Having in consideration the curves obtained for the tested parameters regarding gliding speed (A), gliding weight (B) and wetting time (C), it is observed that higher sensitivity during measurements, especially when measuring the static friction (ML), can be obtained when using the center parameters for all variables, as higher comprehensive gliding profiles can be obtained. For this reason, section 2.4.4. describes gliding

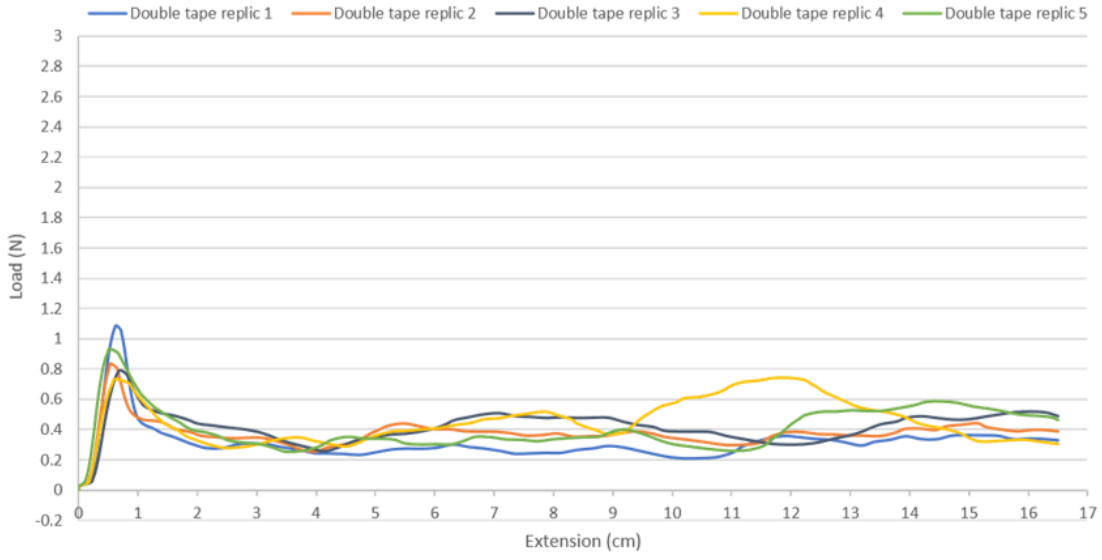
measurements performed at a speed of 2.6 cm/s, with substrate weight of 50 grams and no wetting time applied.

Appendix C. *Evaluation of the gliding performance for gelatin-coated discs presenting different film-layer thicknesses.*



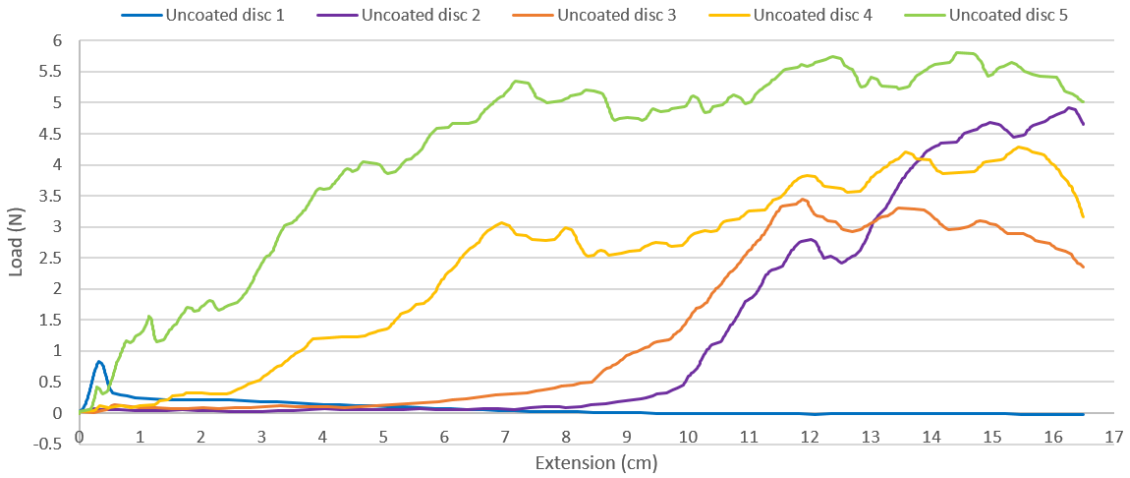
Different coating thicknesses ranging between 100 µm and 300 µm regarding gelatin-coated discs showed no relevant differences on the obtained gliding profiles, indicating that film thickness does not influences the obtained gliding curves.

Appendix D: *Evaluation of double-sided carbon tape as optimal mucin binder substrate (n=5).*



Double-sided carbon tape (carbon-filled material, acrylic adhesive, thickness: 0.16mm) and universal double-sided tape (polyethylene material, natural rubber adhesive, thickness: 0.18 mm) were evaluated for their fixing capacity and provide homogeneous surface layer. For both adhesive tapes, the artificial mucous layer was prepared as described in section 2.4.3. Subsequently, the measurements were recorded after placing an uncoated disc by the left end of the artificial mucous layer. Five assessment were performed for each specimen and the reproducibility was evaluated. A lower coefficient of variation was obtained for gliding measurements performed on artificial mucous layers prepared with double-sided carbon tape (Appendix B) as compared to universal double-sided adhesive tape (data not shown).

Appendix E: *Evaluation of the same artificial mucous layer for several measurements:*



The gliding measurements performed on the same artificial mucous layer with uncoated discs confirmed the destruction of the integrity of the layer right after the first measurement (n = 5). For this reason, it was decided that all measurements should be performed in freshly moistened artificial mucous layers.

- 9 -

An investigation into the relationship between film coating materials and predicted oro-esophageal gliding performance for solid oral dosage forms

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All authors have read and agreed to the published version of the manuscript.

Abstract

Oral drug therapy is generally provided in the form of solid oral dosage forms (SODF) that have to be swallowed intact and move throughout the oro-esophageal system to release the drug content in the stomach or intestine. Previous studies have provided evidence that the oro-esophageal transit of SODF depend on the shape, size, density and surface characteristics of the SODF. To better estimate the impact of the surface characteristics during esophageal transit, an *in vitro* system has been implemented to investigate the gliding performance of different SODF coatings across an artificial mucous layer. In this work, different coating formulations comprised of film-forming and slippery-inducing agents were evaluated using the established *in vitro* artificial mucous system. Polyvinyl alcohol (PVA), polyethylene glycol (PEG) hydroxypropyl methylcellulose (HPMC) and PVA/PEG copolymer (Kollicoat IR) were applied as film-forming agents, whereas sodium alginate, carrageenan, xanthan gum and gellan gum were accessed both as film-forming and slippery-inducing agents, including their subsequent combinations with lecithin and/or sodium lauryl sulfate (SLS). Two additional coatings (PEG-12 Carnauba and PEG-8 Beeswax) composed of polar waxes were also investigated. Xanthan gum and gellan gum displayed a general tendency for superior performance when applied as film-forming agents, being this effect enhanced when combined with carnauba wax/SLS and xanthan gum, as slippery-inducing agents, respectively. Optimal performance was also demonstrated by the polar waxes. The multivariate approach applied allowed a higher granularity in the analysis of the gliding results and supported a better identification of combinations of excipients and respective concentrations required for improved gliding performance.

Keywords: coating gliding performance, film-forming agents, mucosal gliding properties, oro-esophageal transit, predictive swallowability, slippery-inducing agents, Solid oral dosage forms, swallowing-enhancing coatings

1. Introduction

Solid oral dosage forms (SODF) are a major therapeutic intervention in healthcare provision due to non-invasiveness and patient independent handling. Their administration requires that the SODF moves through the oro-esophageal system in order to release its drug content in the stomach or small intestine.

Growing evidence has aroused over the past years for concerns related to the ability of patients to safely swallow SODF, with special considerations on pediatrics, multimorbid and older individuals (Batchelor and Marriott, 2015; Carnaby-Mann and

Crary, 2005; Schiele et al., 2013, 2015; Stegemann et al., 2012). The prevalence of swallowing problems has shown a negative impact on the administration and management of SODF, affecting the effectiveness of drug therapies due to poor patient compliance or increased medication errors related to inappropriate medicine alterations (Fusco et al., 2016; Kelly et al., 2010; Kirkevold and Engedal, 2010). Furthermore, patients with impaired swallowing functions are more susceptible to medication-induced esophageal injuries, as the likelihood for unintended adhesion of the SODF to the oro-esophageal mucosal tissue is higher (Kikendall et al., 1983; Teplick et al., 1980).

Previous studies have shown that the surface polymer characteristics of SODF have a strong influence on both adhesive and gliding profiles throughout the esophagus (Channer and Virjee, 1985; Marvola et al., 1983). In order to improve swallowability and increase safety during oral administration, the SODF should be non-mucosal adherent and slide easily throughout the esophagus along with the peristaltic movements. As such, in order to increase safety and effectiveness of prescribed SODF treatments, further research needs to be placed on the development of appropriate polymer coating compositions that can optimize the gliding properties of SODF across the oro-esophageal mucosa (Chapter 4).

Different *in vitro* systems have been proposed throughout the years to estimate the interaction of SODF polymer surface compositions with mucosal tissues. These methods were based on particle interactions or mechanical forces evaluations (Ivarsson and Wahlgren, 2012; Woertz et al., 2013), as well as on the measurement of the gliding resistance forces across artificial mucous layers or *ex vivo* animal derived esophageal tissue (Smart et al., 2013, 2015). As the *in vitro-in vivo* correlation for the different suggested methods is still pending (Mccargar et al., 2001), the artificial mucous layer system is featured by a simple set up that reproduces the swallowing trajectory and provides the gliding resistance from the initial contact with the mucous until later gliding phases.

In this work, the artificial mucous layer system was used to investigate the gliding performance of different polymer surface compositions. Several formulations composed of film- and slippery-inducing agents were developed and evaluated for their potential applicability to enhance swallowability for SODF. Furthermore, multivariate analysis based on Principal Component Analysis (PCA) was conducted to identify specific combinations of coating excipients that can better contribute for enhanced gliding performance.

2. Experimental section

2.1. Materials

Polyvinyl Alcohol, grade EG-05PW (PVA), was a kind gift from Nippon Gohsei (Uto, Japan). Polyethylene glycol MW 1500 (PEG), was purchased to Alfa Aesar (Lancashire, UK) and sodium alginate was obtained from Roth (Karlsruhe, Germany). Sodium lauryl sulfate (SLS) and lyophilized mucin from porcine stomach were purchased from Sigma-Aldrich (Munich, Germany). Gellan gum was supplied by CP Kelco (Atlanta, USA) and Kollicoat IR (PVA/PEG copolymer) was donated by BASF (Ludwigshafen am Rhein, Germany). Lecithin, carrageenan and xanthan gum were kindly provided by Cargill (Baupte, France). PEG-12 Carnauba and PEG-8 Beeswax were donated by Koster Keunen (Bladel, Netherlands). Finely powdered carnauba wax was a kind gift from Freund Corporation (Tokyo, Japan) and double-sided adhesive carbon tape was purchased to Science Services (Munich, Germany). Gelatin strips were donated by Capsugel (Colmar, France) and the water used was purified through a Milli-Q system (Merck Millipore, Darmstadt, Germany).

2.2. Preparation of aqueous coating formulations

The aqueous coating compositions (Table 1) were prepared by mixing the appropriate amounts of formulation ingredients (using a magnetic stirrer) in purified water. The preparation was executed in three steps, with initial dispersion of the film-forming polymers, followed by the addition of the remaining additives, and finished by adjusting the final weight of the formulation with water. Subsequently, the formulations were stirred at 300 RPM for 3 h until complete homogenization. Moderate heating was applied (40 °C) to coating formulations containing gellan gum to improve polymer dispersion.

2.3. Preparation of film coatings

The films were produced from the aqueous polymer compositions using previously described solvent casting techniques (drying overnight in a vacuum oven at 50 °C) (Hossain et al., 2018; Siemann, 2005). The thickness of the obtained polymer film coatings was approximately 200 ± 15 µm.

2.4. Preparation of coated discs

2.4.1. Film coatings

The polymer films were precisely cut using a scalpel and fixed into the surface of the testing discs using universal double-sided adhesive tape. The surface area of the films was 7.065 cm^2.

2.4.2. Wax melts

PEG-12 Carnauba and PEG-8 Beeswax (Table 1, F34 and F35) were melted over a beaker of boiling water. Subsequently, the testing discs were coated by dipping its lower surface into the molten (using tweezers), and allowed to solidify at room temperature. If required, the procedure was repeated until a coating thickness of 200 µm could be achieved.

2.5. Evaluation of the gliding performance

The *in vitro* apparatus used consisted of the artificial mucous layer system described in Chapter 6 (Drumond and Stegemann, 2019). All evaluations were performed at room temperature and fresh artificial mucous layers were prepared for every coated disc gliding assessment. After humidification of the mucous layer, the coated testing disc containing on top a 50-g weight was directed to the left end of the gliding region and the measurement was promptly initiated after contact of the coating with the mucous layer (no wetting time), in tension mode. The force (resistance) required to glide the coated disc at a constant speed of 2.6 cm/s through a gliding distance of 16.5 cm was measured with the load cell and automatically recorded with the equipment's Bluehill® software. Three replicates were performed for each polymer coating composition.

2.6. Multivariate analysis

Principal Component Analysis (PCA) was used to dimensionality-reduce the different gliding variables into smaller data sets containing only formulations composed of the same film-forming agent (Otsuka et al., 2011, Van Snick et al. 2018). The purpose was to identify which concentrations and combinations of slippery-inducing agents could better contribute for enhanced gliding performance regarding each group of film-forming agents (PVA, Kollicoat IR, HPMC, sodium alginate, carrageenan, xanthan gum and gellan gum). The gliding outputs selected for the analysis were both static and dynamic frictions (Dynamic F), as these are important indicators of enhanced gliding performance. The analysis was performed using Minitab® 18 software (SquareCircle Global FZ LLC).

Table 1. Film coating compositions prepared and evaluated for gliding performance.

Coating	Film-forming agents									Slippery-inducing agents					
	PVA	Kollicoat IR	HPMC	Sodium alginate	Carrage	Xanthan Gum	Gellan Gum	PEG	Carnauba wax	Lecithin	Carrage	Xanthan Gum	Gellan Gum	Sodium alginate	SLS
F1	2.0	-	-	-	-	-	-	1.0	0.10	-	-	-	-	-	0.20
F2	2.0	-	-	-	-	-	-	1.0	0.30	-	-	-	-	-	0.40
F3	2.0	-	-	-	-	-	-	1.0	0.50	-	-	-	-	-	0.60
F4	4.0	-	-	-	-	-	-	1.0	0.10	-	-	-	-	-	0.20
F5	4.0	-	-	-	-	-	-	1.0	0.30	-	-	-	-	-	0.40
F6	4.0	-	-	-	-	-	-	1.0	0.50	-	-	-	-	-	0.60
F7	6.0	-	-	-	-	-	-	1.0	0.10	-	-	-	-	-	0.20
F8	6.0	-	-	-	-	-	-	1.0	0.30	-	-	-	-	-	0.40
F9	6.0	-	-	-	-	-	-	1.0	0.50	-	-	-	-	-	0.60
F10	2.0	-	-	-	-	-	-	1.0	-	0.30	-	-	-	-	-
F11	4.0	-	-	-	-	-	-	1.0	-	0.70	-	-	-	-	-
F12	6.0	-	-	-	-	-	-	1.0	-	1.10	-	-	-	-	-
F13	4.0	-	-	-	-	-	-	1.0	-	0.70	-	-	-	-	0.40
F14	2.0	-	-	-	-	-	-	1.0	-	-	0.30	-	-	-	-
F15	4.0	-	-	-	-	-	-	1.0	-	-	0.70	-	-	-	-
F16	6.0	-	-	-	-	-	-	1.0	-	-	1.10	-	-	-	-
F17	6.0	-	-	-	-	-	-	1.0	-	-	1.10	-	-	-	0.60
F18	2.0	-	-	-	-	-	-	1.0	-	-	-	0.10	-	-	-
F19	4.0	-	-	-	-	-	-	1.0	-	-	-	0.30	-	-	-
F20	6.0	-	-	-	-	-	-	1.0	-	-	-	0.50	-	-	-
F21	2.0	-	-	-	-	-	-	1.0	-	-	-	0.10	-	-	0.20
F22	2.0	-	-	-	-	-	-	1.0	-	-	-	-	0.10	-	-
F23	3.0	-	-	-	-	-	-	1.0	-	-	-	-	0.15	-	-
F24	4.0	-	-	-	-	-	-	1.0	-	-	-	-	0.20	-	-
F25	2.0	-	-	-	-	-	-	1.0	-	-	-	-	0.10	-	0.20

Table 1 (cont.). Film coating compositions prepared and evaluated for gliding performance.

Coating	Film-forming agents							Slippery-inducing agents							
	PVA	Kollicoat IR	HPMC	Sodium alginate	Carrage	Xanthan Gum	Gellan Gum	PEG	Carnauba wax	Lecithin	Carrage	Xanthan Gum	Gellan Gum	Sodium alginate	SLS
F26	2.0	-	-	-	-	-	-	1.0	-	-	-	-	-	0.10	0.20
F27	4.0	-	-	-	-	-	-	1.0	-	-	-	-	-	0.30	0.40
F28	6.0	-	-	-	-	-	-	1.0	-	-	-	-	-	0.50	0.60
F29	-	2.0	-	-	-	-	-	1.0	0.10	-	-	-	-	-	0.20
F30	-	4.0	-	-	-	-	-	1.0	0.30	-	-	-	-	-	0.40
F31	-	6.0	-	-	-	-	-	1.0	0.50	-	-	-	-	-	0.60
F32	2.0	2.0	-	-	-	-	-	1.0	0.30	0.30	-	-	-	-	0.40
F33	2.0	2.0	-	-	-	-	-	1.0	0.30	0.70	-	-	-	-	0.40
F34*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F35*	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F36	-	-	2.0	-	-	-	-	1.0	0.10	-	-	-	-	-	0.20
F37	-	-	4.0	-	-	-	-	1.0	0.30	-	-	-	-	-	0.40
F38	-	-	6.0	-	-	-	-	1.0	0.50	-	-	-	-	-	0.60
F39	-	-	2.0	-	-	-	-	1.0	-	0.30	-	-	-	-	0.20
F40	-	-	4.0	-	-	-	-	1.0	-	0.70	-	-	-	-	0.40
F41	-	-	6.0	-	-	-	-	1.0	-	1.10	-	-	-	-	0.60
F42	-	-	2.0	-	-	-	-	1.0	-	-	1.10	-	-	-	0.20
F43	-	-	3.0	-	-	-	-	1.0	-	-	0.70	-	-	-	0.40
F44	-	-	4.0	-	-	-	-	1.0	-	-	0.30	-	-	-	0.60
F45	-	-	2.0	-	-	-	-	1.0	-	-	-	0.50	-	-	0.20
F46	-	-	3.0	-	-	-	-	1.0	-	-	-	0.30	-	-	0.40
F47	-	-	4.0	-	-	-	-	1.0	-	-	-	0.10	-	-	0.60
F48	-	-	2.0	-	-	-	-	1.0	-	-	-	-	0.20	-	0.20
F49	-	-	3.0	-	-	-	-	1.0	-	-	-	-	0.15	-	0.40
F50	-	-	4.0	-	-	-	-	1.0	-	-	-	-	0.10	-	0.60

Table 1 (cont.). Film coating compositions prepared and evaluated for gliding performance.

Coating	Film-forming agents								Slippery-inducing agents						
	PVA	Kollicoat IR	HPMC	Sodium alginate	Carrage	Xanthan Gum	Gellan Gum	PEG	Carnauba wax	Lecithin	Carrage	Xanthan Gum	Gellan Gum	Sodium alginate	SLS
F51	-	-	2.0	-	-	-	-	1.0	-	-	-	-	-	0.50	0.20
F52	-	-	3.0	-	-	-	-	1.0	-	-	-	-	-	0.30	0.40
F53	-	-	4.0	-	-	-	-	1.0	-	-	-	-	-	0.10	0.60
F54	-	-	-	0.75	-	-	-	1.0	0.10	-	-	-	-	-	0.20
F55	-	-	-	1.00	-	-	-	1.0	0.30	-	-	-	-	-	0.40
F56	-	-	-	1.25	-	-	-	1.0	0.50	-	-	-	-	-	0.60
F57	-	-	-	0.75	-	-	-	1.0	-	0.30	-	-	-	-	0.20
F58	-	-	-	1.00	-	-	-	1.0	-	0.70	-	-	-	-	0.40
F59	-	-	-	1.25	-	-	-	1.0	-	1.10	-	-	-	-	0.60
F60	-	-	-	0.75	-	-	-	1.0	-	-	1.10	-	-	-	0.20
F61	-	-	-	1.00	-	-	-	1.0	-	-	0.70	-	-	-	0.40
F62	-	-	-	1.25	-	-	-	1.0	-	-	0.30	-	-	-	0.60
F63	-	-	-	0.75	-	-	-	1.0	-	-	-	0.50	-	-	0.20
F64	-	-	-	1.00	-	-	-	1.0	-	-	-	0.30	-	-	0.40
F65	-	-	-	1.25	-	-	-	1.0	-	-	-	0.10	-	-	0.60
F66	-	-	-	0.75	-	-	-	1.0	-	-	-	-	0.20	-	0.20
F67	-	-	-	1.00	-	-	-	1.0	-	-	-	-	0.15	-	0.40
F68	-	-	-	1.25	-	-	-	1.0	-	-	-	-	0.10	-	0.60
F69	-	-	-	-	0.75	-	-	1.0	0.10	-	-	-	-	-	0.20
F70	-	-	-	-	1.00	-	-	1.0	0.30	-	-	-	-	-	0.40
F71	-	-	-	-	1.25	-	-	1.0	0.50	-	-	-	-	-	0.60
F72	-	-	-	-	0.75	-	-	1.0	-	0.30	-	-	-	-	0.20
F73	-	-	-	-	1.00	-	-	1.0	-	0.70	-	-	-	-	0.40
F74	-	-	-	-	1.25	-	-	1.0	-	1.10	-	-	-	-	0.60
F75	-	-	-	-	0.75	-	-	1.0	-	-	-	0.50	-	-	0.20

Table 1 (cont.). Film coating compositions prepared and evaluated for gliding performance.

Coating	Film-forming agents									Slippery-inducing agents					
	PVA	Kollicoat IR	HPMC	Sodium alginate	Carrage	Xanthan Gum	Gellan Gum	PEG	Carnauba wax	Lecithin	Carrage	Xanthan Gum	Gellan Gum	Sodium alginate	SLS
F76	-	-	-	-	1.00	-	-	1.0	-	-	-	0.30	-	-	0.40
F77	-	-	-	-	1.25	-	-	1.0	-	-	-	0.10	-	-	0.60
F78	-	-	-	-	0.75	-	-	1.0	-	-	-	-	0.20	-	0.20
F79	-	-	-	-	1.00	-	-	1.0	-		-	-	0.15	-	0.40
F80	-	-	-	-	1.25	-	-	1.0	-		-	-	0.10	-	0.60
F81	-	-	-	-	0.75	-	-	1.0	-		-	-	-	0.50	0.20
F82	-	-	-	-	1.0	-	-	1.0	-		-	-	-	0.30	0.40
F83	-	-	-	-	1.25	-	-	1.0	-	_	-	-	-	0.10	0.60
F84	-	-	-	-	-	0.40	-	1.0	0.10	_	-	-	-	-	0.20
F85	-	-	-	-	-	0.50	-	1.0	0.30	_	-	-	-	-	0.40
F86	-	-	-	-	-	0.60	-	1.0	0.50	-	_	-	-	-	0.60
F87	-	-	-	-	-	0.40	-	1.0	-	0.30	_	-	-	-	0.20
F88	-	-	-	-	-	0.50	-	1.0	-	0.70	_	-	-	-	0.40
F89	-	-	-	-	-	0.60	-	1.0	-	1.10	-	-	-	-	0.60
F90	-	-	-	-	-	0.40	-	1.0	-	-	1.10	-	-	-	0.20
F91	-	-	-	-	-	0.50	-	1.0	-	-	0.70	-	-	-	0.40
F92	-	-	-	-	-	0.60	-	1.0	-	-	0.30	-	-	-	0.60
F93	-	-	-	-	-	0.40	-	1.0	-	-	-	-	0.20	-	0.20
F94	-	-	-	-	-	0.50	-	1.0	-	-	-	-	0.15	-	0.40
F95	-	-	-	-	-	0.60	-	1.0	-	-	-	-	0.10	-	0.60
F96	-	-	-	-	-	0.40	-	1.0	-	-	-	-	-	0.50	0.20
F97	-	-	-	-	-	0.50	-	1.0	-	-	-	-	-	0.30	0.40
F98	-	-	-	-	-	0.60	-	1.0	-	_	-	-	-	0.10	0.60
F99	-	-	-	-	-	-	0.10	1.0	0.10	_	-	-	-	-	0.20
F100	-	-	-	-	-	-	0.20	1.0	0.30	_	-	-	-	-	0.40

Table 1 (cont.). Film coating compositions prepared and evaluated for gliding performance.

Coating	Film-forming agents									Slippery-inducing agents					
	PVA	Kollicoat IR	HPMC	Sodium alginate	Carrage	Xanthan Gum	Gellan Gum	PEG	Carnauba wax	Lecithin	Carrage	Xanthan Gum	Gellan Gum	Sodium alginate	SLS
F101	-	-	-	-	-	-	0.30	1.0	0.50	-	-	-	-	-	0.60
F102	-	-	-	-	-	-	0.10	1.0	-	0.30	-	-	-	-	0.20
F103	-	-	-	-	-	-	0.20	1.0	-	0.70	-	-	-	-	0.40
F104	-	-	-	-	-	-	0.30	1.0	-	1.10	-	-	-	-	0.60
F105	-	-	-	-	-	-	0.10	1.0	-	-	1.10	-	-	-	0.20
F106	-	-	-	-	-	-	0.20	1.0	-	-	0.70	-	-	-	0.40
F107	-	-	-	-	-	-	0.30	1.0	-	-	0.30	-	-	-	0.60
F108	-	-	-	-	-	-	0.10	1.0	-	-	-	0.50	-	-	0.20
F109	-	-	-	-	-	-	0.20	1.0	-	-	-	0.30	-	-	0.40
F110	-	-	-	-	-	-	0.30	1.0	-	-	-	0.10	-	-	0.60
F111	-	-	-	-	-	-	0.10	1.0	-	-	-	-	-	0.50	0.20
F112	-	-	-	-	-	-	0.20	1.0	-	-	-	-	-	0.30	0.40
F113	-	-	-	-	-	-	0.30	1.0	-	-	-	-	-	0.10	0.60
F114	-	-	-	-	-	-	0.20	1.5	-	-	-	0.30	-	-	0.40
F115	-	-	-	-	-	-	0.20	2.0	-	-	-	0.30	-	-	0.40
F116	-	-	-	-	-	-	0.20	2.5	-	-	-	0.30	-	-	0.40
F117	-	-	-	-	-	-	0.20	3.0	-	-	-	0.30	-	-	0.40

*F34 – 100% melted wax PEG-12 Carnauba

*F35 – 100% melted wax PEG-8 Beeswax

Positive control – Gelatin film strip

Negative control – Uncoated disc

3. Results

3.1. Evaluation of the gliding performance

The relevant gliding performance parameters (ML, PW_{ad}, *m*, FL, GW_{ad}, TW_{ad}) obtained from the different formulations tested are summarized in Table 2. In addition, the static and dynamic frictions for each formulation were calculated based on their gliding curves and will be further analyzed in more detail. For an easier identification and interpretation of the results, the tested formulations were combined in groups based on their film-forming agent: PVA (F1-F28), Kollicoat IR (F29-F33), waxes (F34-F35), HPMC (F36-F48), sodium alginate (F54-F68), carrageenan (F69-F83), xanthan gum (F84-F98) and gellan gum (F99-F117).

Table 2. Gliding performance parameters obtained for the film coatings tested (n=3)*.

Coating	ML (N)	PWad (mJ)	*m*	FL (N)	Gwad (mJ)	TWad (mJ)	Static friction	Dynamic friction
F1	0.36±0.09	4.04±0.79	0.00±0.00	0.03±0.01	3.95±0.56	7.99±0.78	0.0058	0.0008
F2	0.43±0.12	6.59±0.14	0.02±0.00	0.01±0.00	10.16±2.36	16.75±2.36	0.0069	0.0015
F3	0.72±0.21	6.24±0.58	0.02±0.01	0.01±0.00	7.41±1.45	13.65±2.33	0.0116	0.0012
F4	0.42±0.11	3.56±0.22	0.00±0.00	0.01±0.00	5.01±1.98	8.57±1.54	0.0068	0.0008
F5	0.72±0.13	5.09±0.14	0.02±0.00	0.04±0.01	9.24±3.20	14.32±2.22	0.0116	0.0010
F6	0.50± 0.17	5.61±0.26	0.00±0.00	0.05±0.01	10.09±1.47	15.70±1.69	0.0080	0.0016
F7	0.47±0.15	5.38±0.47	0.02±0.01	0.05±0.01	14.27±3.45	19.65±2.65	0.0076	0.0020
F8	0.33±0.11	3.33±0.12	0.01±0.00	0.10±0.03	21.18±6.84	24.51±3.54	0.0053	0.0024
F9	0.41±0.17	5.77±0.27	0.00±0.00	0.06±0.02	8.63±2.22	14.40±1.74	0.0066	0.0014
F10	1.20±0.35	12.65±1.3	0.01±0.00	0.04±0.01	25.65±7.69	38.30±9.54	0.0193	0.0019
F11	1.78±0.48	3.29±0.05	0.01±0.00	0.01±0.00	8.55±1.25	11.85±4.50	0.0287	0.0007
F12	1.13±0.29	1.84±0.02	0.01±0.00	0.03±0.01	14.86±2.44	16.70±3.65	0.0182	0.0009
F13	1.79±0.33	6.09±0.95	0.01±0.00	0.07±0.03	15.70±1.85	21.79±7.44	0.0289	0.0018
F14	2.02±0.54	9.20±0.85	0.04±0.02	0.26±0.01	69.14±12.3	78.34±15.65	0.0326	0.0076
F15	2.17±0.47	7.48±0.47	0.00±0.00	0.14±0.01	28.36±7.58	35.84±8.78	0.0350	0.0030
F16	1.34±0.26	3.89±0.54	0.00±0.00	0.14±0.01	23.90±4.36	27.79±9.66	0.0216	0.0024
F17	0.59±0.15	2.92±0.35	0.01±0.00	0.08±0.00	23.63±8.24	26.55±4.87	0.0095	0.0025
F18	0.44±0.01	1.98±0.01	0.01±0.00	0.02±0.00	8.42±1.54	10.40±1.54	0.0071	0.0009
F19	0.64±0.253	2.65±0.03	0.00±0.00	0.07±0.00	16.95±3.65	19.60±6.54	0.0103	0.0018
F20	0.96±0.17	6.60±0.78	0.00±0.00	0.19±0.00	16.39±4.58	22.99±2.54	0.0155	0.0025
F21	0.34±0.01	4.84±0.04	0.00±0.00	0.02±0.01	6.28±1.11	11.12±1.87	0.0055	0.0010
F22	0.46±0.03	11.22±2.4	0.01±0.00	0.02±0.00	10.79±0.56	22.01±4.65	0.0074	0.0023
F23	0.78±0.11	1.34±0.58	0.03±0.15	0.22±0.01	60.58±15.6	61.92±12.36	0.0126	0.0068
F24	0.99±0.33	2.81±0.47	0.01±0.00	0.80±0.20	133.85±39.2	136.67±32.1	0.0160	0.0134
F25	0.33±0.15	1.26±0.04	0.01±0.00	0.09±0.00	26.50±4.36	27.76±6.88	0.0053	0.0027
F26	0.35±0.09	3.21±0.69	0.01±0.00	0.09±0.00	22.38±4.20	25.58±9.84	0.0056	0.0025
F27	0.34±0.07	1.49±0.35	0.01±0.00	0.02±0.00	10.76±1.36	12.25±4.32	0.0055	0.0011
F28	0.32±0.01	2.98±0.54	0.01±0.00	0.07±0.00	15.46±2.44	18.44±2.54	0.0052	0.0018
F29	1.50±0.49	2.19±0.15	0.01±0.00	0.17±0.01	25.42±5.64	27.60±4.54	0.0242	0.0026
F30	0.73±0.29	0.85±0.04	0.00±0.00	0.08±0.01	15.01±1.74	15.86±3.25	0.0118	0.0014

Table 2. Gliding performance parameters obtained for the film coatings tested (n=3)*.

Coating	ML (N)	PWad (mJ)	*m*	FL (N)	Gwad (mJ)	TWad (mJ)	Static friction	Dynamic friction
F31	1.04±0.44	1.29±0.33	0.00±0.00	0.07±0.01	17.06±4.56	18.35±1.45	0.0168	0.0017
F32	0.54±0.29	5.50±1.40	0.00±0.00	0.12±0.03	19.16±1.36	24.66±4.55	0.0087	0.0023
F33	0.47±0.30	2.49±0.25	0.01±0.05	0.11±0.04	31.86±4.87	34.35±6.87	0.0076	0.0033
F34	0.22±0.11	2.13±0.34	0.01±0.03	0.02±0.00	5.19±1.20	7.32±1.44	0.0035	0.0006
F35	0.34±0.12	3.08±0.99	0.01±0.01	0.03±0.00	9.55±0.39	12.63±1.20	0.0055	0.0011
F36	0.87±0.33	2.79±0.77	0.00±0.00	0.08±0.01	12.66±1.22	15.46±0.98	0.0140	0.0014
F37	0.88±0.24	2.52±0.14	0.00±0.00	0.06±0.01	16.11±0.87	18.63±1.77	0.0142	0.0014
F38	1.62±0.75	8.71±1.45	0.02±0.03	0.05±0.01	23.11±0.95	31.90±9.85	0.0261	0.0024
F39	0.60±0.14	3.83±0.23	0.00±0.00	0.14±0.00	28.42±1.47	32.24±8.98	0.0097	0.0030
F40	0.55±0.12	2.67±0.05	0.00±0.00	0.21±0.01	27.23±2.47	29.90±7.98	0.0089	0.0028
F41	0.65±0.19	6.26±0.98	0.00±0.00	0.15±0.00	27.10±2.98	33.35±8.29	0.0105	0.0031
F42	0.95±0.25	13.54±2.45	0.01±0.00	0.23±0.00	46.38±5.68	59.92±14.87	0.0153	0.0058
F43	0.50±0.10	3.73±0.45	0.00±0.00	0.31±0.01	47.80±8.39	51.53±11.25	0.0081	0.0051
F44	0.66±0.14	2.37±0.47	0.02±0.03	0.16±0.00	34.63±9.65	37.00±9.87	0.0106	0.0038
F45	0.56±0.11	4.05±0.96	0.01±0.00	0.03±0.00	12.92±0.74	16.98±4.85	0.0090	0.0014
F46	0.70±0.25	6.14±0.65	0.01±0.00	0.03±0.00	14.44±1.36	20.58±9.33	0.0113	0.0018
F47	0.69±0.21	6.38±1.05	0.01±0.00	0.04±0.00	12.27±0.88	18.65±7.85	0.0111	0.0016
F48	0.71±0.19	4.06±0.45	0.04±0.01	0.07±0.00	52.92±15.6	56.98±16.25	0.0115	0.0056
F49	0.87±0.24	4.46±0.47	0.05±0.01	0.15±0.00	62.33±18.4	66.79±19.84	0.0140	0.0072
F50	0.70±0.11	8.79±0.99	0.02±0.00	0.22±0.01	34.99±9.85	43.78±15.41	0.0113	0.0043
F51	0.56±0.07	3.99±0.87	0.02±0.00	0.10±0.00	30.11±4.85	30.11±11.11	0.0090	0.0027
F52	0.76±0.14	5.73±0.41	0.02±0.00	0.08±0.00	32.21±7.85	37.94±9.87	0.0123	0.0034
F53	0.61±0.13	5.30±0.56	0.01±0.00	0.09±0.00	16.49±1.65	21.79±4.51	0.0098	0.0020
F54	0.74±0.17	1.55±0.04	0.02±0.00	0.25±0.01	61.27±19.3	62.81±15.04	0.0119	0.0068
F55	0.50±0.11	1.30±0.01	0.02±0.00	0.16±0.01	38.02±7.95	39.32±8.70	0.0081	0.0040
F56	0.45±0.09	3.05±0.58	0.01±0.00	0.04±0.00	14.64±1.62	17.69±4.87	0.0073	0.0015
F57	0.90±0.19	1.53±0.25	0.02±0.00	0.31±0.01	81.44±21.6	82.98±17.44	0.0145	0.0089
F58	1.07±0.23	24.23±6.24	0.07±0.02	0.19±0.01	69.84±19.2	94.07±21.36	0.0173	0.0110
F59	0.97±0.22	2.16±0.45	0.01±0.00	0.65±0.25	105.11±39.4	107.27±33.84	0.0156	0.0110
F60	0.53±0.04	4.05±0.95	0.01±0.00	0.45±0.15	64.11±16.2	68.16±14.77	0.0085	0.0068
F61	0.81±0.14	31.64±6.48	0.05±0.02	0.11±0.01	39.76±8.95	71.41±19.65	0.0131	0.0077
F62	0.59±0.05	4.78±0.47	0.02±0.00	0.07±0.00	26.04±4.65	30.81±7.85	0.0095	0.0028
F63	0.57±0.06	4.80±0.88	0.03±0.01	0.14±0.00	44.21±7.65	49.00±9.78	0.0092	0.0047
F64	0.63±0.09	3.62±0.15	0.01±0.00	0.06±0.00	27.82±5.62	31.44±4.68	0.0102	0.0029
F65	0.70±0.10	3.63±0.36	0.01±0.00	0.04±0.00	9.01±1.95	12.64±1.03	0.0113	0.0010
F66	1.38±0.45	9.37±0.77	0.08±0.03	0.16±0.00	70.02±12.35	79.38±14.54	0.0223	0.0110
F67	0.76±0.31	1.90±0.04	0.04±0.01	0.12±0.00	57.61±14.50	59.51±11.33	0.0123	0.0065
F68	1.01±0.44	3.09±0.25	0.04±0.01	0.22±0.01	78.38±19.52	81.47±18.74	0.0163	0.0092
F69	0.79±0.15	5.82±0.98	0.03±0.01	0.07±0.00	32.59±4.56	38.41±9.04	0.0127	0.0034
F70	0.83±0.36	8.52±1.23	0.01±0.00	0.04±0.00	11.85±1.62	20.37±4.65	0.0134	0.0016
F71	0.93±0.33	6.68±0.55	0.01±0.00	0.05±0.00	10.37±0.95	17.05±1.25	0.0150	0.0014
F72	0.63±0.15	5.57±0.97	0.01±0.00	0.05±0.00	10.54±0.25	16.10±0.47	0.0102	0.0013
F73	0.54±0.23	3.71±0.15	0.01±0.00	0.04±0.00	9.21±0.47	12.91±1.44	0.0087	0.0010
F74	0.63±0.04	6.05±0.38	0.01±0.00	0.08±0.00	17.26±0.88	23.31±2.33	0.0102	0.0021
F75	0.48±0.02	4.53±0.77	0.01±0.00	0.06±0.00	15.50±0.98	20.04±2.47	0.0077	0.0017

Table 2. Gliding performance parameters obtained for the film coatings tested (n=3)*.

Coating	ML (N)	PWad (mJ)	*m*	FL (N)	Gwad (mJ)	TWad (mJ)	Static friction	Dynamic friction
F76	0.62±0.11	5.17±1.24	0.02±0.01	0.10±0.05	29.26±2.65	34.43±2.78	0.0100	0.0031
F77	0.57±0.13	5.18±1.39	0.01±0.00	0.09±0.00	18.88±1.85	24.06±1.65	0.0092	0.0021
F78	0.43±0.10	4.16±0.99	0.02±0.00	0.06±0.00	20.19±2.65	24.36±1.77	0.0069	0.0023
F79	0.44±0.18	3.81±0.45	0.02±0.00	0.05±0.00	35.38±4.58	39.19±3.88	0.0071	0.0036
F80	0.58±0.20	5.74±1.40	0.01±0.00	0.04±0.00	9.30±0.58	15.04±1.54	0.0094	0.0011
F81	0.34±0.03	2.55±0.05	0.01±0.00	0.13±0.00	38.10±4.65	40.65±6.87	0.0055	0.0040
F82	0.64±0.04	5.87±1.23	0.02±0.00	0.06±0.00	22.53±2.65	28.41±3.66	0.0103	0.0024
F83	0.71±0.08	8.65±2.54	0.02±0.01	0.36±0.13	35.11±3.52	43.76±7.84	0.0115	0.0040
F84	0.39±0.10	1.94±0.14	0.01±0.00	0.05±0.00	14.12±2.65	16.06±2.69	0.0063	0.0015
F85	0.26±0.09	0.94±0.03	0.00±0.00	0.05±0.00	7.43±1.05	8.37±0.54	0.0042	0.0008
F86	0.40±0.02	2.37±0.55	0.00±0.00	0.05±0.00	11.08±0.99	13.45±0.99	0.0065	0.0012
F87	0.43±0.04	2.99±0.47	0.01±0.00	0.04±0.00	16.14±0.84	19.13±1.00	0.0069	0.0017
F88	0.32±0.02	1.65±0.22	0.01±0.00	0.08±0.00	21.04±3.65	22.69±1.47	0.0052	0.0021
F89	0.42±0.03	3.21±0.36	0.01±0.00	0.05±0.01	14.66±2.54	17.69±1.02	0.0068	0.0015
F90	0.67±0.09	5.18±1.21	0.02±0.01	0.05±0.00	22.91±4.65	28.09±2.36	0.0092	0.0024
F91	0.58±0.01	5.06±1.33	0.01±0.00	0.20±0.00	37.66±3.65	42.79±8.47	0.0094	0.0048
F92	0.59±0.05	3.64±0.55	0.01±0.00	0.15±0.00	24.94±2.22	28.58±4.65	0.0095	0.0026
F93	0.51±0.03	3.17±0.74	0.01±0.00	0.10±0.00	19.09±4.56	22.26±6.87	0.0082	0.0021
F94	0.45±0.02	2.47±0.88	0.00±0.00	0.11±0.00	21.84±1.85	24.31±4.54	0.0073	0.0023
F95	0.45±0.01	3.74±0.33	0.00±0.00	0.13±0.00	20.81±3.65	24.55±4.52	0.0073	0.0023
F96	0.59±0.06	6.53±0.21	0.01±0.00	0.06±0.00	16.16±0.58	22.69±3.99	0.0095	0.0018
F97	0.53±0.05	4.59±0.11	0.02±0.00	0.06±0.00	18.31±0.97	22.91±3.54	0.0085	0.0020
F98	0.55±0.04	4.84±0.14	0.02±0.01	0.11±0.01	25.87±2.54	30.70±4.44	0.0089	0.0027
F99	0.77±0.09	2.90±0.33	0.04±0.01	0.06±0.00	46.63±8.47	49.52±5.21	0.0124	0.0055
F100	0.43±0.01	2.93±0.11	0.02±0.01	0.05±0.00	26.23±5.64	29.16±3.01	0.0069	0.0027
F101	0.42±0.02	2.74±0.02	0.00±0.00	0.05±0.00	11.92±3.65	14.66±1.78	0.0068	0.0010
F102	0.70±0.04	5.75±0.87	0.02±0.00	0.05±0.00	15.36±2.54	21.11±2.01	0.0113	0.0018
F103	0.58±0.03	4.03±0.25	0.03±0.01	0.08±0.00	37.75±6.87	41.78±6.54	0.0094	0.0040
F104	0.57±0.01	3.66±0.33	0.02±0.01	0.07±0.00	24.54±6.65	28.19±3.89	0.0092	0.0026
F105	0.78±0.02	5.82±0.47	0.01±0.00	0.17±0.01	31.76±9.84	37.57±4.54	0.0126	0.0035
F106	0.51±0.00	3.76±0.66	0.01±0.00	0.07±0.00	15.96±1.65	19.72±3.66	0.0082	0.0017
F107	0.56±0.01	3.06±0.21	0.02±0.00	0.07±0.00	60.02±9.54	31.31±2.33	0.0090	0.0029
F108	0.54±0.02	3.51±0.22	0.01±0.00	0.07±0.00	19.60±0.54	23.11±1.02	0.0087	0.0020
F109	0.73±0.06	4.68±0.47	0.00±0.00	0.07±0.00	9.77±1.62	14.44±2.33	0.0118	0.0011
F110	0.90±0.07	5.19±0.89	0.01±0.00	0.03±0.00	9.67±0.99	14.85±2.01	0.0145	0.0011
F111	0.75±0.08	4.97±0.99	0.02±0.01	0.10±0.00	27.74±1.64	32.71±7.85	0.0121	0.0030
F112	0.54±0.04	3.61±0.87	0.01±0.00	0.03±0.00	12.59±0.59	16.21±0.98	0.0087	0.0014
F113	0.72±0.02	5.39±0.22	0.01±0.00	0.05±0.00	14.09±1.33	19.48±1.21	0.0116	0.0016
F114	0.74±0.02	5.32±0.84	0.01±0.00	0.06±0.00	11.87±0.54	17.20±0.99	0.0119	0.0015
F115	0.85±0.11	4.30±0.36	0.02±0.00	0.06±0.00	32.59±9.88	36.89±3.21	0.0137	0.0034
F116	0.95±0.12	3.93±0.58	0.02±0.01	0.06±0.00	18.16±6.54	22.09±2.22	0.0153	0.0020
F117	0.63±0.15	4.74±0.54	0.01±0.00	0.06±0.00	18.42±3.35	23.16±1.74	0.0102	0.0020
Positive	1.71±0.15	8.34±1.36	0.03±0.10	0.07±0.01	25.43±4.25	37.99±1.58	0.0276	0.0030
Negative	0.83±0.12	4.02±0.58	0.02±0.00	0.00±0.00	7.35±1.36	11.37±0.25	0.0134	0.0010

*Average results ± SD of three measurements. SD for static and gliding friction not given (approx. zero).

3.1.1. PVA-based film coatings

The static/dynamic frictions obtained for the PVA-based formulations and their further comparison with negative (uncoated disc, C) and positive (gelatin strip, G) controls can be seen in Figure 1. When comparing the static friction of the formulations with the uncoated disc (Fig. 1A), all formulations composed of carnauba wax/SLS as slippery-inducing agents (F1-F9) have shown superior performance. The same effect was observed for formulations containing sodium alginate/SLS as slippery-inducing agents (F26-F28). For formulations containing carrageenan, lower static friction was only obtained when combined with SLS (F17), while only smaller concentrations and their further combination with SLS led to the same effect for formulations containing xanthan gum (F18, F19, F21) and gellan gum as slippery-inducing agents (F22, F23, F25). The majority of the formulations showed lower static friction as compared to the positive control, with exception for formulations containing lecithin (F11, F13) and carrageenan (F14, F15) as slippery-inducing agents. With regards to the dynamic friction (Fig. 1B), only formulations containing carnauba wax/SLS (F1, F4), lecithin (F11, F12) and xanthan gum (F18) as slippery-inducing agents showed lower dynamic friction, while F5 and F21 exhibited equivalent performance as compared to the uncoated disc. On the other hand, formulations containing carrageenan (F14) and gellan gum (F23, F24) as slippery-inducing agents showed higher dynamic friction when compared to the gelatin strip.

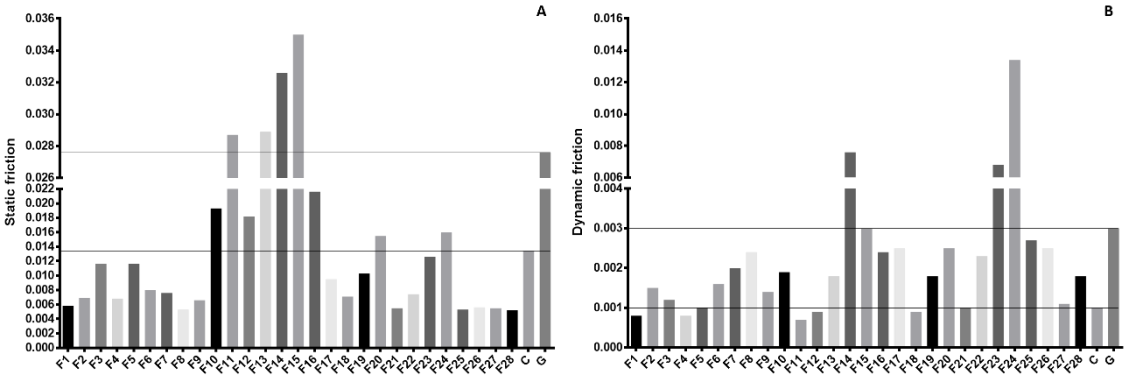

Fig. 1. Static (A) and dynamic (B) friction obtained for PVA-based film coatings.

3.1.2. Kollicoat IR-based film coatings

Formulations composed of Kollicoat IR/PVA (F32, F33) showed lower static friction (Fig. 2A) as compared to the uncoated disc and to formulations containing Kollicoat IR alone (F29-F31) as film-forming agent. The highest static friction was obtained for the positive control (gelatin strip). All formulations showed higher dynamic friction (Fig. 2B) in relation to the uncoated disc and only F33 (carnauba wax/lecithin/SLS) showed higher dynamic friction than the gelatin strip.

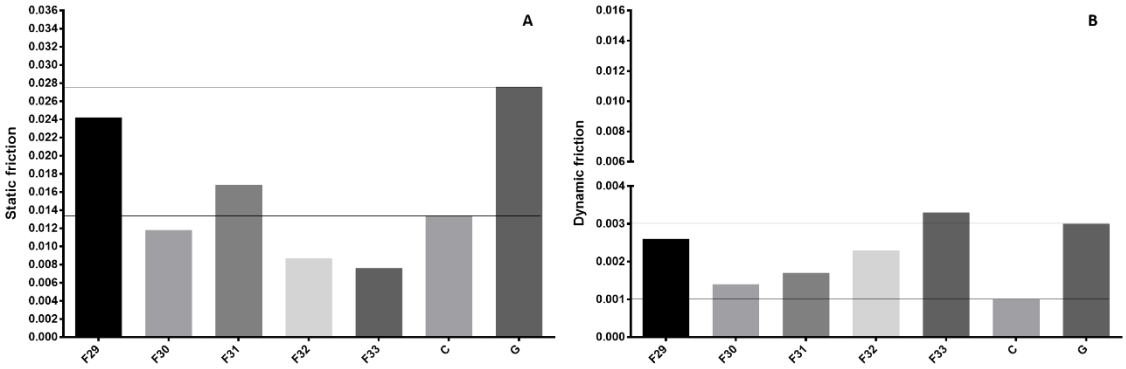

Fig. 2. Static (A) and dynamic (B) friction obtained for Kollicoat IR-based film coatings.

3.1.3. HPMC-based film coatings

Formulations containing HPMC as main film-forming agent showed a general trend for lower static as compared to the uncoated disc (Fig. 3A). Formulations F36, F37, F38 (carnauba wax/SLS), F42 (carrageenan/SLS) and F49 (gellan gum/SLS) showed equivalent or higher static friction. The highest static friction was measured for the positive control. All formulations showed higher dynamic friction (Fig. 3B) in relation to the uncoated disc, whereas formulations composed of carrageenan (F42-F44) and gellan gum (F48-F50) exhibited higher dynamic friction than the positive control.

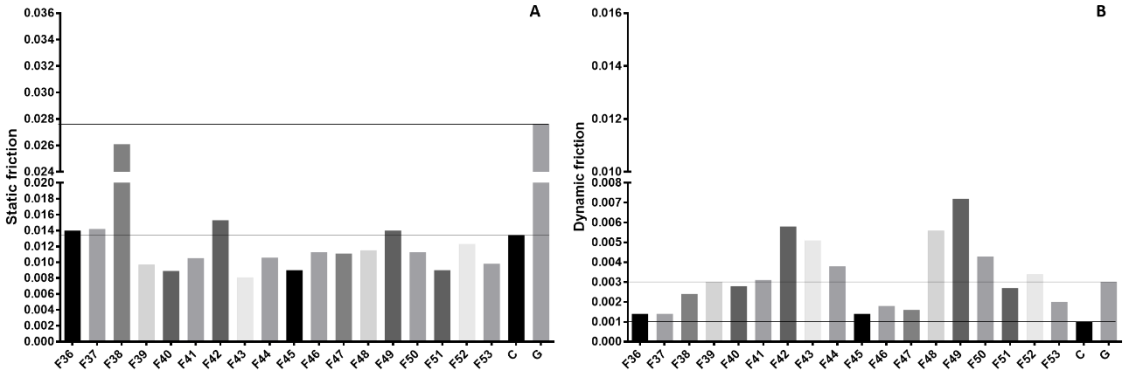

Fig. 3. Static (A) and dynamic (B) friction obtained for HPMC-based film coatings.

3.1.4. Sodium alginate-based film coatings

The majority of the formulations composed of sodium alginate as film-forming agent showed lower static (Fig. 4A). Only formulations F57-F59 (lecithin/SLS), F66 and F68 (gellan gum/SLS) have shown tendency for higher static friction when compared to the uncoated disc. With regards to dynamic friction the opposite was seen, where most of the formulations showed higher dynamic friction in relation to the positive control. Only formulations F56 (carnauba wax/SLS), F62 (carrageenan/SLS) and F62/F65 (xanthan

gum/SLS) showed lower dynamic friction than the gelatin strip, while F65 demonstrated similar dynamic friction as the uncoated disc (Fig. 4B).

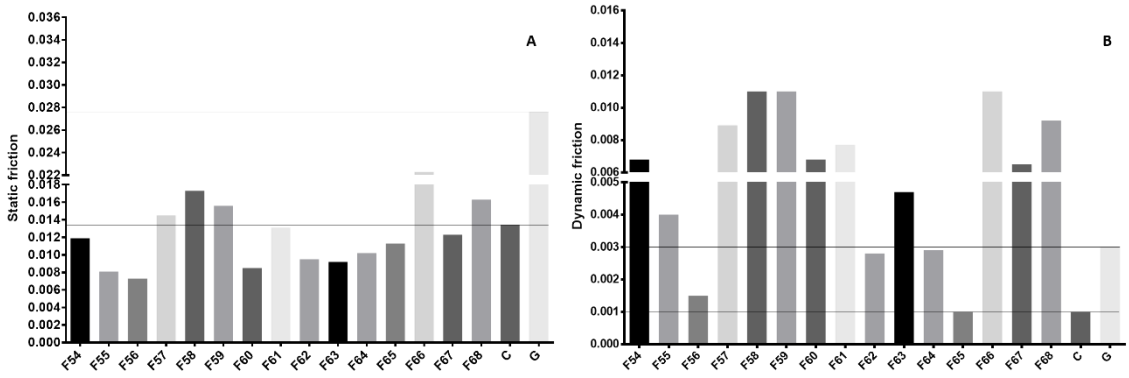

Fig. 4. Static (A) and dynamic (B) friction for sodium alginate-based film coatings.

3.1.5. Carrageenan-based film coatings

All formulations composed of carrageenan as film-forming agent showed lower static, with exception for formulations F70 and F71 (carnauba wax/SLS) that showed equal and slightly higher static frictions as compared to the uncoated disc, respectively (Fig. 5A). Most of formulations exhibited lower dynamic friction in relation to the gelatin strip, with exception for film coatings F69 (carnauba wax/SLS), F79 (gellan gum/SLS), F81/F83 (sodium alginate/SLS). Only formulations F73 (lecithin/SLS) and F80 (gellan gum/SLS) showed equal dynamic friction to the uncoated disc (Fig. 5B).

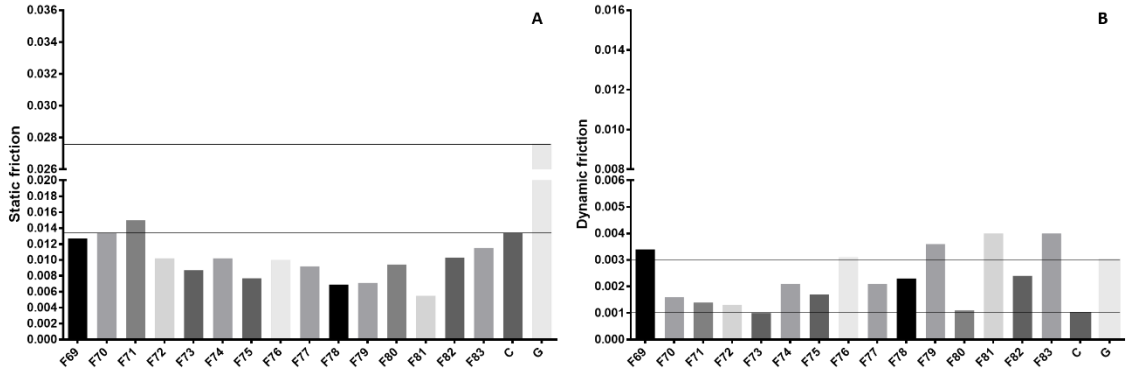

Fig. 5. Static (A) and dynamic (B) friction for carrageenan-based film coatings.

3.1.6. Xanthan gum-based film coatings

The coatings composed of xanthan gum as film forming agent have shown good performance with regards to the static friction, as all have scored considerably lower when compared to the uncoated disc (Fig. 6A). Formulations containing carnauba wax/SLS as slippery inducing agents exhibited equivalent dynamic friction to the

uncoated disc (Fig. 6B), while the remaining formulations showed lower gliding friction as compared to the gelatin strip, with exception for formulation F91 (carrageenan/SLS).

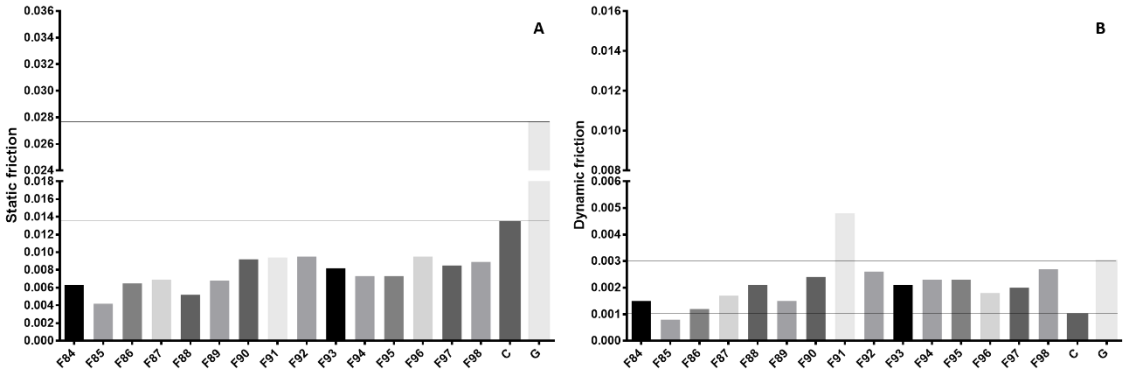

Fig. 6. Static (A) and dynamic (B) friction for xanthan gum-based film coatings.

3.1.7. Gellan gum-based film coatings

Formulations F110 and F116 (xanthan gum/SLS) demonstrated higher static friction in relation to the uncoated disc (Fig. 7A). With regards to the dynamic friction, formulations F101 (carnauba wax/SLS) and F109/F110 (xanthan gum/SLS) showed equivalent performance to the uncoated disc equivalent (Fig. 7B). Most of formulations exhibited lower dynamic friction as compared to the gelatin strip.

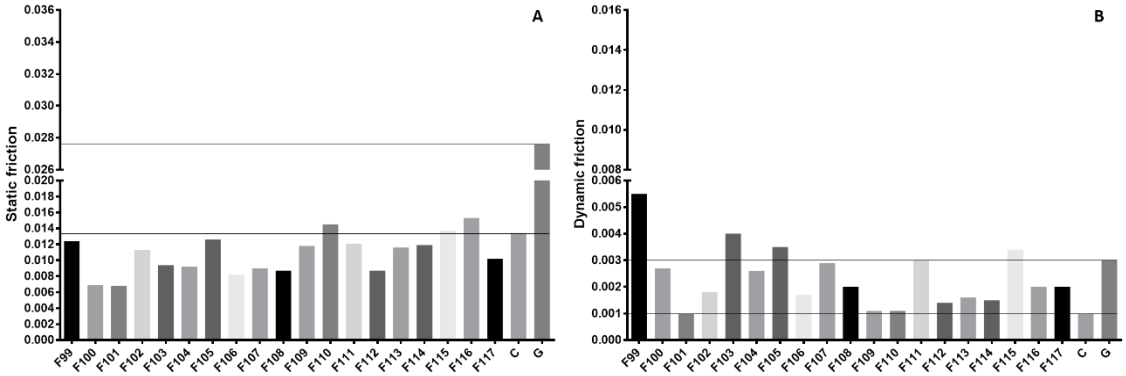

Fig. 7. Static (A) and dynamic (B) friction for gellan gum-based film coatings.

3.2. Multivariate analysis

Principal component analysis (PCA) was applied using static friction and dynamic friction as inputs for enhanced gliding performance, with the aim of identifying specific excipients or groups of excipients that acting as slippery-inducing agents are most suitable for a specific film-forming agent. It is worth noticing that not all data variation is represented in the first and second components.

3.2.1. PCA analysis applying static friction as input for gliding performance

3.2.1.1. PVA-based film coatings (Fig. 8)

For low and medium concentrations of PVA, the increase in the slippery-inducing agent CS/SLS does not appear to reduce static friction, with exception when combined with higher concentrations of PVA (purple). Combinations of PVA with Sodium alginate/SLS as slippery-inducing agent generally shown low static friction for all concentrations tested (light blue). An increase in PVA/gellan gum concentration suggests higher static friction. Its reduction is suggested to be related to lower concentrations of PVA/gellan gum and addition of SLS to the slippery inducing agents (F22 -> F25, red/green). Combinations of PVA/carrageenan show general high static friction, and addition of SLS as slippery-inducing agent does not suggest its reduction (F16 -> F17, yellow/green). Xanthan Gum and lecithin have shown similar trends as slippery-inducing agents. Combinations of PVA/lecithin appear to show high static friction for all concentrations tested, and addition of SLS did not contributed for significant changes (F11 -> F13, dark blue/green). An increase in the concentration for PVA/xanthan gum films led to higher static friction. Low concentrations should be suggested for reducing static friction (F18 -> F21, dark blue/green).

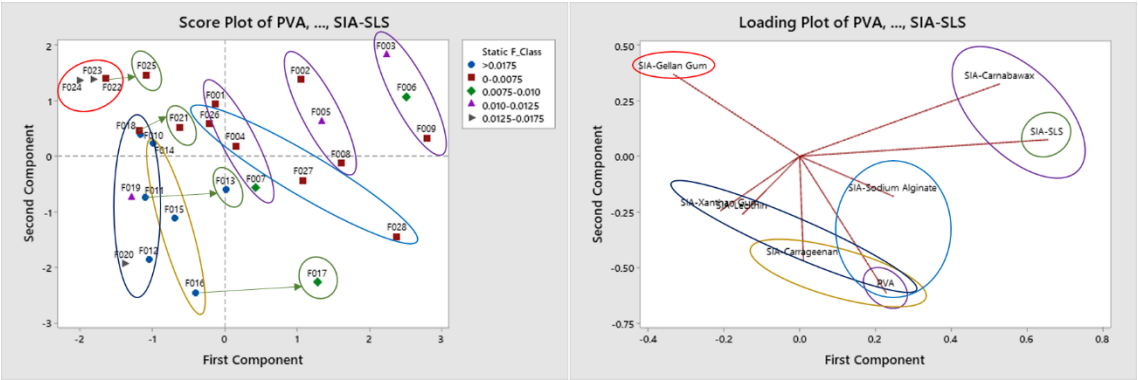

Fig. 8. Score plot and loading plots for PVA-based coatings using static friction as main input for gliding performance.

3.2.1.2. Kollicoat IR-based film coatings (Fig. 9)

Intermediate concentrations of Kollicoat IR combined with carnauba wax/SLS appear to contribute for lower static friction. The upper and lower limits of concentration tested are suggested to increase static friction (blue). In addition, film coating combinations for Kollicoat IR/PVA/lecithin/SLS appear to exhibit lower static friction (orange).

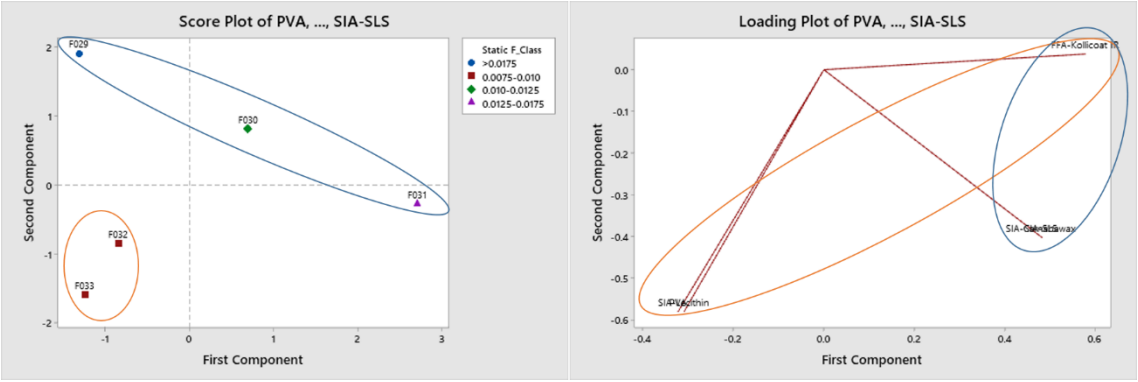

Fig. 9. Score plot and loading plots for PVA/Kollicoat IR-based coatings using static friction as main input for gliding performance.

3.2.1.3. HPMC-based film coatings (Fig. 10)

The increase in HPMC concentration leads to higher static friction when combined with carnauba wax/SLS as slippery-inducing agents. The same assumption can be taken for combinations with lecithin/SLS. Low and medium concentrations of HPMC combined with Lecithin/SLS as slippery-inducing agent appear to exhibit lower static friction (green). Combinations of HPMC with gellan gum/SLS as slippery-inducing agents are suggested to present high static friction, while intermediate concentrations for the same combination appear to reduce this phenomenon (dark blue). A lower concentration of HPMC combined with higher concentration of xanthan gum/SLS as slippery-inducing agents has exhibited lower static friction. The same assumption is present for combinations of HPMC with sodium alginate/SLS (light blue). Intermediate concentrations for HPMC/Carrageenan/SLS have also assisted to reduce this parameter as compared to their upper and lower limits (red).

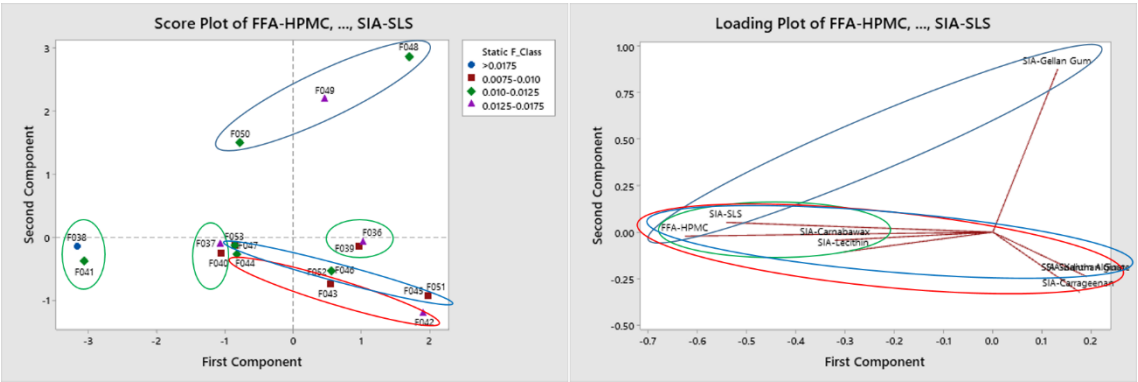

Fig. 10. Score plot and loading plots for HPMC-based coatings using static friction as main input for gliding performance.

3.2.1.4. Sodium alginate-based film coatings (Fig. 11)

The increase in the concentration of sodium alginate in combination with higher concentrations for carnauba wax/SLS appear to contribute for lower static friction, while formulations composed of sodium alginate with lecithin/SLS show significant static friction for all concentrations tested (purple). Intermediate concentrations for films composed of sodium alginate/gellan gum/SLS have suggest lower static friction as compared to their lower and upper limits tested (green). The increase in the concentrations of film-forming agent for combinations of Sodium alginate/Xanthan Gum/SLS have generated higher static friction and, as such, lower concentrations should be preferred (red). Combinations of sodium alginate with carrageenan/SLS have shown a general tendency for higher static friction, with intermediate concentrations suggesting to further increase this parameter (blue).

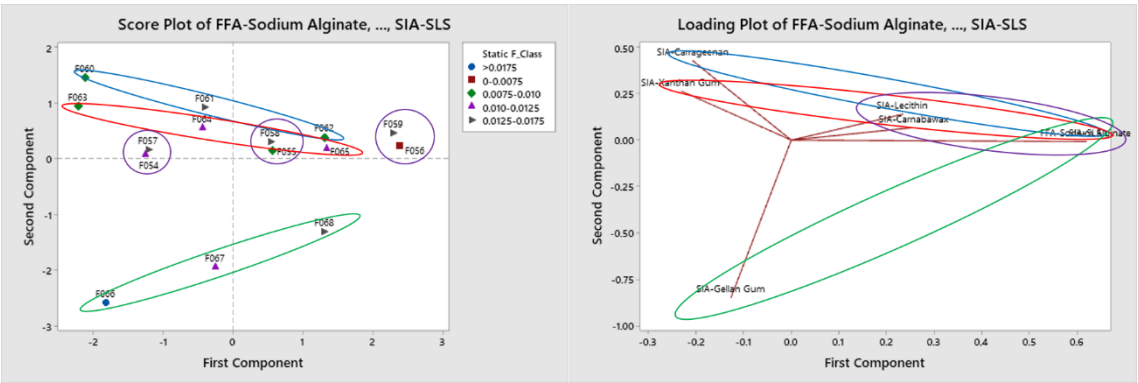

Fig. 11. Score plot and loading plots for sodium alginate-based coatings using static friction as main input for gliding performance.

3.2.1.5. Carrageenan-based film coatings (Fig. 12)

The combination of carrageenan as film-forming agent with higher concentration of gellan gum/SLS as slippery-inducing agent are suggested for lower static friction (blue). The same effect was observed for combinations with sodium alginate/SLS and xanthan gum/SLS. Therefore, lower static friction is suggested to be achieved for lower concentration of the film-forming agent (green). Combinations of carrageenan with carnauba wax/SLS are suggested to have significant static friction for all concentrations tested. Furthermore, carrageenan/lecithin/SLS films exhibited intermediate static friction, with the effect being more susceptible for reduction when applying medium concentrations for both film-forming and slippery-inducing agents (red).

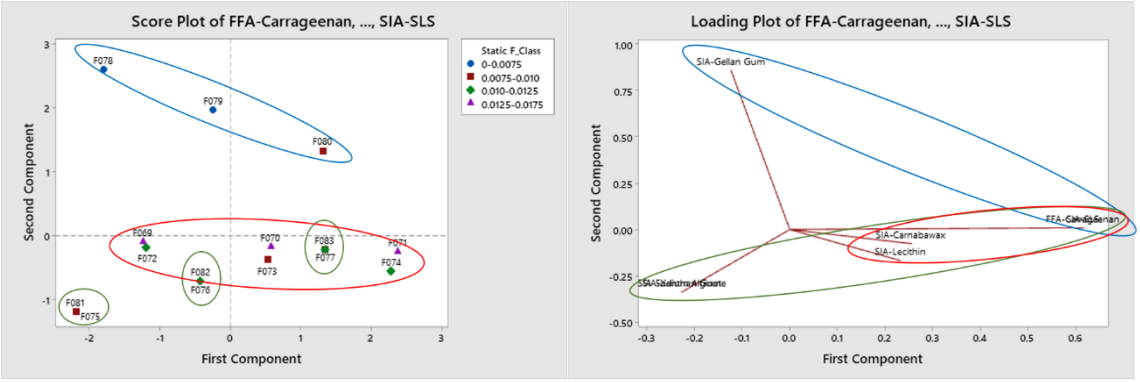

Fig. 12. Score plot and loading plots for carrageenan-based coatings using static friction as main input for gliding performance.

3.2.1.6. Xanthan gum-based film coatings (Fig. 13)

Intermediate concentrations for both xanthan gum and carnauba wax/SLS, or lecithin/SLS as slippery-inducing agents are suggested to present lower static friction as compared to the upper and lower limit of concentration for the film-forming agent (purple). Combinations of xanthan gum with carrageenan/SLS are suggested to present significant static friction for all concentrations tested, while an intermediate concentration of film-forming agent appears to slightly reduce the static friction (blue). Films composed of xanthan gum with sodium alginate/SLS exhibited significant static friction for all concentrations tested, and higher concentration for the film-forming agent is recommended to lower the static friction (red). The same assumption can be taken for films containing xanthan gum/gellan gum/SLS, as the static friction was reduced for increasing concentration of xanthan gum (green).

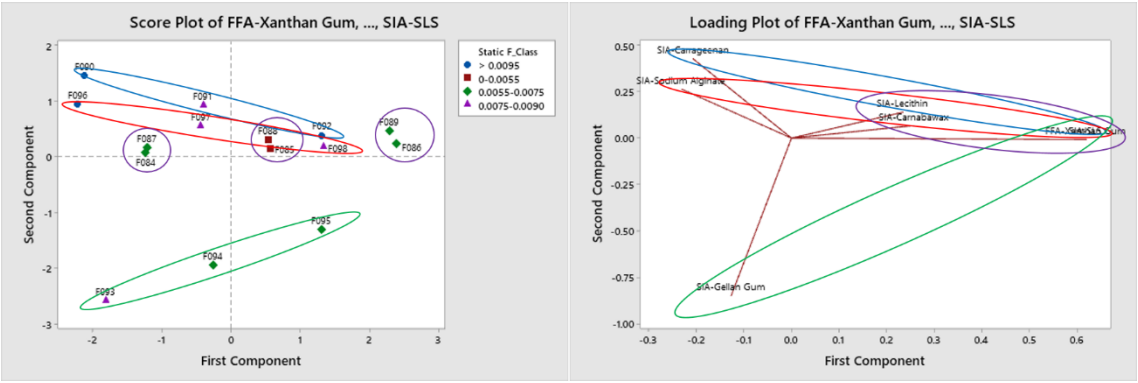

Fig. 13. Score plot and loading plots for xanthan gum-based coatings using static friction as main input for gliding performance.

3.2.1.7. Gellan gum-based film coatings (Fig. 14)

The increase in the concentration of gellan gum as film-forming agent combined with xanthan gum/SLS as slippery-inducing agent appears to increase the static friction. For these compositions, lower concentrations of film-forming agent combined with higher concentrations of xanthan gum/SLS are suggested to reduce the static friction (dark blue). The increase in the concentration of gellan gum when combined with carnauba wax/SLS exhibits higher static friction, and lower concentrations are suggested for reducing this parameter. Furthermore, films composed of higher concentrations for both gellan gum and lecithin/SLS agent appear to promote lower static friction whereas lower concentrations for these polymers led to the opposite effect (purple). Combinations of gellan gum with sodium alginate/SLS are suggested to present lower static friction when applying intermediate concentrations. Further combinations with carrageenan/SLS are most likely to demonstrate lower static friction when applying higher concentration of film-forming agent in combination with lower concentrations for the slippery-inducing agents. Both groups of formulations presented similar trends in the plots (light blue). The increase in the concentration of PEG appears to show little influence in the static friction for formulations composed of gellan gum/xanthan gum/SLS (yellow).

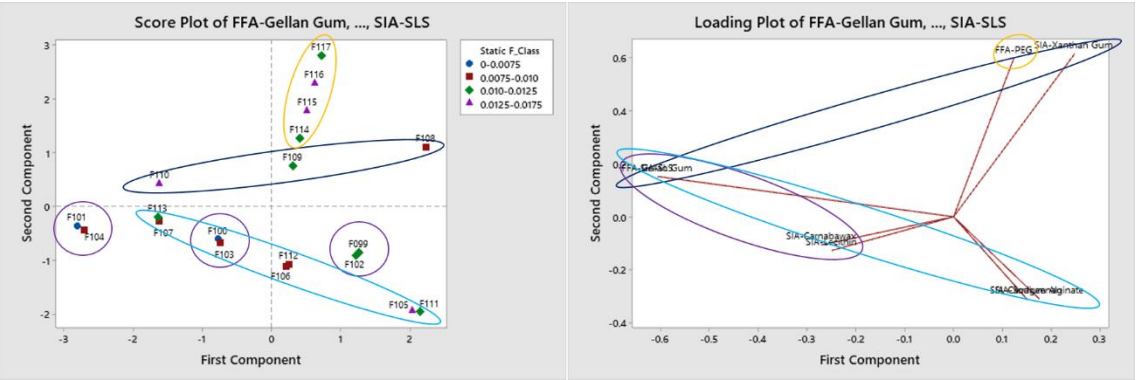

Fig. 14. Score plot and loading plots for gellan gum-based coatings using static friction as main input for gliding performance.

3.2.2. PCA analysis applying dynamic friction as input for gliding performance

3.2.2.1. PVA-based film coatings (Fig. 15)

Combinations of PVA with carnauba wax/SLS as slippery-inducing agent suggested a general tendency for lower dynamic friction (green), while gellan gum appears not to have an optimal effect as slippery-inducing agent for any of the concentrations tested (red). Regarding films composed of PVA/sodium alginate/SLS, intermediate concentrations for the polymers have led to lower gliding friction as compared to their lower and upper limits (purple). The increase in concentrations of polymer for

PVA/lecithin films appears to lead to lower dynamic friction (orange), with the addition of SLS to the formulation not leading to an improvement in the profile (F11 -> F13). The dynamic friction is suggested to increase with higher concentrations for PVA/xanthan gum films, and addition of SLS as slippery-inducing agent is suggested to reduce dynamic friction (blue). The effect of carrageenan as slippery-inducing agent is not possible to addressed, as it showed little influence in the loading plot.

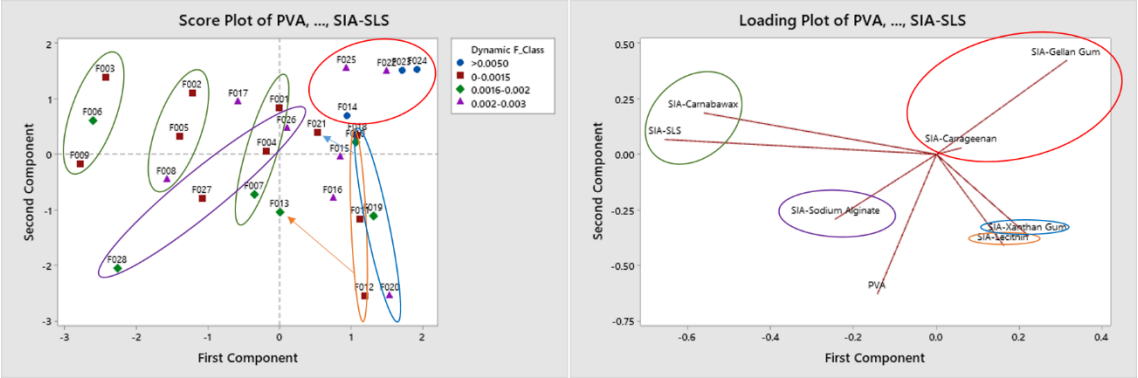

Fig. 15. Score plot and loading plots for PVA-based coatings using dynamic friction as main input for gliding performance.

3.2.2.2. Kollicoat IR-based film coatings (Fig. 16)

Intermediate and high concentrations for carnauba wax/SLS as slippery-inducing agent seem to provide lower dynamic friction (green). The addition of PVA to Kollicoat IR as film-forming agents and of lecithin to carnauba wax/SLS as slippery-inducing agent appears to increase the dynamic friction, with subsequent increasing concentrations of lecithin leading to higher resistance to movement (red).

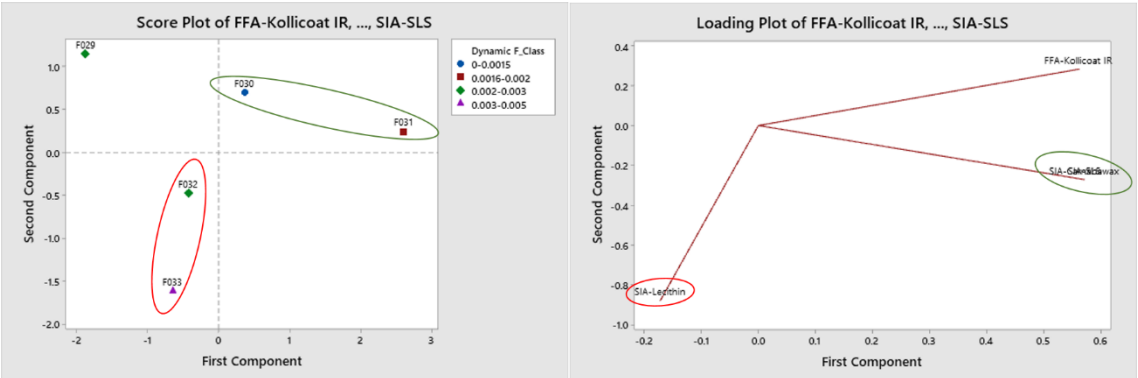

Fig. 16. Score plot and loading plots for Kollicoat IR-based coatings using dynamic friction as main input for gliding performance.

3.2.2.3. HPMC-based film coatings (Fig. 17)

Combinations of HPMC with gellan gum/SLS are suggested to increase gliding friction. This effect is slightly reduced when combining lower concentrations of gellan gum with higher concentrations of SLS as slippery-inducing agents, even when concentration of film-forming agent is increased (red). Films composed of carrageenan/SLS showed high dynamic friction, indicating that this polymer is not optimal for enhanced gliding performance when combined with HPMC (blue). Xanthan gum and sodium alginate films have presented a similar trend, with both exhibiting moderate gliding friction (green). Carnauba wax/SLS and lecithin/SLS have also shown similar trends as slippery-inducing agents, with increasing concentration of HPMC leading to a general increase in the gliding friction. As such low concentrations of film-forming agent are suggested (orange).

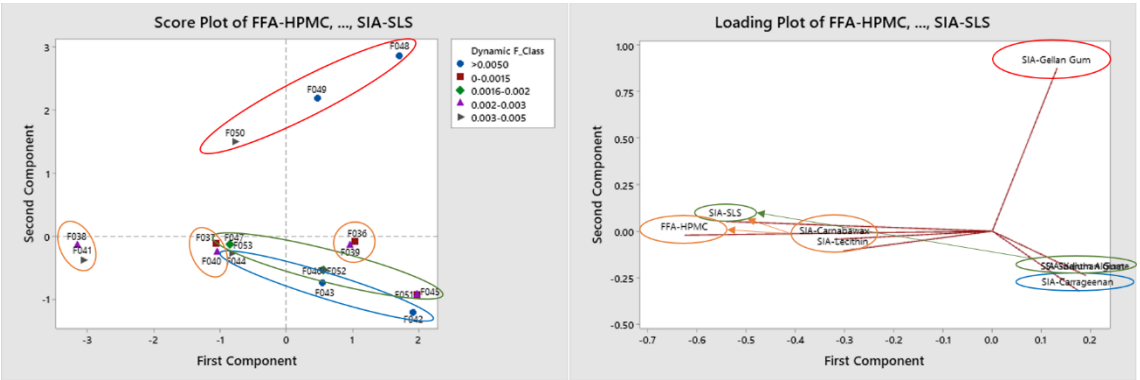

Fig. 17. Score plot and loading plots for HMPC-based coatings using dynamic friction as main input for gliding performance.

3.2.2.4 Sodium alginate-based film coatings (Fig. 18)

Combinations of sodium alginate with gellan gum/SLS as slippery-inducing agent have demonstrated higher gliding friction (red). The same effect is suggested for xanthan gum/SLS and carrageenan/SLS, as the dynamic friction is suggested to increase with higher concentration for both slippery-inducing agents. Lower concentrations for both xanthan gum and carrageenan in combination with higher concentrations of SLS appear to slightly reduce the gliding friction, with this effect being this more prominent for xanthan gum (blue). Lecithin is suggested not to be a good slippery-inducing agent in combination with sodium alginate. Higher dynamic friction was exhibited, even for increasing concentrations of SLS (green). The increase in the concentration of carnauba wax/SLS combined with higher concentration of film-forming agent leads to lower dynamic friction (orange).

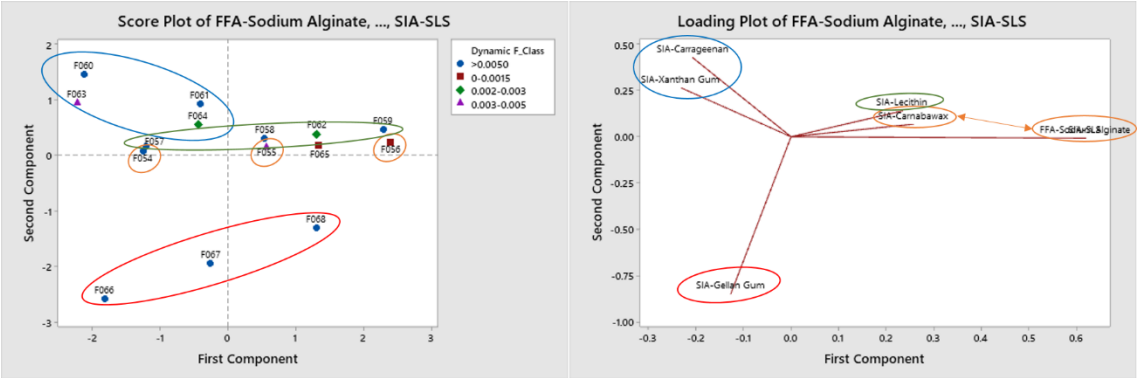

Fig. 18. Score plot and loading plots for sodium alginate-based coatings using dynamic friction as main input for gliding performance.

3.2.2.5. Carrageenan-based film coatings (Fig. 19)

Higher dynamic friction is suggested for combined increasing concentrations of carrageenan and Lecithin/SLS. As such, lower concentrations should be considered for this specific combination of polymers (green). Increasing concentrations of carnauba wax/SLS as slippery-inducing agent appear to reduce the dynamic friction, even for films with increasing concentration of carrageenan (orange). Xanthan gum/SLS and sodium alginate/SLS have shown similar slippery-inducing trend when combined with carrageenan, nevertheless, higher gliding resistance is expected for sodium alginate/SLS combinations (blue). The combination of low gellan gum with high SLS concentrations contributed for reducing the gliding friction in comparison to other films prepared with the same polymers (red). Carnauba wax and lecithin appear to show little influence in the loading plot as compared to other slippery-inducing agents.

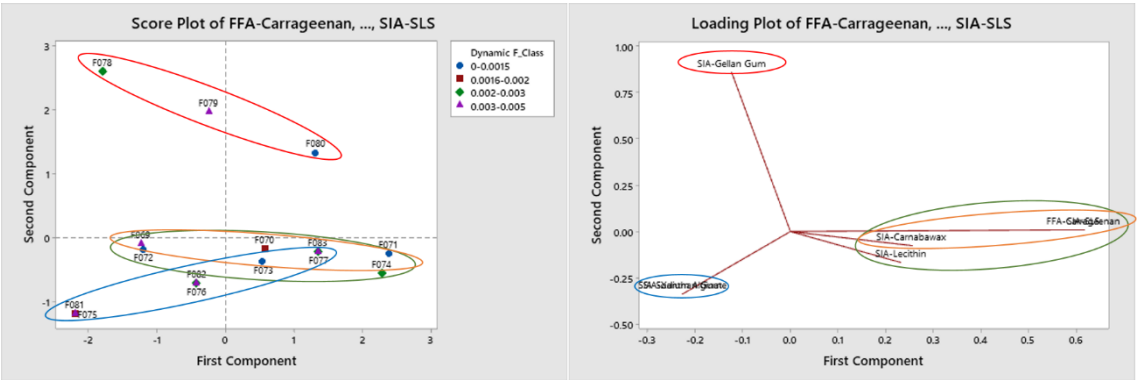

Fig. 19. Score plot and loading plots for carrageenan-based coatings using dynamic friction as main input for gliding performance.

3.2.2.6. Xanthan gum-based film coatings (Fig. 20)

Combinations with carrageenan/SLS and/or gellan gum/SLS are suggested for intermediate dynamic friction with regards to the tested concentrations (red). The increase in concentrations for film-forming agent and lecithin/SLS has exhibited to decrease the measured gliding friction (green). Increasing concentration of sodium alginate/SLS appears increase the gliding friction, as such, lower resistance to movement is expected for low and medium concentrations (orange). Lower dynamic friction is expected for films composed of carnauba wax/SLS as slippery-inducing agents, with all formulations showing lower resistance to movement as compared to others (blue).

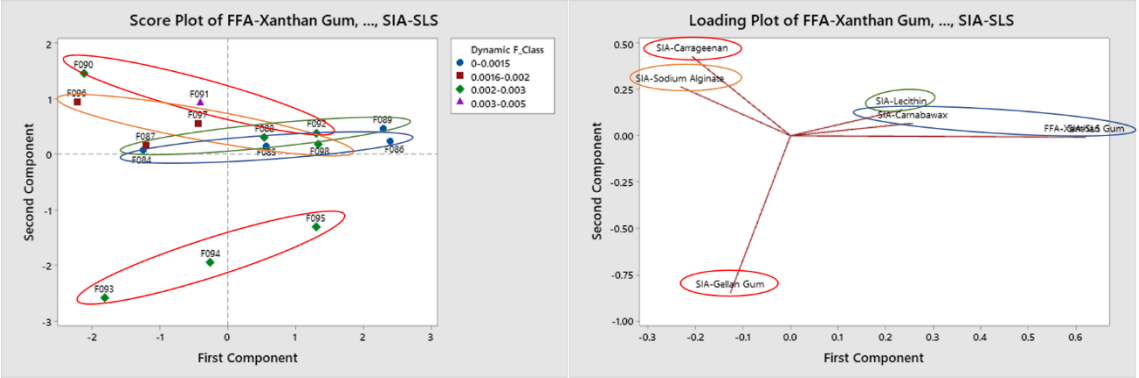

Fig. 20. Score plot and loading plots for xanthan gum-based coatings using dynamic friction as main input for gliding performance.

3.2.2.7. Gellan gum-based film coatings

Lower gliding resistance is obtained for high concentration of gellan gum/carnauba wax/SLS and lower/medium concentrations should be avoided as these showed to increase the gliding friction. Furthermore, the increase in concentrations of gellan gum and lecithin/SLS are also suggested for higher gliding resistance (orange). Intermediate concentrations for films composed of gellan gum/carrageenan/SLS and gellan gum/sodium alginate/SLS appear to provide less gliding resistance in comparison to their lower and upper limits of concentration, with higher concentrations suggesting superior dynamic friction (green). A lower concentration of xanthan gum combined with higher concentrations for both SLS and film-forming agent appear to reduce the gliding resistance (red). The increase of PEG concentration in combination with gellan gum/xanthan gum films does not suggest reduction of the gliding friction.

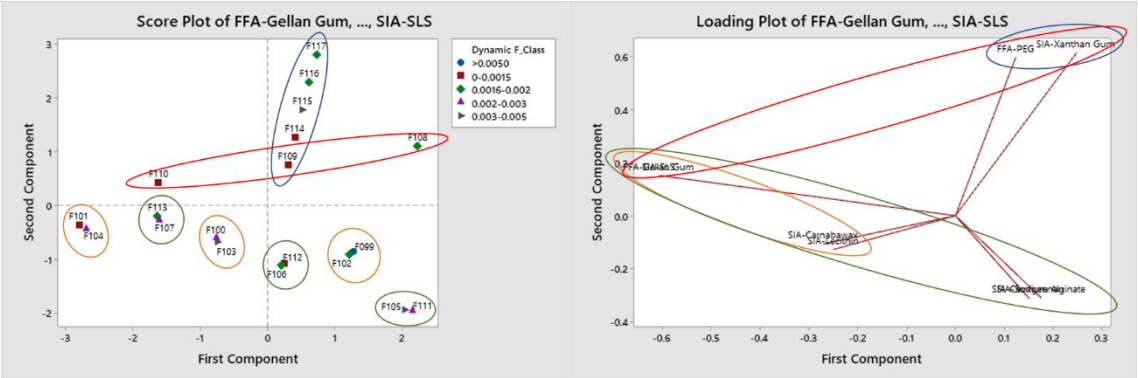

Fig. 21. Score plot and loading plots for gellan gum-based coatings using dynamic friction as main input for gliding performance.

4. Discussion

The *in vitro* gliding system applied in this study enables a detailed characterization of the gliding performance of different polymer-based film coatings across an artificial mucous layer, and can be potentially utilized for screening and formulation design optimization of coating surface treatments that can be applied to SODF to enhance their swallowability and transit times, thus increasing patient compliance with regards to special patient populations (e.g., elderly, dysphagic patients).

Previous studies have already investigated the suitability of different SODF coating excipients to enhance swallowing safety. The results demonstrated that PEG grades and carnauba wax are highly recommended, whereas PVP and high molecular weight HPMC/PVA should be avoided due to a predicted increase in mucoadhesion (Drumond and Stegemann, 2018a; 2018b). In addition, it was noticed that suitable gliding performance could be achieved when applying low molecular weight PVA as film forming agent (Drumond and Stegemann, 2019). These findings were applied in the course of this work and coating formulations were designed and manufactured in combination with other selected excipient materials to create film coatings that could exhibit optimized gliding performance. PEG with a molecular weight of 1500 was applied in a concentration of 1% to combine both slippery-enhancing and plasticizing effects on the produced films (Drumond and Stegemann, 2018a; Roy et al., 2009). Other excipients included HPMC and Kollicoat IR that were applied only as film-forming agents, whereas sodium alginate, carrageenan, xanthan gum and gellan gum were accessed both as film-forming and slippery-inducing agents, including their subsequent combinations with lecithin and/or SLS.

The collected gliding curves are characterized by two main domains: a starting peak related to the force required to overcome the initial static friction, and a second region (after peak drop) representing the dynamic (kinetic) friction of the coating material across

the artificial mucous layer (Chapter 6, Fig. 4). Both static and dynamic frictions are expected to provide a better understanding on the performance of the coating material and should be analyzed in more detail. Coating formulations exhibiting poor static and dynamic frictions when compared to the tested controls are highly desirable, as these are expected to contribute for generating SODF film coating materials presenting *in vivo* free gliding properties (no adherence) across mucosal surfaces.

After careful evaluation of the results for all coating formulations, and in order to achieve the desired free gliding performance, generic suggestions for combinations of slippery-inducing excipients with specific film-forming agents can be proposed. When formulating PVA-based films, preference should be given to combinations with carnauba wax/SLS, sodium alginate/SLS and/or xanthan gum/SLS as slippery-inducing agents, while lecithin/SLS and carrageenan/SLS should be avoided. Combinations of Kollicoat IR and PVA as film-forming agents improve the gliding performance when compared to the polymer alone. Xanthan gum/SLS and carnauba wax/SLS demonstrated to be the slippery-inducing excipients of choice when formulating film coating materials with sodium alginate whereas lecithin and gellan gum should be avoided as these showed increase the gliding friction. With regards to carrageenan-based coating materials, carnauba wax/SLS, gellan gum/SLS and sodium alginate/SLS are not considered suitable excipients, as the first has showed to increase the static friction while all three generally produced a poor gliding performance. Xanthan gum and gellan gum displayed a general tendency for superior performance when applied as film-forming agents. Furthermore, their gliding profiles can be optimized when in combination with carnauba wax/SLS. For gellan gum-based coatings, the performance can also be optimized when applying combinations with xanthan gum/SLS.

Principal Component Analysis (PCA) was applied to further analyze the gliding performance of the coating materials with relation to both static and dynamic frictions as output parameters. The analysis allowed a “spatial distribution” of the data sets in the score plots, which was then complemented by the loading plots showing what specific formulations are driving (and in which magnitude) the dataset with regards to the desired output parameter. The granularity obtained from the analysis supported a better identification of which combinations of excipients and their specific concentrations applied contribute for film coating materials that can generate low static/dynamic friction profiles, and therefore enhanced gliding performance. The main findings from the PCA analysis can be visualized on Tables 3-4, where combinations of excipients and their range of desired concentrations are suggested to improve the gliding performance of the film coating materials based on the measured static and dynamic frictions, respectively.

Table 3. Optimal coating combinations to reduce static friction.

Film-forming agent	Lower static friction obtained when combining
PVA/PEG	PVA/Sodium alginate/SLS in all tested concentrations Higher concentrations of PVA/carnauba wax/SLS Lower concentrations of PVA/xanthan gum/SLS Lower concentrations of PVA/gellan gum/SLS
Kollicoat IR/PEG	Intermediate concentrations of Kollicoat IR/carnauba wax/SLS Kollicoat IR/PVA/Lecithin/SLS tested concentrations
HPMC/PEG	Lower concentrations of HPMC/lecithin/SLS Intermediate concentrations of HPMC/Gellan Gum/SLS Lower concentration of HPMC/higher concentration of xanthan gum/SLS Lower concentration of HPMC/higher concentration of sodium alginate/SLS Intermediate concentrations of HPMC/carrageenan/SLS
Sodium Alginate/PEG	Higher concentrations of sodium alginate/carnauba wax/SLS Intermediate concentrations of sodium alginate/gellan gum/SLS Lower concentrations of sodium alginate/xanthan gum/SLS
Carrageenan/PEG	Lower concentration of carrageenan/higher concentration of gellan gum/SLS Lower concentration of carrageenan/higher concentration of xanthan gum/SLS Lower concentration of carrageenan/higher concentration of sodium alginate/SLS Intermediate concentrations of carrageenan/lecithin/SLS
Xanthan Gum/PEG	Intermediate concentrations of xanthan gum/carnauba wax/SLS Intermediate concentrations of xanthan gum/lecithin/SLS Higher concentrations of xanthan gum are suggested for remaining combinations
Gellan Gum/PEG	Lower concentration of gellan gum/higher concentration of xanthan gum/SLS Lower concentration of gellan gum/higher concentration of carnauba wax/SLS Higher concentration of gellan gum/higher concentration of lecithin/SLS Intermediate concentrations of gellan gum/sodium alginate/SLS Higher concentration of gellan gum/lower concentration of carrageenan/SLS

Table 4. Optimal coating combinations to reduce dynamic friction.

Film-forming agent	Lower dynamic friction obtained when combining
PVA/PEG	PVA/carnauba wax/SLS in all tested concentrations Intermediate concentrations of PVA/sodium alginate/SLS Higher concentrations of PVA/lecithin Lower concentrations of PVA/xanthan gum/SLS
Kollicoat IR/PEG	Intermediate or high concentrations of Kollicoat IR/carnauba wax/SLS
HPMC/PEG	Lower concentrations of HPMC/higher concentration of carnauba wax/SLS Lower concentrations of HPMC/higher concentration of lecithin/SLS
Sodium Alginate/PEG	Lower concentrations of xanthan gum/higher concentrations of SLS Lower concentrations of carrageenan/higher concentrations of SLS Higher concentrations of sodium alginate/carnauba wax/SLS
Carrageenan/PEG	Higher concentrations of carnauba wax/SLS Lower concentrations of carrageenan/lecithin/SLS Lower concentrations of gellan gum/higher concentrations of SLS
Xanthan Gum/PEG	Higher concentrations of xanthan gum/lecithin/SLS Xanthan gum/carnauba wax/SLS in all tested concentrations Lower concentrations of sodium alginate/SLS
Gellan Gum/PEG	Higher concentrations of gellan gum/carnauba wax/SLS Intermediate concentrations of gellan gum/carrageenan/SLS Intermediate concentrations of gellan gum/sodium alginate/SLS Higher concentration of gellan gum/SLS, lower concentration of xanthan gum

It is worth noticing that the waxes evaluated in this work were not included in the multivariate analysis, as these were tested as single materials and not in a combination of different polymer excipients. Both waxes tested (PEG-12 Carnauba and PEG-8 Beeswax) exhibited good performance, which is somehow expected for waxy materials presenting hydrophobic characteristics. In a general way, favorable gliding properties were obtained for coating combinations where xanthan gum and/or gellan gum were applied as film-forming agents. Furthermore, sodium alginate and SLS showed beneficial effects when applied as slippery-inducing agent.

Previous works have already demonstrated the benefits of using xanthan gum as slippery-inducing agent to improve the easiness of swallowing valsartan tablets, thus the results obtained in this work are in accordance to the literature (Mahdi and Maraie, 2015). Regarding sodium alginate, although being a polysaccharide known for exhibiting mucoadhesive properties (Ali and Bakalis, 2011; Kesavan et al., 2010; Wittaya-Areekul et al., 2006), it has already been demonstrated that these properties can be inhibited when in combinations with SLS, thus improving the gliding properties of the produced films (Hanna et al., 2013). In addition, other works have also confirmed the usability of alginates in the development of tablets to improve swallowability and medication administration (Ito et al., 2017).

The data generated in this work may assist and provide guidance to pharmaceutical technology researchers when formulating easy-to-swallow SODF coating materials, with the aim to increase administration safety and compliance regarding special patient populations (Drumond et al., 2017; Drumond, 2019). Nevertheless, it is important to keep in mind that the strategies and formulation approaches suggested in this work are confined to the design space investigated, and additional investigations outside the ranges applied may lead to disputative gliding results.

Prospective work should include selection of optimal *in vitro* gliding formulations to further evaluate their gliding performance using *ex vivo* esophageal tissue, followed by their final screening and subsequent applicability as SODF coatings using film coating and hot-melt coating process technologies. Lastly, *in vivo* evaluations using real-time magnetic marker monitoring (Weitschies et al., 2001) and/or video fluoroscopy (Okabe et al., 2008) should be addressed to the concerned patient populations (e.g., older patients, dysphagic patients, etc.) in order to access the safety and swallowing efficacy of SODF treated with the investigational film coating materials

5. Conclusion

This work applied the previously developed *in vitro* artificial mucous system to evaluate the gliding performance of coating formulations designed with different combinations of film-forming and slippery-inducing agents. A multivariate analysis was performed to evaluate the gliding profiles and better identify which combinations of excipients, including their specific concentrations, are desired to reduce gliding friction. Lastly, an overview of different formulation strategies to be adopted when formulating film coating materials intended to display enhanced gliding performance across artificial mucus layers are also suggested.

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Concluding remarks and future work

This doctoral thesis addressed the emerging topic of patient centric pharmaceutical drug product design, which in recent years has been getting more attention within the pharmaceutical industry. The old assumption of “one size fits all” with regards to drug product management and oral administration of solid oral dosage forms (SODF) is no longer viable in current days, having in consideration that the average lifespan of current societies is gradually increasing over the years and leading to older patient populations worldwide. Such patient populations are affected by chronic diseases and comorbidities associated to the normal ageing process and certain health risk factors determined by race, genetics, geographic region, environmental conditions, among others. As such, when developing new drug therapies, the needs of the target patient population should be incorporate in the drug product design, as it will contribute for higher patient acceptability and increase efficacy of prescribed treatments, reflected by the reduction of dose omissions and/or drug product manipulations to facilitate administration.

In order to implement such strategies, fundamental changes are yet to be adopted on how healthcare provision is provided to patients. The implementation of patient centric approaches should be recommended and will require adjustment of current development and business models to allow a successful application of patient centric care. Different regulatory initiatives have been implemented and guidelines have been drafted to encourage the different stakeholders to develop better medicines for both pediatric and geriatric populations, which demonstrates the increasing influence of patient centric pharmaceutical drug product design within the different regulatory agencies (Chapter 2). In addition, an increasing amount of scientific literature addressing the topic of patient centric research has been noted in recent years. More careful is being given on accessing how patients manage and administer their medications, including suitable methodologies to measure patient outputs, in order to correlate dosage form and packaging designs to specific patient populations and increase their compliance to prescribed drug treatments. A literature review conducted to identify scientific evidence for appropriateness, acceptability, usability and preferences of pharmaceutical preparations among all patient populations has identified two main areas investigating both packaging and dosage form design, and suggestions for selecting specific designs were discussed based on specific patient populations and their geographical regions (Chapter 3). Nevertheless, no studies evaluating the methodologies for testing the appropriateness and usability of drug products by patients were identified, which indicates that more interdisciplinary scientific efforts are required to develop and increase research in understanding patient needs and preferences.

One main limitation that patients usually experience when administering drugs is related to their inability or difficulty to swallow conventional SODF such as tablets or

capsules. Specific designs such as size and shape of SODF have proved to be relevant, however, their surface characteristics are expected to have a higher impact on administration, as this feature combined with the patient's swallowing reflex will govern the transit of the dosage form throughout the oro-esophageal system. Increasing scientific literature has also been noted with regards to administration strategies or development of suitable easy-to-swallow coating technologies that can be applied to solid dosage forms to enhance swallowability. These topics were reviewed in Chapter 4, where specific administration aids such as sprays, gels or *in-situ* coatings to assist deglutition were identified. Furthermore, coating compositions identified in several patients claiming to enhance swallowability of SODF have applied common polymer materials that form a slippery surface immediately upon saliva uptake. Nevertheless, limited clinical evidence is available to confirm the beneficial effects of such technologies to increase administration safety and improved swallowability.

For a proper development of new technologies that can facilitate administration when being applied to dosage forms, careful attention must be given to the mucoadhesive properties of the excipients composing the coating material, as this characteristic is expected to impact negatively the oro-esophageal transit of the dosage form upon swallowing. With this aim in sight, different *in vitro* methods available in the literature were used to screen the mucoadhesive potential of common polymer excipients typically applied in coating formulations. Evaluations applying particle interaction methods and mechanical force methods were executed and suggestions for optimal methodologies (and identification of their limitations) when accessing poor mucoadhesion were given based on a direct comparison between the different methods (Chapters 5 and 6). Moreover, an additional review of available literature describing *in vitro* and *in vivo* methodologies to evaluate esophageal adhesion and oro-esophageal transit, respectively, was performed to better identify an *in vitro* experimental setup that could be implemented and applied to allow the screening of different coating compositions to evaluate their likelihood of enhancing the oro-esophageal transit of solid dosage forms (Chapter 7).

The knowledge acquired from this literature review identified a gap in existing methodology reported in the literature, capable to evaluate the *in vitro* gliding performance of film coating materials that can enhance the swallowing properties of SODF. This subsequently led to the design, development and implementation of the artificial mucous layer *in vitro* system. The method allows the measurement of the gliding performance for different polymer films across artificial mucous layers. From the obtained gliding curves it is then possible to calculate both static friction and dynamic friction, which are then relevant for evaluating the potential of the coating materials for exhibiting

free gliding properties (Chapter 6). Lastly, the same method was applied to screen 117 film coating materials comprised of combinations of different film-forming agents and slippery-inducing agents, many of them chosen from the findings obtained in Chapter 4, and their performance evaluated against both negative (uncoated disc) and positive controls (gelatin). Furthermore, multivariate analysis using principal component analysis was applied to compare the gliding curves using both static and dynamic friction as main output parameter for enhanced gliding performance, which allowed to obtain more granularity in the results and supported the suggestion of desired combinations of excipients and respective concentration ranges to generate coating materials with higher predictive potential for optimized *in vivo* oro-esophageal transit. The data generated from 117 screened formulations, combined with their statistical multivariate analysis, identified specific polymer materials (and their suitable concentrations) as optimal film-forming agents (e.g., xanthan gum and gellan gum) and slippery-inducing agents (e.g., sodium alginate and SLS).

Prospective work should include selection of optimal coating formulations for further evaluation of their gliding performance using *ex vivo* esophageal tissue, followed by their subsequent applicability as SODF film coatings by applying different coating manufacturing technologies. Last but not least, *in vivo* evaluations to access the safety and swallowing efficacy of coated SODF using validated methods (e.g., video fluoroscopy) to confirm the predictability of the developed *in vitro* model should also be considered for future work.

- Appendix I -

Curriculum Vitae

Nélio Drumond

Curriculum Vitae

Name: Nélio Duarte Drumond Freitas

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Work experience

2020-Present	Senior Principal Scientist, *Takeda Pharma*
2018-2020	Principal Scientist, *Catalent Pharma Solutions*
2015-2018	Lead Formulation Scientist, *Graz University of Technology*
2013-2015	Lead Formulation Scientist, *Kemin Pharma*
2013	Research Fellow, *iMed.ULisboa*

Education

2015-2021	Doctor of Philosophy (PhD), *Graz University of Technology*
2006-2012	Doctor of Pharmacy (PharmD), *University of Lisbon*

- Appendix II -

List of publications

Peer reviewed articles:

1. Nélio Drumond, Diana van Riet-Nales, Fatma Karapinar-Çarkit, Sven Stegemann, Patients' appropriateness, acceptability, usability and preferences for pharmaceutical preparations: Results from a literature review on clinical evidence, *Int J Pharm 521 (2017) 294-305*.

2. Nélio Drumond, Sven Stegemann, Polymer adhesion predictions for oral dosage forms to enhance drug administration safety. Part 1: *In vitro* approach using particle interaction methods, *Colloids Surf. B Biointerfaces 165 (2018) 9-17*.

3. Nélio Drumond, Sven Stegemann, Polymer adhesion predictions for oral dosage forms to enhance drug administration safety. Part 2: *In vitro* approach using mechanical force methods, *Colloids Surf. B Biointerfaces 166 (2018) 17-23*.

4. Nélio Drumond, Sven Stegemann, Polymer adhesion predictions for oral dosage forms to enhance drug administration safety. Part 3: Review of *in vitro* and *in vivo* methods used to predict esophageal adhesion and transit time, *Colloids Surf. B Biointerfaces 165 (2018) 303-314*.

5. Nélio Drumond, Sven Stegemann, An evaluation of the gliding performance of solid oral dosage form film coatings using an artificial mucous layer, *Colloids Surf. B Biointerfaces 177 (2019) 235-241*.

6. Nélio Drumond, Future Perspectives for Patient-Centric Pharmaceutical Drug Product Design with Regard to Solid Oral Dosage Forms. *J Pharm Innov (2019).*

7. Nélio Drumond, Sven Stegemann, An investigation into the relationship between xanthan gum film coating materials and predicted oro-esophageal gliding performance for solid oral dosage forms. *Pharmaceutics 2020, 12(12), 1241.*

8. Nélio Drumond, Sven Stegemann, Better medicines for older patients: Considerations between patient characteristics and solid oral dosage form designs to improve swallowing experience. *Pharmaceutics 2021, 13(1), 32.*

Poster Presentations:

1. Nélio Drumond, Sven Stegemann, A rheological method to predict mucoadhesion between dosage form excipients and human saliva, *12th Austrian Minisymposium in Process Engineering, Graz (Austria), March 2016*.

2. Nélio Drumond, Sven Stegemann, Patient Appropriateness in Product Design: Systematic Review of Clinical Evidence, *2016 AAPS Annual Meeting and Exposition, Denver (USA), November 2016*.

3. Nélio Drumond, Sven Stegemann, *In vitro* methods based on mechanical forces to assess the mucoadhesive potential of water-soluble polymers: Modified balance/surface tensiometer, *13th Austrian Minisymposium in Process Engineering, Innsbruck (Austria), March 2017*.

4. Nélio Drumond, Sven Stegemann, An *in vitro* method to predict the coating influence on the gliding performance of solid oral dosage forms, *2017 AAPS Annual Meeting and Exposition, San Diego (USA), November 2017*.

5. Nélio Drumond, Sven Stegemann, Formulation and methodological assessment of patient centric technologies for solid oral dosage forms, *11th PBP World Meeting, Granada (Spain), March 2018*.

6. Nélio Drumond, Sven Stegemann, Evaluation of polymer mucoadhesiveness based on particle size and zeta potential measurements, *14th Austrian Minisymposium in Process Engineering, Linz (Austria), April 2018*.

Oral Presentations:

1. Nélio Drumond, A review on research evidence for Patient Centric Pharmaceutical Drug Product Design, *APV Seminar on Better Medicines for Older Adults, Graz (Austria), November 2017*.

2. Nélio Drumond, Sven Stegemann, An *in vitro* method to predict the coating influence on esophageal adhesion and gliding performance of solid oral dosage forms, *11th Annual Meeting of the PSSRC, Graz (Austria), June 2017*.

3. Nélio Drumond, Sven Stegemann, Comparison of two *in-vitro* methods to predict mucoadhesion between dosage form excipients and human saliva, *10th Annual Meeting of the PSSRC, Copenhagen (Denmark), July 2016*.