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Evaluation of taste masking of pharmaceutical Products

MASTERARBEIT

Zur Erlangung des akademischen Grades

Diplom-Ingenieur

Masterstudium Chemical and Pharmaceutical Engineering

eingereicht an der

Technischen Universität Graz

Betreuer

Univ.-Prof. Dr. phil. nat. Andreas Zimmer

Institut für Pharmazeutische Technology

Graz, Februar 2017

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Danksagung

Zunächst möchte ich mich bei all denjenigen bedanken, die mich während der Anfertigung dieser Masterarbeit unterstützt und motiviert haben.

Bei Herrn Prof. Dr. Andreas Zimmer bedanke ich mich für die Bereitstellung dieses interessanten Themas und für die sehr nette und hilfreiche Betreuung. Ebenfalls möchte ich mich bei Frau Dr. Sharareh Salar-Behzadi bedanken, die mich über den gesamten Zeitraum meiner Masterarbeit immer bei all meinen Fragen unterstützt hat.

Zusätzlich gilt mein Dank allen Mitarbeitern vom RCPE. Ohne deren Hilfe und produktive Vorschläge meine Arbeit nicht möglich gewesen wäre. Besonders bedanken möchte ich mich da bei Herrn Diogo Gomes Lopes M.Sc, der immer einen konstruktiven Tipp für mich parat hatte.

Ein besonders großer Dank geht an meine Familie, ohne deren Rückhalt das Studium nicht möglich gewesen wäre. Insbesondere geht mein Dank an meine Schwester Andrea Schibschid und an Dr. Bernd Grobauer, die mir in vielen Situationen sehr geholfen haben.

Kurzzusammenfassung

Die Geschmacksmaskierung von Arzneimitteln hat in der pharmazeutischen Industrie in den letzten Jahren immer mehr an Bedeutung gewonnen. Die sogenannte Patienten-compliance nimmt heutzutage, besonders in der Pädiatrie einen wichtigen Stellenwert in der Herstellung von Darreichungsformen ein. Die Maskierung von bitter schmeckenden Arzneimitteln stellt dabei eine der größten Herausforderungen dar, da Menschen diesen Geschmack unterschiedlich intensiv empfinden.

Ziel dieser Diplomarbeit war es, eine *in vitro* Methode zu entwickeln um den bitteren Geschmack von bitter schmeckenden Arzneistoffen zu identifizieren. Da ein Probandentest mit einem hohen Zeit- und Kostenaufwand verbunden ist, ist eine Labormethode sichtlich sinnvoller.

Die hierbei verwendeten Wirkstoffe sind Ibuprofen-Natrium und Paracetamol. Beide wurden in einem Wirbelschichtapparat mit speziellen Lipiden mit unterschiedlicher Zusammensetzung an Lipiden und Emulgatoren mittels Hot-Melt-coating Technik überzogen. Zuvor wurden Paracetamol Pellets mit 50% Wirkstoffanteil und Ibuprofen Granulate mit 94% Wirkstoff hergestellt. Um ein Freisetzungsprofil von den Darreichungsformen zu erhalten wurden ein Standard Dissolutionstest und ein Dissolutionstest mittels Durchflusszelle durchgeführt. Mit diesen Verfahren konnten zusätzlich erste Annahmen über die Qualität des Überzuges und somit über den Geschmack gemacht werden. Um das Freisetzungsprofil im menschlichen Mund zu simulieren, wurde ein *in vitro* simuliertes Mund-Freisetzungsprofil erstellt. Dieses wurde mit annähernd ähnlichen physiologischen Zuständen durchgeführt, wie sie im menschlichen Mund zu finden sind. Die Qualität der Überzüge und somit auch den bitteren Geschmack zu bestimmen zu können, wurden die Freisetzungsprofile innerhalb 30 Minuten analysiert. Damit die Methoden anschließend qualifiziert werden konnten, hat eine Probandenstudie mit 11 freiwilligen Personen stattgefunden.

Aus diesen Ergebnissen lässt sich das Fazit ziehen, dass die *in vitro* simulated mouth studie und die Dissolution sehr gute Korrelationen bezüglich Geschmacksmaskierung liefern.

Abstract

Patient compliance is playing an increasingly important role in the manufacturing of dosage forms, especially in pediatrics and geriatrics. One relevant technique in achieving patient compliance is taste masking. The masking of bitter tasting drugs represents one of the greatest challenges, because of the variation of taste sensation in individuals.

The target of this thesis was to develop an *in vitro* method to evaluate the bitter taste of drugs. Since an *in vivo* test with human volunteers is associated with a high expenditure of time and costs, a laboratory method would have obvious advantages.

The active pharmaceutical ingredients (API) used in this work were ibuprofen sodium and paracetamol in the form of granules and pellets with 94% and 50% API content respectively, coated in a fluidized bed apparatus with different compositions of lipids and emulsifiers using the hot-melt-coating technique. In order to obtain a release profile of the dosage forms, a standard dissolution test and a dissolution test using a flow-through cell were performed. With these methods, estimations about the quality of the coating and taste masking could be achieved. To simulate the release profile in the human mouth, an *in vitro* simulated mouth release dissolution profile was created. This was carried out with physiological conditions approximately similar to those found in the human mouth. To determine the quality of the coatings and therefore the taste masking, the release profiles of the API within 30 minutes were analyzed. For qualification of these methods, a study with eleven human volunteers was conducted.

These results show that an *in vitro* simulated mouth study and dissolution testing provides very good correlations with respect to taste masking.

Table of Content

1.0 Introduction

The target of this thesis was to find *in vitro* methods to evaluate the bitter taste of different APIs with the aim of assessing taste masking quality of paracetamol pellets and ibuprofen sodium granules. Taste masking is an important topic in the pharmaceutical industry, particularly for the improvement of patient compliance. Especially bitter taste is easily perceived as unpleasant, hence masking the bitter taste of drugs is essential for better patient compliance. The identification of unpleasant taste is very complicated: *in vivo* tests using human panels seems unavoidable. However, such tests are time consuming, expensive, and need ethical permission. Thus, the development of *in vitro* methods for the evaluation of the bitter taste of drugs could be very useful.

To develop such analytical methods, ibuprofen sodium and paracetamol were used as active pharmaceutical ingredients (API). The ibuprofen sodium granules were produced via roller compaction, the paracetamol pellets with a single screw extruder and spheronization. The granules and pellets were then coated with hot-melt coating with different amounts of lipids and various percentages of emulsifiers in a fluidized-bed coating apparatus. The lipid used was Dynasan® 116 and the emulsifier was Tween 65®.

One method used was dissolution testing; the release profiles of different samples was assessed in distilled water over a time of two hours. Samples were taken manually at different times to compare the amount of released drug over time. Another applied method was a flow-through cell; the dissolution medium (distilled water) flew through a cell with a constant flow-through rate. Samples were taken after several times. To ensure good taste masking quality; an *in vitro* simulated mouth study was applied. An Erlenmeyer flask was filled with simulated saliva (phosphate buffer pH 6.8) and shaked for defined times in an incubator. The released API was detected with an UV-vis Photometer, the concentration of released API was increased, if the absorption of the UV-vis increases. The data gathered from these methods was correlated to the results of an *in vivo* taste masking study using 11 volunteers. The methods and theoretical backgrounds are described, the results are presented and discussed.

2.0 General Part

2.1 Physiology and anatomy of taste sensation

2.1.1 Oral cavity

The oral cavity is the area, where the ingestion begins. It is formed by the following parts: the lips and cheeks externally, the teeth and the alveolar bone internally, the roof; which is formed by the hard and soft palate and at the bottom by the floor. An oral mucosa with a non-uniform appearance covers all parts of the oral cavity [1].

2.1.2 Oral mucosa

Mucous membranes are distributed in the human body, for example in nasal passages, the gastrointestinal tract, the oral cavity and other body cavities, which are connected with the exterior. They have two separate components, a covering epithelium and an underlying connective tissue. The oral mucosa has different functions like protection (major function), sensation (temperature, touch and pain receptors), secretion (saliva) and thermal regulation (some animals regulate the body temperature with the oral mucosa) [2].

The oral mucosa can be divided into three main types by function: the masticatory mucosa (25% of the total area) covers the gingiva and the hard plate; the lining mucosa (60% of the total area) wraps the inside of the lips, underside of the tongue, floor of the mouth, cheeks, and the soft palate; the smallest mucosa, the so-called, specialized mucosa (15% of the total area), covers the dorsum of the tongue [2].

2.1.3 Saliva

Saliva is a fluid, which controls the humidity of the oral cavity. It is produced in the salivary glands. Saliva has many functions like protection, buffering, pellicle formation, maintenance of tooth integrity, antimicrobial activity, tissue repair, digestion, and taste (solubilizing food substances for the taste sensors in the buds). The pH value of the saliva is 6.7 – 7.4 and the flow rate under unstimulated conditions is 0.2 – 0.4 mL/min, whereas the flow rate under stimulated conditions is about 2.0 – 5.0 mL/min [2]. The characteristics of saliva are listed in Table 1.

Parameter	Characteristics
Volume	600 - 1000 mL/d
Electrolytes	Na^+, K^+, Cl^-, HCO_3^-, Ca^{2+}, Mg^{2+}, HPO_4^{2-}, SCN^-, F^-
Secretory proteins/peptides	Amylase, proline-rich proteins, mucins, histatin, cystatin, peroxidase, lysozyme, lactoferrin, defensins, cathelicidin-LL37
Immunoglobulins	Secretory immunoglobulin A, immunoglobulin G and M
Small organic molecules	Glucose, amino acids, urea, uric acid, lipid molecules
Other components	Epidermal growth factor, insulin, cyclic adenosine monophosphate-binding proteins, serum albumin

Table 1: Composition of Human Saliva [2]

The protection function of saliva can be described as below: Saliva washes non-adherent bacteria and other wastes out of the mouth. The Sugars contained in the saliva inhibit the availability of acidogenic plaque microorganisms. Mucins and glycoproteins act as a lubricant, preventing the oral tissues from sticking together and act as a barrier against noxious stimuli, microbial toxins and minor trauma [2].

Bicarbonate, phosphate and ions serve as buffering agents. They protect the teeth from demineralization caused by bacterial acids produced during sugar metabolism. Also, the metabolism of saliva proteins and peptides through bacteria, produces matters (urea and ammonia) that have an influence of the pH value of the saliva [2].

Pellicle is a thin layer on the surface of the teeth and on the oral mucosa. Some saliva proteins bind calcium and form the pellicle layer to protect the tooth surface. Saliva proteins can also inhibit the formation of plaque. They bind to the oral bacteria which are responsible for the plaque [2].

Acidic proline-rich proteins and statherins are important for the solubility of calcium and phosphate ions. The high concentrations of these ions increase the surface hardness and the resistance against demineralization of the teeth, on the basis of a posteruptive maturation of the enamel [2].

The antimicrobial effect of saliva stems from the antimicrobial activity of proteins like lysozyme, lactoferrin, peroxidase, and a secretory leukocyte protease inhibitor in the saliva. Also, peptides like α-defensins, β-defensins, cathelicidin-LL37, and histatins effects antimicrobial. Several peptides and proteins also have an antiviral function. The secretory immunoglobulin A forms agglutinations of specific microorganisms. The resulting clumps cannot attack oral tissues [2].

Saliva also includes small amounts of growth factors and other biological active peptides and proteins. As has been verified by experiments, these substances promote wound healing, tissue growth and differentiation [2].

Enzymes in the saliva, such as amylase (breaks down carbohydrates) and lipase (digest fats), are responsible for the first digestion of food [2, 3].

Saliva solubilizes the food. Proteins in the saliva, which are produced by minor glands in the vicinity of the circumvallate papillae, bind the taste substances and present them to the taste receptors [2].

2.1.3.1 Salivary glands

The salivary glands produce the saliva. Humans have three pairs of major salivary glands and a number of smaller minor salivary glands. The major salivary glands are the parotid, submandibular, and sublingual glands. The three major glands are located at the mandibular ramus (parotid glands), beneath the lower jaws (submandibular glands) and inferior to the tongue but anterior to the submandibular glands (sublingual glands). They are connected with the mouth via a duct system. The minor glands, (labial, lingual, palatal, buccal, glossopalatine, and the retromolar glands) are located in the submucosal layer [2, 50].

Every major salivary gland produces saliva with different composition. The parotid glands secret a watery saliva including a high amount of enzymes like amylase, proteins, proline-rich proteins and glycoproteins. The submandibular glands produce a serous fluid (contains amylase) and a mucus saliva (contains mucins). The sublingual glands also produce a mucus saliva with mucins [2].

The shallow part of the largest salivary gland, the parotid gland, is located subcutaneously in front of the external ear. The deeper part is behind the ramus of the mandible [2].

2.1.4 Taste receptors

Taste receptors are located on the superior surface of the tongue, on the palate, and on the epiglottis. They consist of 100 clusters of polarized neuroepithelial cells, which build compact columnar pseudostratified islands. Humans have approximately 5.000 taste receptors in the oral cavity, with regional differences in the sensitivity to different compounds. The five basic tastes of humans are sweet, umami, sour, salty, and bitter [4].

The mechanism behind the taste receptors is an opening or closing of ion channels. When a taste receptor gets in contact with a chemical stimulus, the ion channel will be opened or closed, and Na^+, K^+ and Ca^{2+} can flow in or out of the cell. This produces depolarizing potentials. The depolarization of the taste cell increases by increasing the concentration of the tastant. [5].

The salty taste (NaCl) receptor is a Na^+ channel on the apical membrane. When the NaCl concentration on the tongue increases, the depolarization also increases in the cell. Hormones like aldosterone and antidiuretic hormones are regulating the Na^+ channels and are responsible for the water and electrolyte balance. H^+ (responsible for sour taste) can also diffuse through the Na^+ channels, which is the reason why sour taste may cover salty taste [5].

Sour taste (acids) activates Cl^- and proton-gated-cation channels [5].

G-protein-coupled receptors (GPCRs), located on the apical surface are stimulated by sweet tasting compounds. Sweet tastants (saccharides) activate the adenylate cyclase, which increases the concentration of the second messenger cAMP. This second messenger closes (directly or indirectly) the basolateral K^+ channels. If synthetic sweeteners (saccharine) get in contact with the receptors, they activate the phospholipase C, which produces IP_3 and DAG. IP_3 increases the concentration of intracellular Ca^{2+}, which leads to transmitter release. DAG activates PKA and PKA activates phosphorylates, which closes the K^+ channels [5].

The umami taste (taste of amino acids) receptor is a metabotropic glutamate receptor, that activates the GPCRs [5].

Different bitter tastants (alkaloids, urea) trigger different receptors of transduction pathways. Organic compounds bind to GPCRs which activates gustducin. The gustducin activates phosphodiesterase which lowers the cyclic nucleotide concentration and closes these channels. Otherwise, GPCRs are stimulated directly from many bitter compounds and activate PLC, which in turn activates the IP_3 production [5].

2.2 Manufacturing process

2.2.1 Pellets

Pellets are defined as small, free flowing agglomerates, spherical, or semispherical particles made up of fine powders or granules of bulk drugs and excipients. The suitable size of pellets is defined to be in a range of 600 - 1000µm [6, 7].

2.2.1.1 Advantages of Pellets

Any desired dose can be created simply by using the respective weight of pellets, changes in the formulation are not necessary. Due to their spherical appearance, pellets have improved flow characteristics, useful for automated processes for which exact dosing is required e.g. capsule filling. Spheres are easier to coat because of the absence of edges and needs lower coating amounts, comparing to granules, which makes a coating process more economical. Spheronization increases hardness, density and decreases the friability, which in turn results in reduced amount of fine particles in the bulk. Due to the improved flowability of pellets, the packaging is easier and the design and formulation of solid dosage forms is more flexible [8].

2.2.1.2 Disadvantages of Pellets

The production of pellets is more expensive compared to the manufacturing of granules or tablets. The equipment is more specialized, controlling the manufacturing process is complicated and requires trained personal. For example, when the wet extrusion and spheronization for producing pellets is used, the adjustment of required binding liquid and the spheronization time are critical for the quality [9].

2.2.2 Pelletization Methods

2.2.2.1 Wet extrusion/spheronization

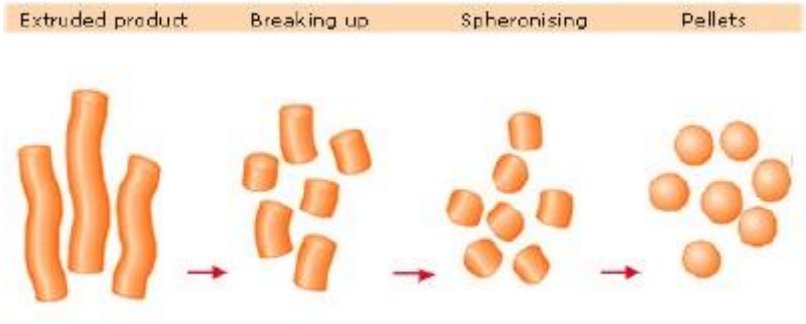

Figure 1: Scheme of pelletization stages of extrusion and spheronization [7]

The extrusion/spheronization process is a multiple step technology to form spherical-sized particles (Figure 1). The process is used to produce multiparticulate systems for immediate or controlled release applications. Extrusion/spheronization normally includes five steps, a sixth step is optional. The first step consists of mixing the dry components to get a homogenous mixture. In the second step, binding liquid is added to the mixture to get a plastic wet mass. Third, the extruder is filled with the wet mass, to form round stripes of uniform diameter. As fourth step, the spheronization of the round stripes to provide spherical pellets is carried out (Figure 2). Then (fifth step), the matter is dried so as to achieve the desired moisture content and the optimal hardness. The optional sixth step is a sieving process, which yields a targeted size distribution. Based on the type of transport of the mass, there are different mechanical transport systems like a screw, gravity or piston type extruder. The most used spheronizer type is the revolving grooved plate, with a variable speed drive unit at the base of a smooth walled drum [6]. The process variables of a wet extrusion/spheronization process are shown in Figure 3.

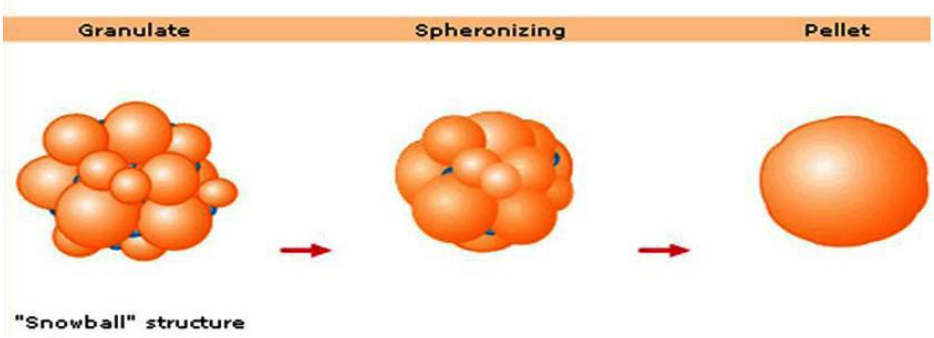

Figure 2: Spheronization steps [10]

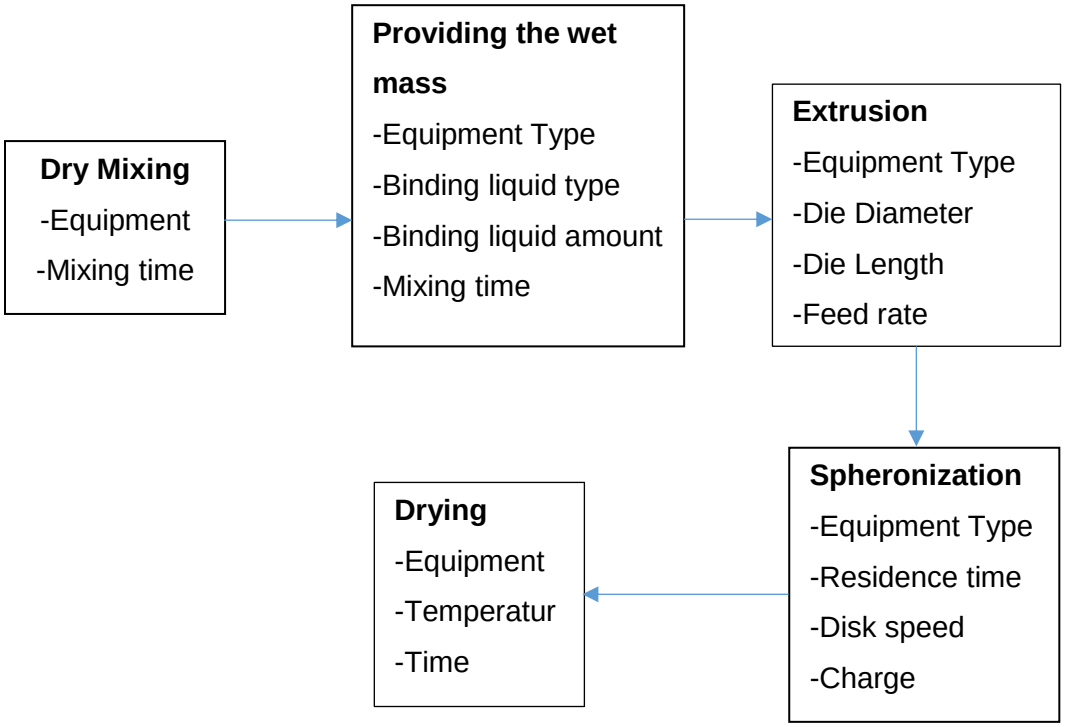

Figure 3: Process flow chart of the wet extrusion/spheronization process, showing the process and formulation variables of each individual step [6]

2.2.2.2 Direct Pelletizing

In direct pelletization, the powder is mixed and moistened with a solvent or binder (see Figure 4, “spraying” and “rolling”). It forms agglomerates without extrusion, which are then rounded out through rotation into uniform and dense pellets. The speed of rotation has a direct influence on the density and size of the pellets. The pellets are dried in a fluid bed and the systems can be made inert if organic solvents are needed [7, 11].

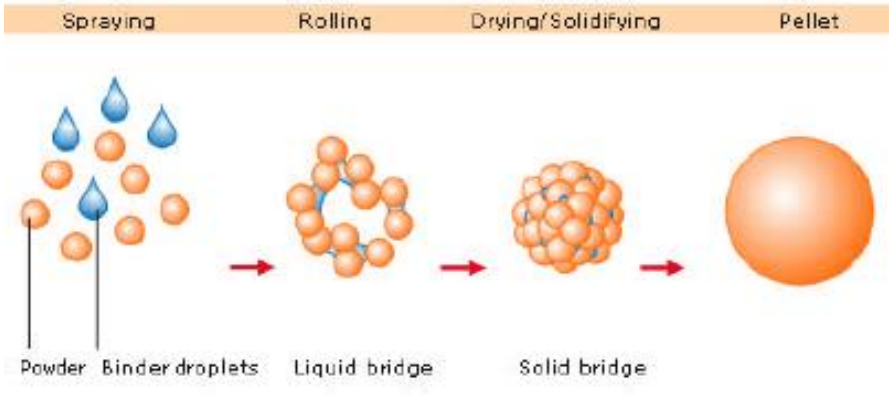

Figure 4: Schematic forming of a pellet via direct pelletizing [12]

2.2.2.3 Pelletizing by Layering

There are two kinds of layering techniques: *solution & suspension layering* and *dry powder layering*. In the solution & suspension layering (Figure 5), the solution or suspension of a drug is layered on a seed material (usually, a coarse crystal or nonpareil). With this method, pellets with uniform size distribution and optimal surface morphology can be produced. A suitable process for layering solutions and suspension on seed materials is the Wurster coating process (Figure 6). This process has a cylindrical partition located in the center of the product chamber and a perforated air distributor plate with a special configuration. The inaccessibility of the nozzles (item ‘D’ in Figure 6) is one disadvantage of the Wurster process. The operation has to be stopped, if the nozzles are clogged at any time during the process and the spray guns must be removed for cleaning [13, 14].

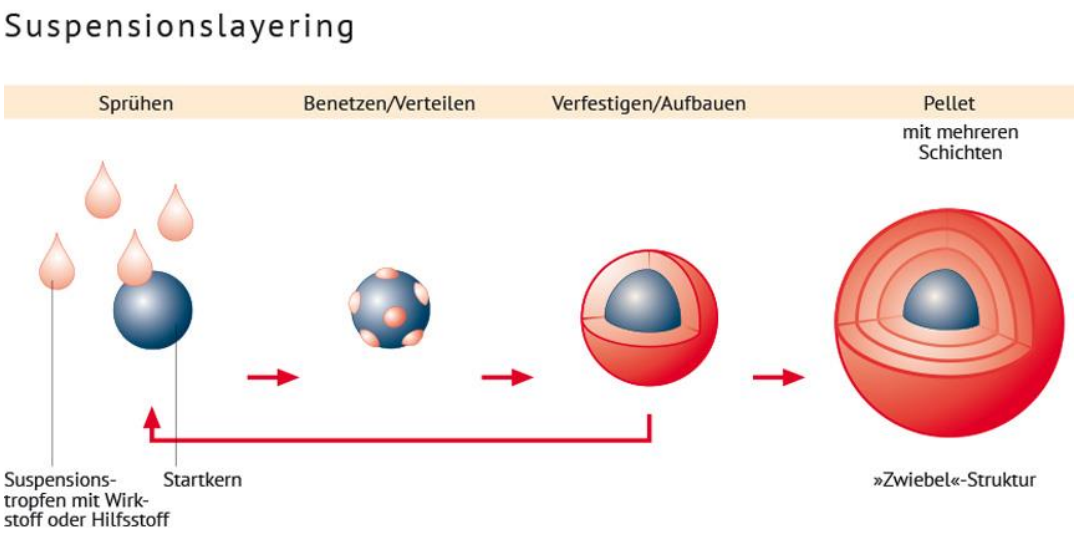

Figure 5: Schematic Representation of Pelletizing with Solution/suspension layering [15]

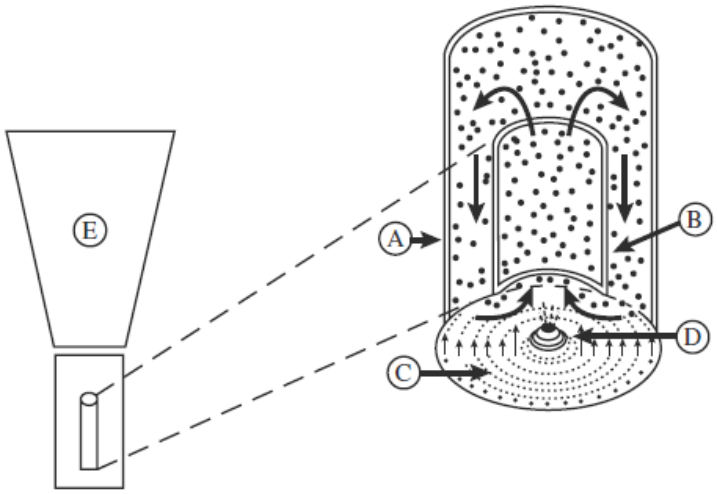

Figure 6: Schematic Representation of Wurster Product Chamber and Process (A) Product chamber, (B) Partition, (C) Perforated air distributor plate, (D) Nozzle, (E) Expansion chamber [10]

Dry powder layering is similar to *solution & suspension layering*. Instead of solutions or suspensions, dry powder is used for layering (Figure 7). Usually, this process is carried out in standard coating pans. The nonpareils or seeds (neutral or inert pellets, beads and spheres) are put into a rotating pan and moisturized by spraying of an adhesive solution. When the wet seed reaches the front end of the pan, the dry powder is added and sticks to the seeds with the help of liquid and solid bridges, see Figure 7 [13, 14, 16].

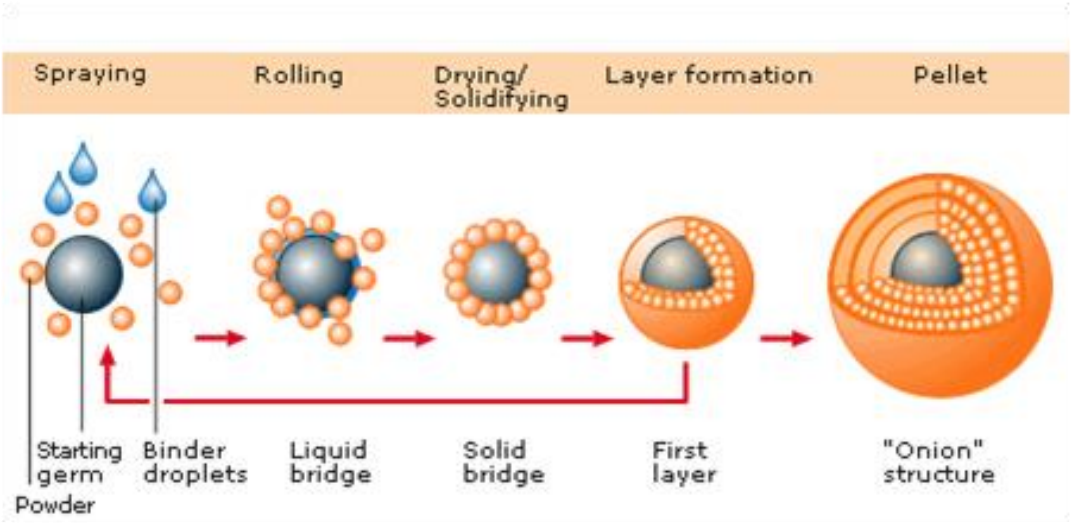

Figure 7: Schematic forming of a pellets via powder layering [17]

2.2.2.4 Spray congealing

In this method, the drug can be melted, dispersed or dissolved in hot melts of gums, waxes, fatty acids or other melting solids. Afterwards the dispersion is sprayed into a stream of air or other gases, which have a temperature under the melting point of the ingredients of the formulations. Using this method, immediate- and controlled-release pellets can be prepared. This depends on the physicochemical properties of the ingredients and other formulation variables [7].

2.2.2.5 Spray-drying

The drug is dissolved in a solution or suspension. Afterwards, the solution or suspension is sprayed into a hot stream to produce dry and spherical particles (Figure 9). This technique increases the solubility of poorly soluble drugs and therefore increases the bioavailability. This technique is also applied for handling heat sensitive pharmaceuticals, such as amino acids, antibiotics, ascorbic acid, liver extracts, pepsin and similar enzymes, protein hydrolysate, and thiamine. Spray drying is not a typical procedure for producing pellets [12, 13]. Figure 8 shows a schematic representation of a general spray-drying process.

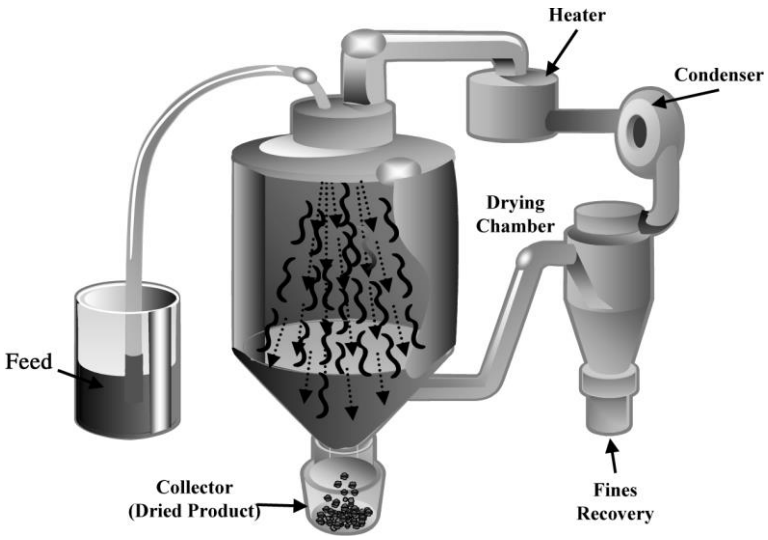

Figure 8: A schematic representation of a general spray-drying process [18]

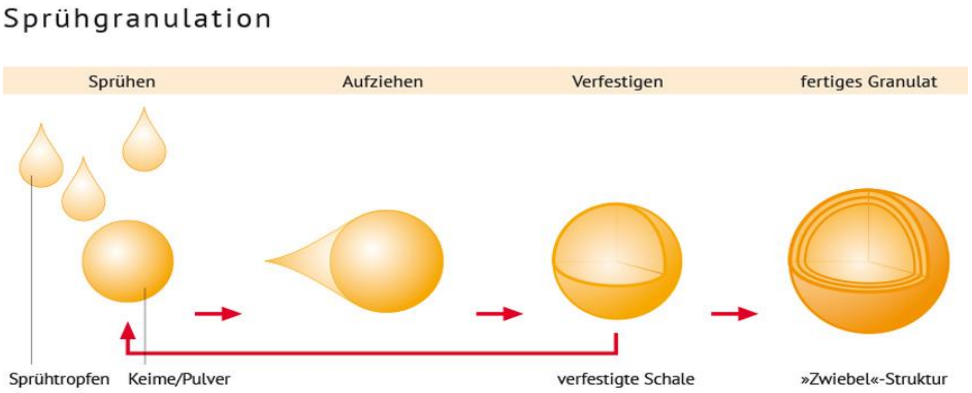

Figure 9: Principle of spray-drying [19]

2.2.2.6 Cryopelletization

In this method, the droplets of liquid (which can be in the form of solution, suspension, or emulsion) are brought into contact with liquid nitrogen at –160 °C, using liquid nitrogen as solidifying medium. The droplets will be freeze very fast due to the rapid heat transfer that occurs between the droplets and the liquid nitrogen [16].

The amount of liquid nitrogen depends on the solids content and temperature of the solution or suspension. 3 - 5 kg of liquid nitrogen are required for the preparation of 1 kg of pellets. The pellets are dried in a conventional freeze dryer. This technique can be used to produce pellets for immediate and controlled release formulation [14, 16].

2.2.2.7 Compression

In the compression method, pellets are formed through the compaction technique: the desired size and shape of pellets is yielded by compacting mixtures or blends of API and excipients under pressure. The process and formulation variables, which determine the quality of pellets, are similar to those used in tablet manufacturing [7].

2.2.2.8 Balling

Balling is also called spherical agglomeration. In this technique, powders are converted into spherical pellets via a continuous rolling or tumbling motion (Figure 10). The preparation of pellets can be divided in two categories: liquid-induced and melt-induced agglomeration. In liquid-induced agglomeration, a defined amount of liquid is added into the powder; in melt-induced agglomeration, the powder is heated to high temperatures. The instruments used for balling range from conventional horizontal drum pelletizers, inclined dish pelletizers, or tumbling blenders to rotatory fluid-bed granulators and high-shear mixers. Balling is mostly used in iron ore and fertilizer industries. It has limited application in the pharmaceutical industry [14].

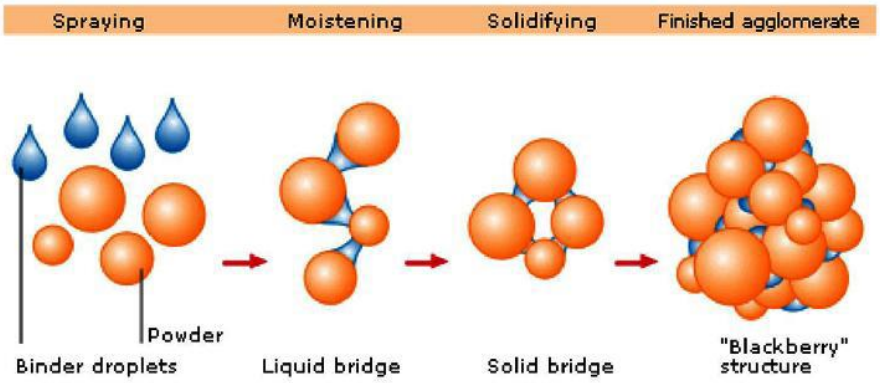

Figure 10: Principle of Balling (spherical agglomeration) [10]

2.2.2.9 Hot-Melt Extrusion

Hot-melt extrusion (HME) is one of the most widely applied processing technologies in the plastic, rubber, and food industry. More than half of all plastic products, including plastic bags, sheets, and pipes are manufactured by this process [16].

In this technique, raw materials under an increasing temperature are pumped through a defined die by a rotating screw. The rotating screw impose mixing and agitation and thus forms a better dispersion [20].

HME can be used for improving the solubility of drugs with low water solubility by forming a molecular dispersion. All components used in the HME process should be thermally stable over the short period of the heating process. Figure 11 illustrates the principle of the hot-melt-extrusion process [12].

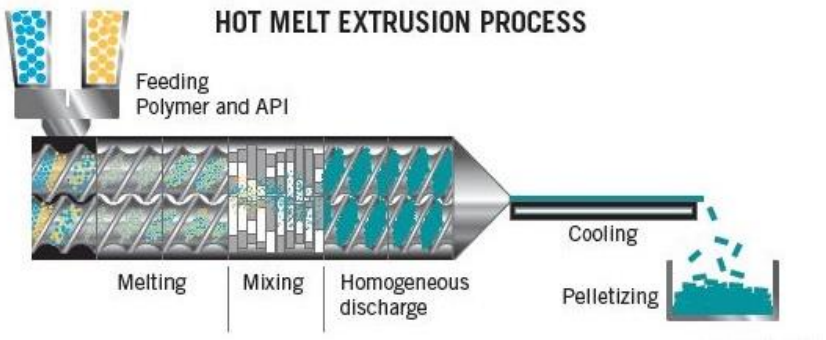

Figure 11: Principle of hot-melt-extrusion process [21]

2.2.3 Coating

The origins of the coating process in the pharmaceutical industry goes back to the kitchen of confectioners in the early nineteenth century. This was the beginning of sugar coating, which was then transferred to pharmacists so as to improve the performance of medicine. The pharmaceutical coating era started in 1950 with the development of the film coating technique using new coating equipment and innovations in polymer chemistry. Perforated pans and fluid bed coaters were invented and improved the coating of solid oral dosage forms [22].

Coating is used for protecting the drug against environmental factors such as oxygen, humidity or light, taste masking, coloration, and modified drug release. In addition, coating can be used to make drugs easier to swallow, give them a more pleasant appearance, and improve mouth-feeling [22, 23].

2.2.3.1 Hot-melt-coating

By Hot-melt-coating, the coating excipients are molten outside of the fluid bed in a suitable container, while the feed material to be coated is suspended in a fluid bed coater. The molten excipients are then sprayed onto the feed material using a heated nozzle (the result is shown in Figure 12) [23, 26, 51].

Bed spray coating provides numerous outstanding advantages due to the avoidance of organic and aqueous solvents. This results in a faster and more cost-effective manufacturing process, since time-consuming evaporation steps or costly solvent recovery and disposal are not required. Additionally, the most frequently applied excipients originate from lipids, which exist in nature, are comparatively cheap and “generally recognized as safe” (GRAS) [23, 51].

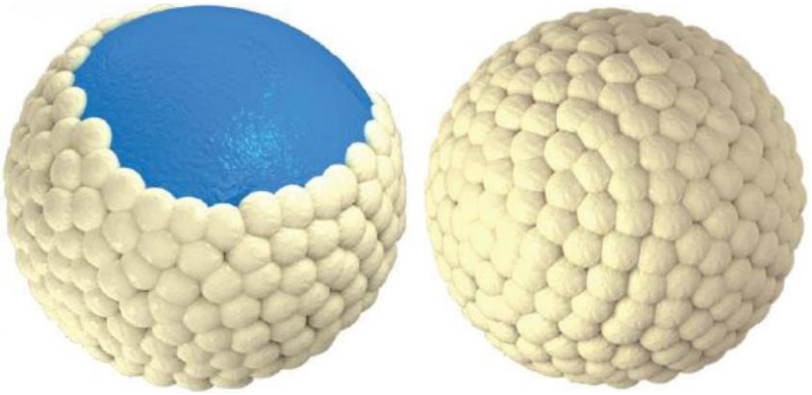

Figure 12: Schematic representation of the hot-melt coated particles. The deposition of lipid droplets (white) at the surface of the substrate (blue) forms a coating after solidification [22]

Excipients for hot-melt-coating are waxes, hydrogenated vegetable oils, polyoxylglycerides, fatty acids and animal fats. To establish the appropriate lipid excipient as coating material for a given substrate, certain criteria must be examined: its effect on drug release, its ability to protect the API against degradation, its ability to mask the substrate's taste, and further a number of critical physicochemical characteristics like melting or crystallization point [22].

Table 2 shows some examples of lipid excipients used in hot-melt-coating.

Excipients	Chemical compostion	Characteristics (MP: Melting point)	Functionality	Examples
Waxes	Esters of fatty acids and long chain alcohols	Hydrophobic MP: 62 - 86°C	Prolonged release	Carnauba wax, candelilla wax, beeswax
Vegetable oils	Mixture of triglycerides, free fatty acids, phospholipids	Often digestible MP: 60 - 71°C	Prolonged release; taste-masking	Hydrogenated cottonseed oil, hydrogenated palm oil, hydrogenated soybean oil
Polyoxylglycerides	Mixture of glycerides and esters of fatty acid and PEG	Partially digestible MP: ≈ 50°C	Prolonged release; immediate release	Stearoyl polyoxyl-6 glycerides
Fatty acids	Long chain fatty acids	MP: 60 - 90°C	Prolonged release	Palmitic acid, stearic acid, behenic acid
Partial glycerides	Mixture of mono-, di-, and triglycerides	MP: 54 - 74°C	Prolonged release; taste-masking; lubrication	Glyceryl palmitostearate, glyceryl monostearate
Animal fats	Clarified butter	MP: ≈ 80°C	Prolonged release	Cow ghee

Table 2: Lipid excipients used in hot-melt coating [22, 26]

2.2.3.2 Hot-melt-coating equipment

Various types of equipment can be used for hot-melt coating: fluid-bed coaters (top-, bottom, or tangential spray), pan coaters, and the turbo jet. Pan coaters are less attractive than the other techniques, because the coating material must be dissolved in a solvent [22]. For this thesis, the pellets and the granules were hot-melt-coated using a fluid bed coater.

Using fluid bed technology, the feed material is placed in a process container and held in the fluidized state by a controlled air or gas flow [27].

There are three main types of fluid-bed processors: top-spray fluid-bed coater, bottom-spray fluid-bed coater, and tangential-spray bed coater, which are illustrated in Figure 13 [24, 27].

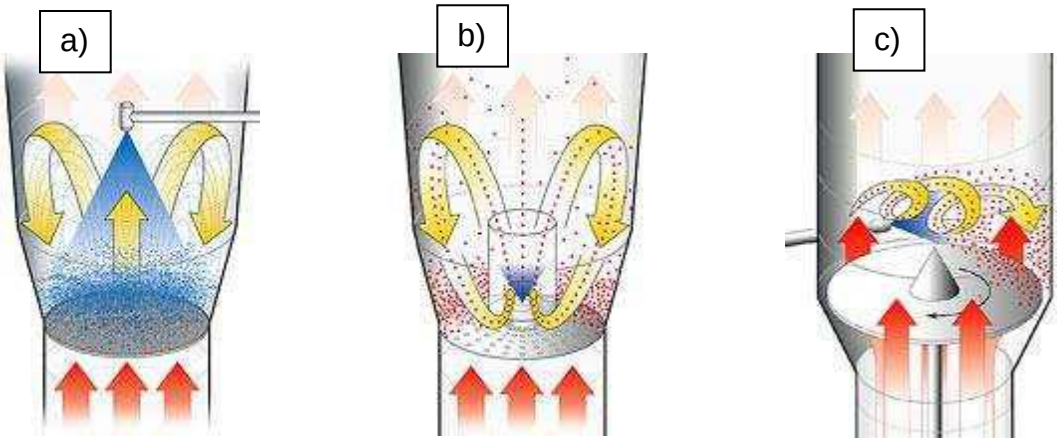

Figure 13: Schematic presentation of a) Top-spray, b) bottom spray and c) tangential spray bed apparatuses [Pictures are a copyright of Glatt Group, Inc., Binzen, Germany]

The Innojet® Laboratory System Ventilus® V-2.5 is a system based on the so-called “air-flow bed” technology and was developed by Dr. h.c. Herbert Hüttlin. The “air-flow bed” optimizes the core processes of the fluid bed: the tangentially and orbital targeted process air results a spirally and orbital product flow, so that the bulk hovers, and float without any friction. The “air-flow bed” process reduces processing time and coating formulation [28].

2.2.4 Evaluation of taste masking

2.2.4.1 In vitro simulated mouth (flask method)

Cantor et al. (2015) used the Erlenmeyer flask for evaluation of the taste masking efficiency of clindamycin HCl coated with Eudragit EPO®. A defined amount of Eudragit® EPO-coated clindamycin beads or a tablet was weighed and put into a 125 mL Erlenmeyer flask. Subsequently, 50 mL of a phosphate buffer with pH 6.8 was added to the Erlenmeyer flask: The buffer simulates the human saliva in the oral cavity. The flask was then placed on a reciprocal shaker. The conditions were 50 rpm with a shaking time of 30, 60 or 120 s, simulating the activity in the mouth. Afterwards, the samples were filtered through a 0.45 µm filter. The amount of drug release was determined by HPLC analysis. Less than 1% API was released after 2 minutes, confirming the efficiency of taste masking. According to the reference, up to 10% API release after 5 minutes is also a criterion for taste masking efficiency [30, 49].

2.2.4.2 In vivo studies

There are several examples in the literature for using *in vivo* studies for the evaluation of taste masking. These studies are important for ranking taste masking quality of prepared drugs.

Applicability of *in vivo* studies is restricted due to the economical and time consuming aspects of training assessor panels for descriptive analysis. In the past few years, new approaches for sensory characterization have been developed. With new methodologies, the applicability of *in vivo* studies can be increased and provided with semi trained assessors [31].

New methodologies are based on the assessment of individual attributes (intensity scales, check-all-that-apply questions also called CATA, flash profiling, paired comparison), analysis of general differences (sorting, projective mapping of Napping®), comparing the given products with product standards (polarized sensory positioning), and general assessment of personalized products (opened-end questions) [31]. The new methodologies are explained in the following paragraphs.

Sorting is by classifying dependent on the criteria. This technique is often used as a systemic method for data collection. The data analysis of sorting is to create a map with the analogies and contrasts between the samples [31]. Sorting is frequently used in psychology, anthropology and sociology [32, 33].

Flash profiling is used for sensory description and is a mix of FCP (free choice profiling) with a comparative appraisal of the samples via ranking. Ranking data is responsible for data analysis and a Generalized Procrustes Analysis (GPA) is applied to achieve product and attributes configurations [31].

In projective methods like mapping and Napping®, samples are presented to the examiner at the same time and afterwards positioned in an A4 or A3 blank paper. Samples are ordered according to analogies and contrasts. The more similar the samples are, the closer they are on the sheet. All coordinates of the position of the samples will be measured for data analyzing [31].

Check-all-that-apply (CATA) are questionnaires, which are mostly used in marketing research. Answers are prepared for questions, and participants can select the best answer [31].

For getting an intensity rating of a set of attributes, intensity scales are used. The main detriment of this method is that the human volunteers must be trained, which leads to higher cost, and time consumption [31].

Polarized sensory positioning is a method, in which samples are evaluated by a fixed set of reference samples. MDS (Multidimensional Scaling) and PCA (Principal Component Analysis) are used for data evaluation [31].

One of the most common used methods is the paired comparison. This method is used to determine specific sensory characteristics whether two samples are identical or different. The data is analyzed using least squares logarithmic regression (LSLR) [31].

2.2.4.3 Electronic tongue

Electronic tongues (E-tongues) became popular in the past few years for the evaluation of *in vitro* taste performance for repeatable analysis of pharmaceutical products. This technique consists of an array of chemical sensors and a pattern recognition system, which is able to determine single substances as well as complex mixtures of various substances. E-tongues simulate human sense of taste that allows for the identification and classification of liquid samples [34].

At time of writing, two types of e-tongues are employed for taste assessments in pharmaceutical formulations: The taste-sensing system TS-5000Z (Intelligent Sensor Technology (INSENT), Japan) and the αAstree e-tongue (Alpha MOS, France) [34].

After successful use in food industry, the usage of these systems has increased in the pharmaceutical industry within the past few years. This is due to the increased importance of developing palatable formulations, especially for children. In contrast to the challenges regarding hazards for taste assessors due to possible toxicity and the subjectivitiy of taste assessors, electronic tongues could offer a safe and objective alternative for taste assessment of drugs. The most common used sensor is the potentiometric sensor [35].

The INSENT taste sensing system is a potentiometric multichannel taste sensor, developed by scientists at Kuyushu University in Japan and is now distributed by Intelligent Sensor Technology (INSENT) Inc. (Japan). The taste sensing system can be loaded with up to eight lipid membrane sensors, with each sensor representing one gustatory stimulus or mouth feeling as for example sourness, saltiness, sweetness, umami, and the three types of bitterness specific for molecules with different ionic character. The change of the membrane potential is measured by implementation of an Ag/AgCl reference electrode, which is separately attached to each sensor head [35].

The α-Astree electronic tongue is also a potentiometric-based system with a seven-sensor probe. This electronic tongue has an Ag/AgCl reference electrode and an auto sampler with 16 or 48 possible sample positions. For the seven-sensor probe, three sets of sensors are available: one for food application, one for pharmaceutical applications, and one set for bitterness intensity measurement of new chemical

entities. Compared to the INSENT taste masking system, the α-Astree electronic tongue sensors are not assigned to a specific taste quality of gustatory feeling. The sensor technology is based on chemically-modified field-effect-transistor technology (ChemFET) [35].

3.0 Material and Methods

3.1 API

Active pharmaceutical ingredients (API) are substances or combinations of substances that are used in pharmaceutical products. They furnish pharmacological activity or otherwise have a direct effect in diagnosis, cure, mitigation, treatment of prevention of disease, or have direct effect in restoring, correcting, or modifying physiological functions in human beings [36].

3.1.1 Paracetamol

Paracetamol, also called N-acetyl-p-aminophenol ($C_8H_9NO_2$, MW = 151.2 g/mol) is a white crystalline powder with a solubility of 12.78 mg/mL in water at 20 °C, and a light bitter taste, which comes from the hydroxyl group. It is an analgesic drug with antipyretic properties [37, 39].

Paracetamol is used in this thesis, because of its bitter taste and it is on the WHO (World Health Organization) Mode List of Essential Medicines, which are the most important medications needed in a basic health system [39]. Figure 14 shows the chemical structure of paracetamol

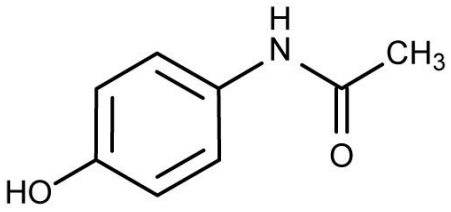

Figure 14: Chemical structure of Paracetamol [39]

The mechanism of action is not fully proved, but the main action is to inhibit the enzyme Cyclooxygenase-2 (COX-2). This enzyme regulates the building of prostaglandins, which is released in the case of inflammation in the body. Prostaglandins stimulate the pain continuously and irritates nerve endings. Paracetamol eliminates the fever

substances (Pyrogens) in the brain, which regulate the body temperature and is eliminated in the liver [38].

In the liver, paracetamol conjugates and gets oxidized by CYPs. By oxidation, the toxic by-product N-Acetyl-p-benzoquinone (genotoxic and carcinogenic) is produced, which induces apoptosis (process of programmed cell death) and necrosis (cell death by autolysis). In high concentrations, paracetamol is toxic for the liver [37].

The oral single dose of paracetamol is 500 mg for adults; in pediatrics, the dose depends on the body weight. Rare side effects increased liver enzymes, and very rare side effects are blood disorders, bronchospasm of predisposed patients, hypersensitivity reactions, skin reactions, risk of an analgesic nephropathy, and digestive problems [37 - 39].

3.1.2 Ibuprofen Sodium

Ibuprofen sodium is a white crystalline salt derivate of ibuprofen ($C_{13}H_{17}O_2Na$, MW = 228.3 g/mol) and is highly water soluble (100mg/ml).

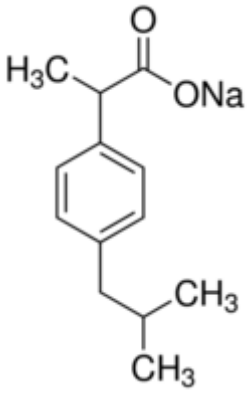

Figure 15: Chemical structure of ibuprofen sodium [40]

Ibuprofen is a derivate of the propionic acid and a non-steroidal anti-inflammatory drug with analgesic and antipyretic properties. The exact mechanism of action is unknown but it inhibits non-selectively COX-1 and COX-2, which are responsible for the formation of the prostaglandins, the mediators of pain, inflammation, and fever.

Antipyretic effects may, due to action on the hypothalamus, result in an increased peripheral blood flow, vasodilation, and subsequent heat dissipation. The inhabitation of COX-1 causes some of the side effects of ibuprofen including gastrointestinal ulceration. The maximal oral single dose of ibuprofen is 800 mg for adults [41, 42].

Adverse side effects of ibuprofen are nausea, dyspepsia, diarrhea, constipation, gastrointestinal bleeding, headache, dizziness, rash, salt, and fluid retention and hypertension [42].

Infrequent adverse side effects are esophageal ulceration, heart failure, hyperkalemia, renal impairment, confusion, and bronchospasm [42].

Ibuprofen is used in this thesis, because it is on the WHO (World Health Organization) Mode List of Essential Medicines, which are the most important medications needed in a basic health system [42]. Figure 16 shows the chemical structure of ibuprofen.

The very bitter taste of ibuprofen comes from the phenyl group ($C_6H_5CH_3$) [29].

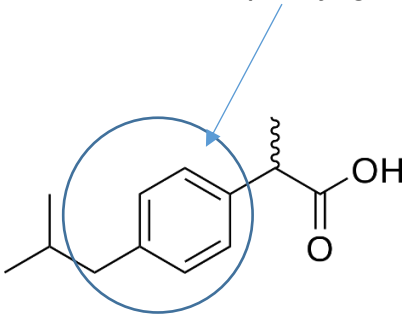

Figure 16: Chemical structure of ibuprofen [42]

3.2 Coating Agents

3.2.1 TWEEN® 65

Tween® 65 (provided by Croda GmbH, Germany) is the commercial name of polysorbate 65 ($C_{100}H_{194}O_{28}$). It is a solid, light yellow substance and soluble in alcohol and lipids. The IUPAC name is Polyoxyethylen(20)-sorbitan-tristearat [46]. Figure 17 demonstrates the chemical structure of Tween® 65.

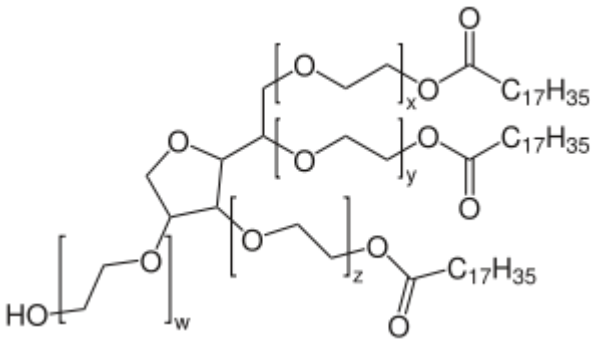

Figure 17: Chemical structure of Tween® 65 [46]

Tween® 65 is synthetically received from sorbitol, a sugar alcohol. Tween® 65 is a strong non-ionic emulgator with no chemical degradation after exposure to acids and/or temperature. This surfactant, e.g., stabilized the structure of lipids. Tween® 65 has an HLB Value of 10.5, so it is possible to produce O/W-emulsions. It is biodegradable and the ADI-Value is 10 mg/kg. In this thesis, we used Tween® 65 as an emulsifier. Emulsifiers are surfactants, which are lowering the surface tension between two immiscible phases. Tween® 65 has an amphiphilic character, which means that it has hydrophilic and hydrophobic groups [43 - 46].

3.2.2 Dynasan® 116

Dynasan® 116 (provided by IOI Oleo GmbH, Witten, Germany) is the commercial name of tripalmitin ($C_{51}H_{98}O_6$). It is a white to almost white fine crystalline powder [25]. Figure 18 shows the chemical structure of Dynasan® 116.

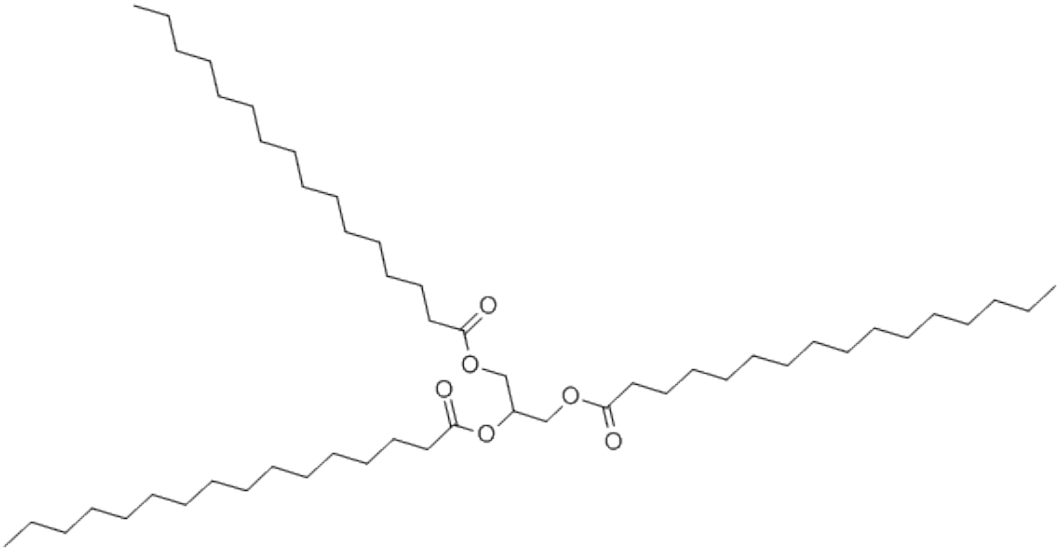

Figure 18: Chemical structure of Dynasan® 116 [25]

Dynasan® 116 is a triacylglyceride (TAC) with three palmitic acid residues [47]. We used Dynasan® 116 in this study as the main coating material.

3.3 Pellets production

The API used was paracetamol (a gift from Hermes Arzneimittel GmbH, Germany). The excipients were Ludiflash® (provided by BASF, Ludwigshafen, Germany) and Avicel® 101 (Werba-Chem GmbH, Vienna, Austria). The pellets were produced with 50% (w/w) API, 40% (w/w) Ludiflash® and 10% (w/w) Avicel® 101. No concentrations above 50% were used in this study, because pre-studies showed no proper results: the plasticity of paracetamol at higher percentages is too low. All materials were weighed and then mixed with an open planetary mixer (Kenwood Chef, Kenwood, Hampshire, Great Britain). For the wet granulation, a mixture of ethanol and distilled water 40% (w/w) was manually added into the planetary mixer. After mixing, the wet mass was added into an axial single screw extruder (Extruder Pharmex T35, Gabler Maschinenbau GmbH, Lübeck, Germany, Figure 20) and extruded through an 800 µm plate (Figure 22). The screw turned with a constant speed of 80 rpm. The stripes immediately fell into a spheronizer (Sphaeromat 250 T, Gabler Maschinenbau GmbH, Lübeck, Germany, Figure 21) with a cross-hatched friction plate of 250 mm diameter.

The spheronizer rotated with 700 rpm for 30 s. All experiments were carried out six times at room temperature. The wet pellets were dried in an exsiccator with Silica gel of 2 - 5 mm particle size with indicator (Carl Roth GmbH + Co. KG, Karlsruhe, Germany) for a minimum of 12 hours. Figure 19 demonstrates an axial endplate feed screw extruder.

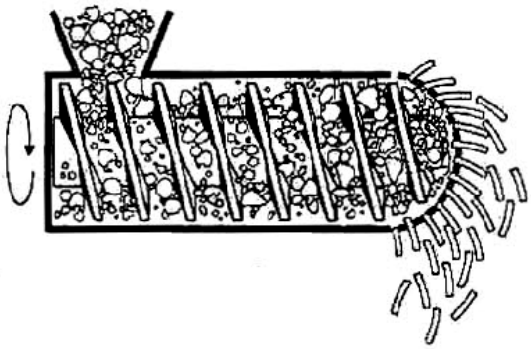

Figure 19: Axial/Endplate Feed screw Extruder [12]

Figure 20: Extruder Pharmex T35, Gabler Maschinenbau GmbH, Lübeck, Germany

Figure 21: Spheronizer

Figure 22: Stripes after extrusion

3.4 Hot-melt-coating of paracetamol pellets

For taste masking, the pellets were coated with a hot-melt-coating process using a fluid bed Innojet® Laboratory System Ventilus® V-2.5/1 with an Innojet® Hot-Melt-Device IHD-1 (Figure 23). 400 g of paracetamol pellets were coated with a mixture of Dynasan® 116 and different percentages of Tween® 65 as emulsifier. The mixture of Dynasan® 116 and Tween® 65 was weighed and molten in an extern vessel. Table 3 shows the parameters used for hot-melt-coating and the composition of the formulations.

Coating ratio [%]	Spraying pressure [bar]	Spraying rate [g/min]	Air flow rate [m^3/h]	Ratio of Tween® 65 in coating [%]	Ratio of Dynasan® 116 in coating [%]	Inlet Temperature [°C]
35	1	10	75	20	80	25
20	0,5	5	75	30	70	25
10	0,6	5	75	30	70	25

Table 3: Parameter used for hot-melt-coating paracetamol pellets

Figure 23: Hot-melt-coating apparatus

3.5 Production of hot-melt-coated ibuprofen sodium granules

The hot-melt-coated ibuprofen sodium granules had been produced previously by Diogo Gomes Lopes (PhD student at KF University of Graz). The ibuprofen sodium granules were manufactured using a roller compactor (Alexanderwerk WP120 Pharma, Alexanderwerk, Germany). After granulation, the granules had been hot-melt-coated with a fluid bed Innojet® Laboratory System Ventilus® V-2.5/1 with an Innojet® Hot-Melt-Device IHD-1 (Figure 23). Table 4 shows the parameters used for hot-melt-coating and the composition of the formulations.

Coating ratio [%]	Spraying pressure [bar]	Spraying rate [g/min]	Air flow rate [m^3/h]	Ratio of Tween® 65 in coating [%]	Ratio of Dynasan® 116 in coating [%]	Inlet Temperature [°C]
50	0.8	7.5	30	5	95	25
42.5	1.1	5	37.5	10	90	30
35	1.4	7.5	30	5	95	25

Table 4: Parameters used for Hot-melt-coating ibuprofen sodium granules

3.6 Analytics

3.6.1 Dissolution test of coated paracetamol pellets and ibuprofen sodium granules

A dissolution tester without autosampler was used (Erweka dissolution tester DT 820-USP Apparatus 2, Germany).

After warming up the dissolution medium in the vessels, amounts of pellets or granules equal to 25 mg of paracetamol or 600 mg of ibuprofen sodium was weighed and added to the vessels (for paracetamol, the single dose was reduced, because the UV photometer was not able to measure higher doses of paracetamol and to prevent dilution failures). All samples were tested for 2 hours and the dissolution tests were undertaken in triplicates. The conditions of the dissolution test for paracetamol are shown in Table 5.

Dissolution tester	Erweka dissolution tester DT 820 without autosampler
RPM	100
Method	USP type 2 - paddles
Dissolution medium	Distilled water
Volume [ml]	900
Medium temperature [°C]	37°C
Sampling points [min]	5, 15, 20, 25, 30, 45, 60, 90, 120
Sample volume [ml]	1

Table 5: Dissolution test conditions for paracetamol pellets

Because of the different formulations that had been prepared in the case of paracetamol, the sample amount had to be varied according to each respective formulation. Table 6 shows the sample weight used for each formulation, always yielding a dose of 25 mg of paracetamol.

Formulation	Single dose [mg]	Weighing [mg]
35% coating amount with 20% Tween® 65 and 80% Dynasan® 116	25	76.9
20% coating amount with 30% Tween® 65 and 70% Dynasan® 116	25	62.5
10% coating amount with 30% Tween® 65 and 70% Dynasan® 116	25	56.0
Without coating	25	50.0

Table 6: The amount of paracetamol pellets used for the dissolution test

The ibuprofen sodium composition and physical properties are shown in Table 7. The dissolution conditions of ibuprofen sodium are shown in Table 8.

Active compound	Ibuprofen sodium
Excipients (% w/w)	2.5 Sorbitol (Parteck SI 150) 3.5 Isomalt (GalenlQ 721)
Friability (% w/w)	52.5
Bulk density [mg/ml]	0.5 mg/ml

Table 7: Ibuprofen sodium composition and physical properties

Dissolution tester	Erweka dissolution tester DT 820 without autosampler
RPM	100
Method	USP type 2 – paddles
Dissolution medium	Phosphoric Buffer pH 6,80
Volume [ml]	900
Medium temperature [°C]	37°C
Sampling points [min]	1, 5, 15, 20, 25, 30, 45, 60, 90
Sample volume [ml]	1,5

Table 8: Dissolution test conditions of ibuprofen Sodium

The calibration standards were prepared by dissolving pure API in the required amount in the dissolution medium. The calibration standards were made for 120%, 100%, 80%, 60% and 40% of the concentration in the dissolution vessels.

3.6.2 Flow-through-cell (open loop)

Another method to provide a dissolution test is the USP type 4 apparatus (Figure 24). Using the flow-through cell, a constant flow of the dissolution medium (in this case distilled water) is applied through an amount of 5 g glass beads with a diameter of 1 mm and one single dose of ibuprofen sodium (600mg) and paracetamol (500mg), respectively, are placed in the cell. The calibration of the pump is very important for the work with a flow through cell. For an efficient calibration, it is necessary to use the flow medium with 37 °C temperature. Samples were taken at different times (see Table 9) and time measurement started, when water and pellets got in contact for the first time.

The extruding liquid was collected *(open loop)* and at certain sampling times, 1 ml of the liquid was directly filled into a HPLC vial. The conditions used are shown in Table 9.

Dissolution tester	Pharma Test Flow-through-cell (prototype)
Flow through [mlmL/h]	450
Method	USP type 4 – flow-through-cell (*open loop*)
Dissolution medium	Distilled water
Medium temperature [°C]	37°C
Sampling points [min]	1, 5, 15, 30, 45, 60, 90, 120
Sample volume [mL]	1

Table 9: Flow-through-cell conditions

Figure 24: Flow-through-cell apparatus USP 4

3.6.3 UV-vis

All samples were analyzed with an UV-Vis photometer (Perkin Elmer Lambda 950, USA). The absorption was measured for paracetamol in wave lengths between 240 and 250 nm and for ibuprofen sodium between 260 and 270 nm. The samples were measured by filling in a 1.5 mL quartz glass cuvette (Hellma Analytics QS High Precision Cell 10mm light path, Germany); the reference solution was distilled water.

3.7 Evaluation of taste masking

3.7.1 In vitro taste masking study: Simulated mouth (flask method)

The target of this *in vitro* taste masking study was to simulate the human mouth and evaluate the taste masking of hot-melt-coated products in the laboratory. The simulated saliva was a phosphate buffer with a pH value of 6.8 similar to the pH of human saliva in the mouth.

3.7.2 Simulated Saliva production

The simulated Saliva was produced in accordance with the European Pharmacopeia (Ph. Eur.) 8.0 buffer solution pH 6.8.

One g of potassium dihydrogen phosphate, ≥ 98%, 2 g disodium hydrogen phosphate, ≥ 99% (both Sigma-Aldrich Chemie GmbH, Munich, Germany) and 8,5 g of sodium chloride (Carl Roth GmbH + Co KG, Karlsruhe, Germany) were dissolved in 900 mL of ultrapure water. The pH value was measured with a pH-meter (inoLab® 720, WTW GmbH, Germany) and adjusted, when the pH-value is too high or too low. Afterwards, the volume was adjusted to 1000 mL [48].

In case of hot-melt-coated ibuprofen sodium granules, TWEEN® 20 was added to the simulated saliva, to increase the wetting. Regarding paracetamol, all pellets were wetted with the simulated saliva, so TWEEN® 20 was not necessary.

3.7.3 Flask method

Twelve 25 mL Erlenmeyer flasks were used. Every Erlenmeyer flask was filled with 10 mL of the simulated saliva and sufficient amounts of coated pellets or granules containing one dose (500 mg of paracetamol or 600 mg of ibuprofen sodium). The samples were shaken for 30 s, 60 s, 90 s, and 120 s on a laboratory shaker (VWR Incubator LG Shaker, Leuven, Belgium) at 50 rpm and 37 °C in order to simulate agitation in the mouth. Samples were taken manually after 30 s, 60 s, 90 s, and 120 s. The particle size of the ibuprofen sodium granules was so small that direct sampling was not possible (the granules adhered on the surface of the pipette tip): The simulated saliva, containing the ibuprofen sodium granules, was filtered through a 4 - 12 µm hardened, ashless filter paper for quantitative analysis (Hahnemühle FineArt GmbH, Dassel, Germany). All samples were measured with a UV photometer and the results were expressed as the mean value of three replicates.

3.8 *In vivo* taste masking study

An *in vivo* taste masking study was carried out to correlate the measured results with a human taste panel. The eleven human volunteers, 6 women and 5 men were not trained. Their age ranges from 24 years to 48 years; two participants were smoker, and the study was open and monocentric.

For preparation, the volunteers received a row of low-concentrated solutions of paracetamol and ibuprofen sodium. The selected concentrations were from the *in vitro* study of coated particles after 30 s (for paracetamol 1_P, 2_P, 4_P (Table 10), and for ibuprofen sodium 1_I, 2_I and 4_I (Table 11)). When the concentrations were too low to have discernible bitter taste, four higher concentrations were produced. The concentrations are shown in Table 10 for paracetamol and in Table 11 for ibuprofen sodium.

Solution	Concentration of paracetamol [mg/ml]
1_P	0.02
2_P	0.1
3_P	0.4
4_P	0.7
5_P	0.9
6_P	1.1
7_P	1.3
8_P	1.5

Table 10: Concentrations of paracetamol solutions for the preparation of volunteers

Solution	Concentration of ibuprofen sodiu [mg/ml]
1_I	0.41
2_I	1.5
3_I	2.0
4_I	2.5
5_I	3
6_I	3.5
7_I	4
8_I	4.5

Table 11: Concentrations of ibuprofen sodium solutions for the preparation of volunteers

Every human volunteer received 1 mL of the solution, which was taken in the mouth for assessing the bitter taste for 30 s. The bitter taste was evaluated by volunteers by giving scores from 1 (does not taste bitter) to 5 (extremely bitter). After 30 s, the volunteers spitted the solution out and washed out their mouth three times with water. The concentrations of the tested solutions are shown in Tables 12 and 13 for paracetamol and ibuprofen sodium, respectively.

Solution	Concentration [mg/ml]
1_P	0.02
2_P	0.1
3_P	0.4
4_P	0.7
6_P	1.1
8_P	1.5

Table 12: Concentration of tested paracetamol solutions

Solution	Concentration [mg/ml]
1_I	0.41
2_I	1.5
3_I	2.0
4_I	2.5
6_I	3.5

Table 13: Concentration of tested ibuprofen sodium solutions

In the second part, after three hours regeneration time, the human volunteers received three samples of hot-melt-coated ibuprofen sodium and paracetamol samples. They washed their mouth out with water and swallowed the saliva. Afterwards they received 1 mL of pure water, which they kept in the mouth for the whole test. Then they received a single dose of coated ibuprofen sodium 600 mg or paracetamol 500 mg particles. The taste was evaluated by volunteers in two steps: the first step was marked by the sensation of the first unpleasant taste, the second step by the sensation of a taste so unpleasant that it caused the volunteer to spit the sample out. The volunteers had the particles no longer than two minutes in their mouth. There was a break of three minutes between every sample. This procedure was used for evaluation of all samples listed in Table 14 and Table 15.

Samples	Amount [g]
35% coating amount with 20% Tween® 65 and 80% Dynasan® 116	1.5
20% coating amount with 30% Tween® 65 and 70% Dynasan® 116	1.3
10% coating amount with 30% Tween® 65 and 70% Dynasan® 116	1.1

Table 14: Amount of paracetamol pellets used for the in vivo taste masking evaluation

Samples	Amount [g]
50% coating amount, 5% Tween® 65 with 95% Dynasan® 116	1.3
42,5% coating amount, 10% Tween® 65 with 90% Dynasan® 116	1.1
35% coating amount, 5% Tween® 65 with 95% Dynasan® 116	1.0

Table 15: Amount of ibuprofen sodium pellets used for the in vivo taste masking evaluation

4.0 Results and Discussion

4.1 Dissolution

4.1.1 Dissolution test of coated paracetamol pellets

The following Figures 25, 26, and 27 show the results of the dissolution tests of the paracetamol pellets (carried out in triplicates) after 2 hours for the following coating formulations: 20% Tween® 65 and 80% Dynasan® 116, using 35% coating amount; 30% Tween® 65 and 70 % Dynasan® 116, using 20% coating amount; 30% Tween® 65 and 70 % Dynasan® 116, using 10% coating amount.

According to FDA definition, a formulation is taste masked, if only 10% of API is released within the first 5 minutes of the *in vitro* dissolution testing [49].

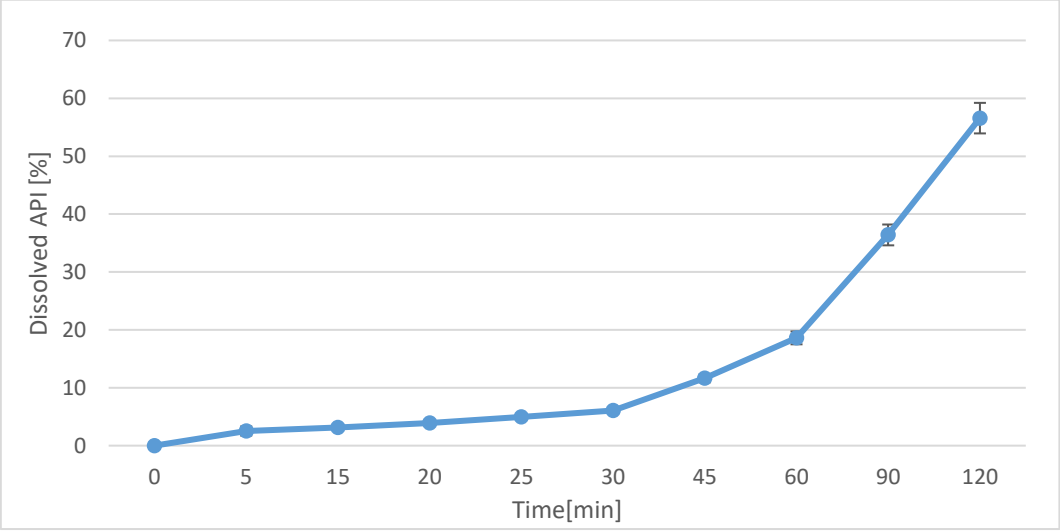

Figure 25: Dissolution profile of paracetamol from coated pellets containing 20% Tween® 65 and using 80 % Dynasan® 116, 35% coating amount

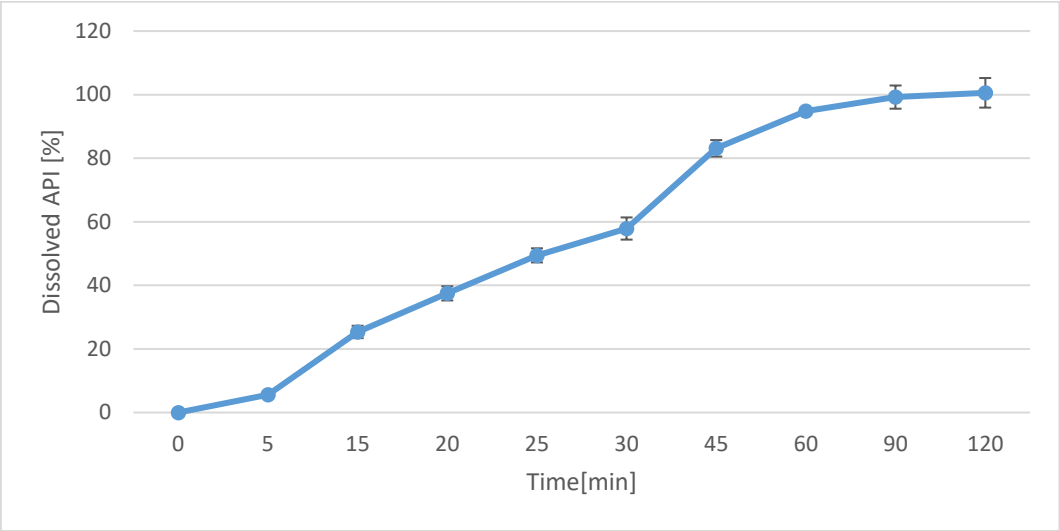

Figure 26: Dissolution profile of paracetamol from coated pellets containing 30% Tween® 65 and using 70 % Dynasan® 116, 20% coating amount

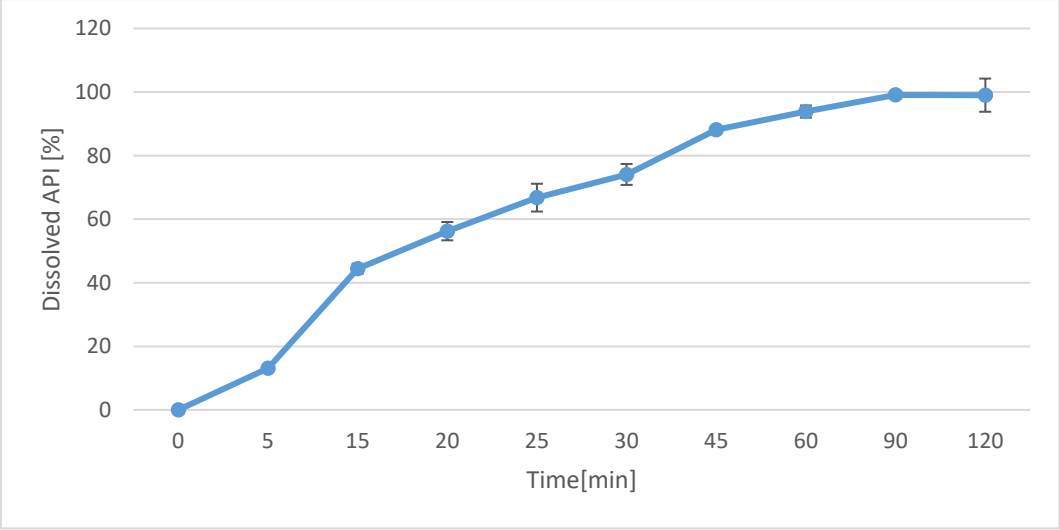

Figure 27: Dissolution profile of paracetamol from coated pellets containing 30% Tween® 65 and using 70 % Dynasan® 116, 10% coating amount

The aim of the hot-melt-coating was to gain an immediate release profile of API, which means the release of 85% API within the first 30 minutes of the dissolution test. Figure 25 shows the release profile of paracetamol using 35% of coating containing 20% Tween® 65 and 80% Dynasan® 116. It can be observed that at 60 min the API release increases rapidly, but at that time the API release is still under 20%. Obviously, the coating amount of these particles is too high: 85% of API release was not achieved

after even 30 minutes. In the first five minutes, only 2.5% of API was released, so according to the FDA's definition, the coating has achieved taste masking.

Figure 26 shows the release profile of paracetamol from pellets coated with 70% Dynasan® 116 and 30% Tween® 65 using 20% of coating. As can be observed, 85% of API was released after 46 minutes. The 100% release was reached after two hours and after five minutes 5.5% of API was released, so according to the FDA's definition, the coating has achieved taste masking.

Figure 27 shows the release profile of paracetamol from pellets coated with 70% Dynasan® 116 and 30% Tween® 65 and using 10% coating amount. The 85% API release is reached after 43.4 minutes. 100% of the API is also released after two hours. The significant difference between using 10% and 20% coating amount is the faster initial API release observed with the 10% coating amount, which can be due to the insufficient coating of particles. The release of 13.1% of API from pellets coated with 10% coating material within the first 5 minutes of the in vitro dissolution test does not meet the FDA's criteria for taste masking.

4.1.2 Dissolution test of coated ibuprofen sodium granules

Figures 28, 29, and 30 show the dissolution profile of the coated ibuprofen sodium granules, measured with HPLC (the HPLC measurements were carried out by Diogo Gomes Lopes (PhD student at KF University of Graz)).

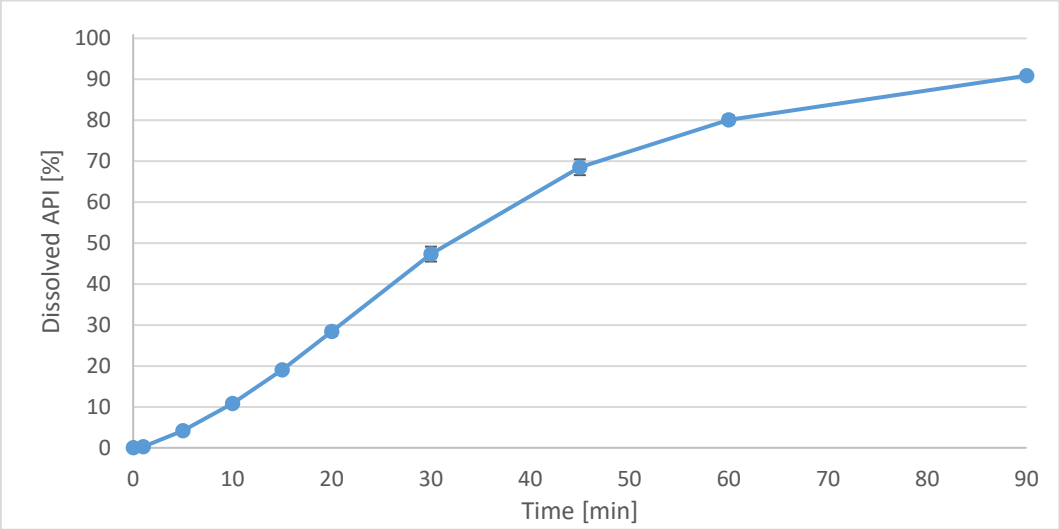

Figure 28: Dissolution profile of ibuprofen from coated granules containing 5% Tween® 65 and using 95 % Dynasan® 116, 50% coating amount

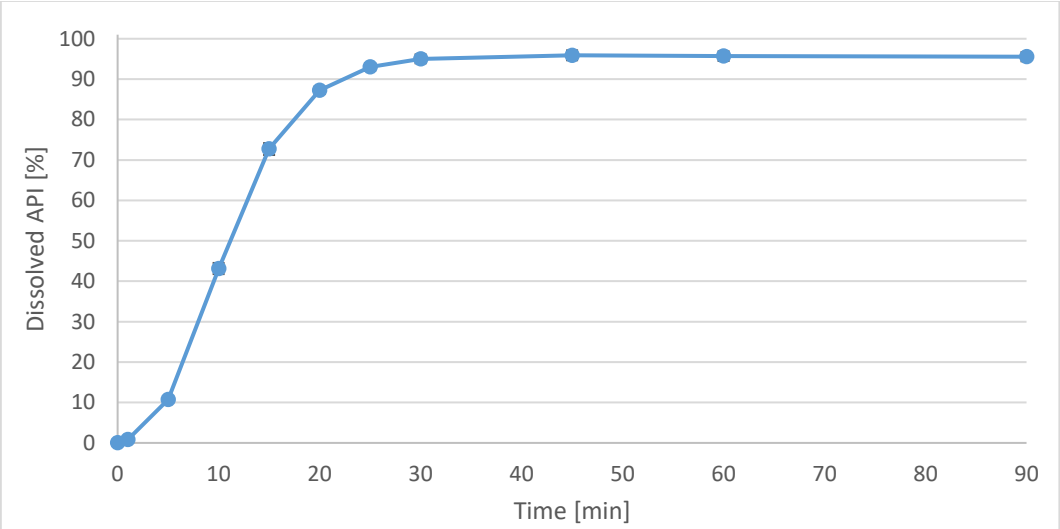

Figure 29: Dissolution profile of ibuprofen from coated granules containing 10% Tween® 65 and using 90 % Dynasan® 116, 42,5% coating amount

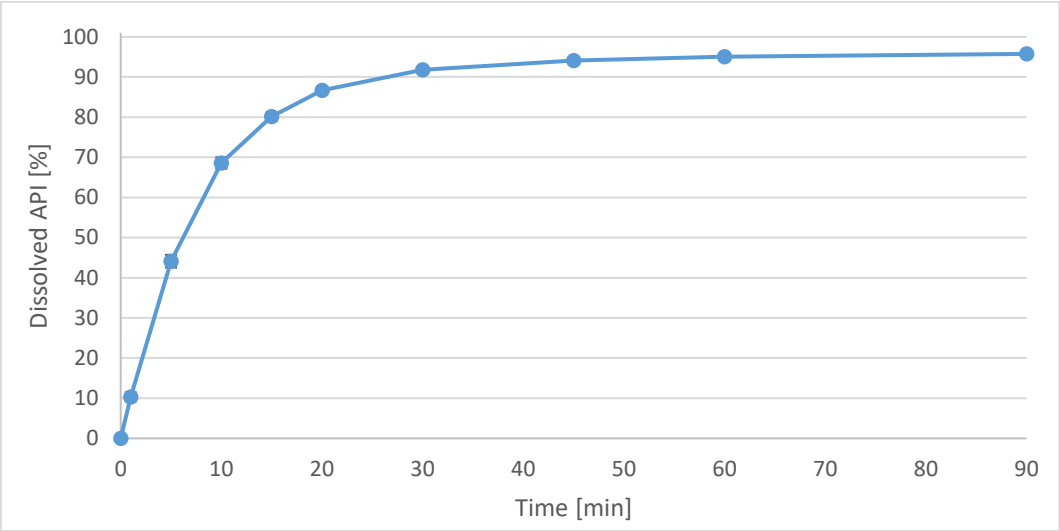

Figure 30: Dissolution profile of ibuprofen from coated granules containing 5% Tween® 65 and using 95 % Dynasan® 116, 35% coating amount

The first profile (Figure 28) indicates a sufficient taste masking of ibuprofen sodium granules, because after 5 minutes the API release is only 4.2%. The 100% release is not reached after 90 minutes and 85% of API release is achieved between 70 minutes and 80 minutes.

Figure 29 shows the profile of the moderate taste masking. After 5 minutes, 10.7% of API is released. The immediate release profile was achieved, because 85% of API was released between 10 and 20 minutes.

Figure 30 shows the release profile of samples with 35% coating amount, 5% Tween® 65 with 95% Dynasan® 116. These particles possess insufficient taste masking, as 44.1% of API was released within the first 5 minutes of the dissolution test.

Comparing the release profiles of paracetamol pellets and ibuprofen sodium granules shows the faster release profile of the ibuprofen granules inspite of having higher coating amounts and less percent of Tween® 65 in the coating formulation. This can be due to the irregular shape of ibuprofen granules, resulting in a less perfection of coating.

4.2 Flow through cell *(open loop)*

4.2.1 Dissolution test of paracetamol pellets using flow through cell

Figures 31, 32, and 33 show the release profiles of the paracetamol from different coated pellets.

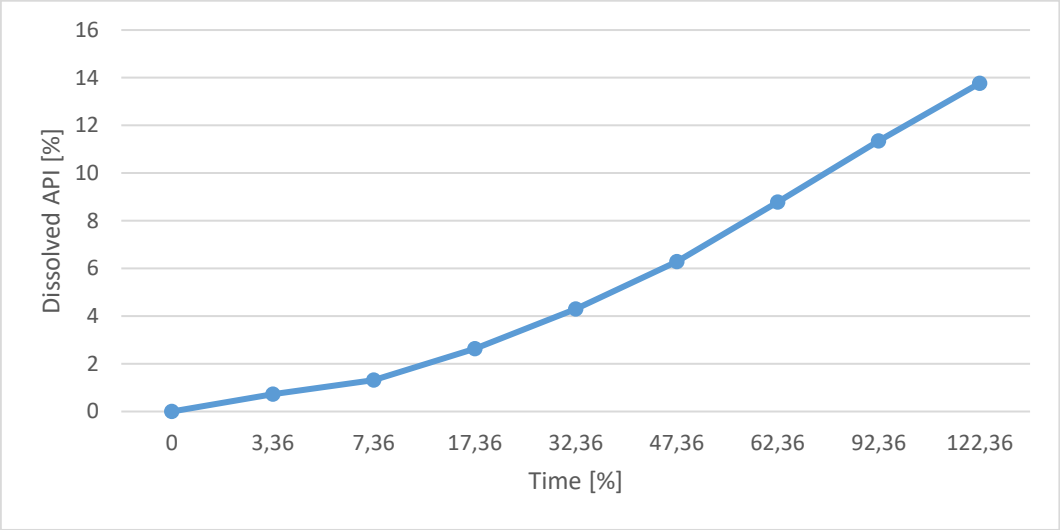

Figure 31: API release profile of paracetamol from coated pellets, 35% coating amount containing 20% Tween® 65 and 80% Dynasan® 116

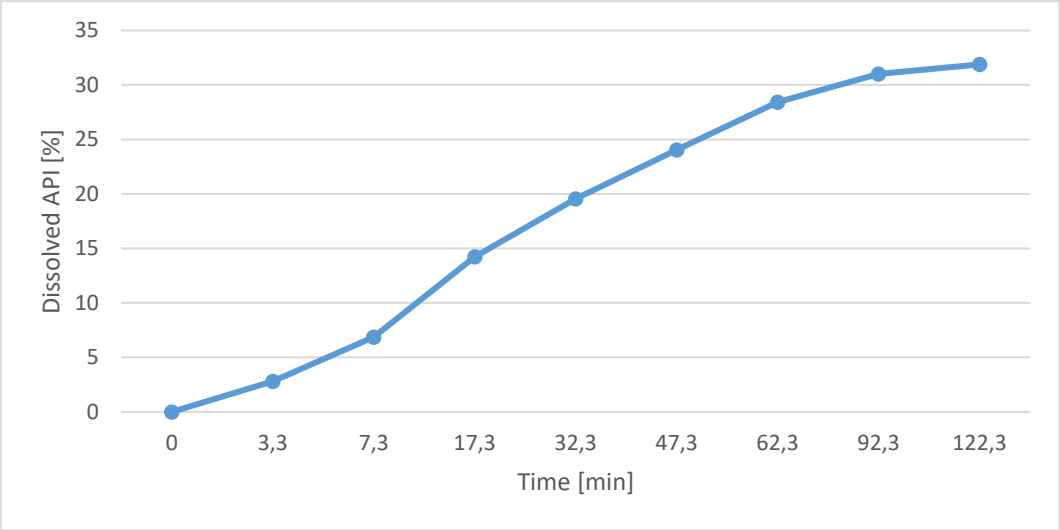

Figure 32: API release profile of paracetamol from coated pellets, 20% coating amount containing 30% Tween® 65 and 70% Dynasan® 116

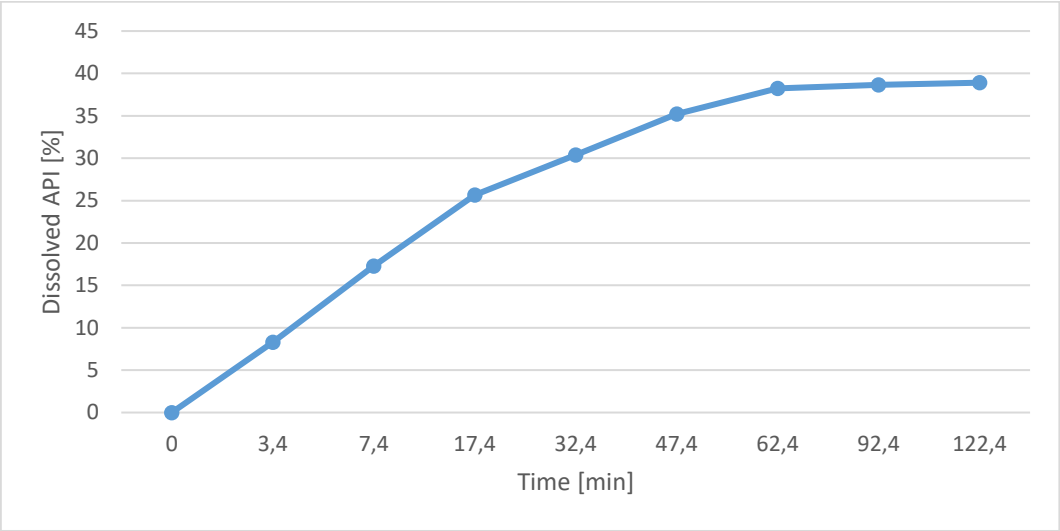

Figure 33: API release profile of paracetamol from coated pellets, 10% coating amount containing 30% Tween® 65 and 70% Dynasan® 116

The API release profile using a flow-through cell looks different from the gained profile using the paddle dissolution tester, because the flow through was 450 mL/h. This flow through is comparable with 450 rpm in a dissolution test apparatus 2, USP.

Using a flow through cell, the sampling was carried out directly at the exit of the cell. After 2 hours, only 13.8% of API was released from the formulation with 35% coating amount containing 20% Tween® 65 and 80% Dynasan® 116 (Figure 31). The 10% API release was reached between 62.3 minutes and 92.3 minutes. If less than 10% API is released after five minutes, the particles are taste masked (according to FDA's criterion of taste masking), so this leads to the assumption that the pellets with 35% coating amount containing 20% Tween® 65 and 80% Dynasan® 116 were sufficiently taste-masked.

The highest API concentration could be measured at 122.3 minutes by pellets with 20% coating amount containing 30% Tween® 65 and 70% Dynasan® 116 (Figure 32). Whether 100% release of API was not achieved, due to the low flow through. 10% of API was released between 7.3 minutes and 17.3 minutes. So, after five minutes less than 10% API was released, indicating sufficient taste masking of the pellets.

In the case of last formulation with 10% coating amount containing 30% Tween® 65 and 70% Dynasan® 116 (Figure 33), the highest concentration of API release was

measured at 122.4 minutes. The 10% API release was located between 3.4 minutes and 7.4 minutes. Judging from the fact that after 3.4 minutes 8.2% and after 7.4 minutes 17.3% API was released, we conclude that this formulation was not sufficiently taste-masked.

4.2.2 Dissolution test of coated ibuprofen sodium granules using flow through cell

Figures 34, 35, and 36 show the release profile of the ibuprofen granules, executed with a flow-through cell.

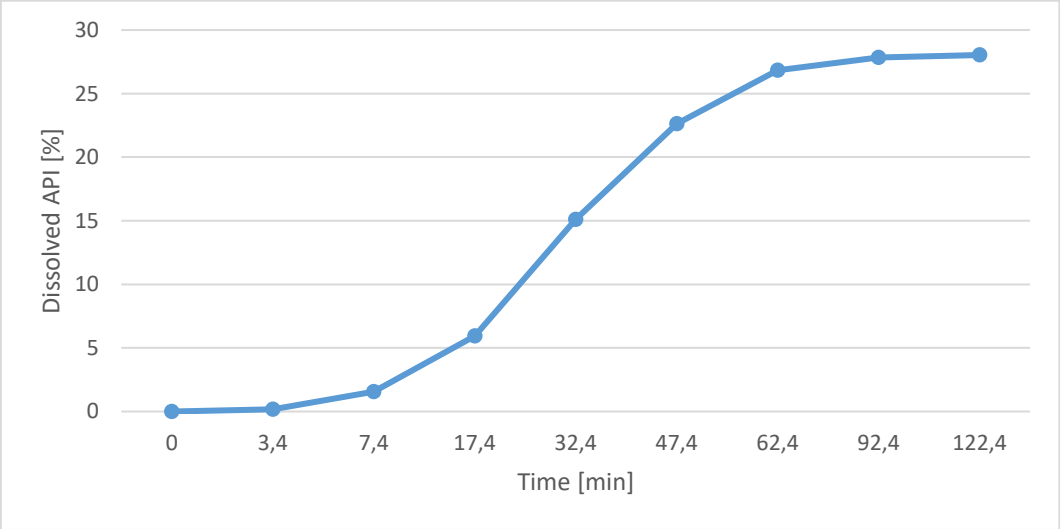

Figure 34: API release profile of ibuprofen sodium from coated granules, 50% coating amount containing 5% Tween® 65 and 95% Dynasan® 116

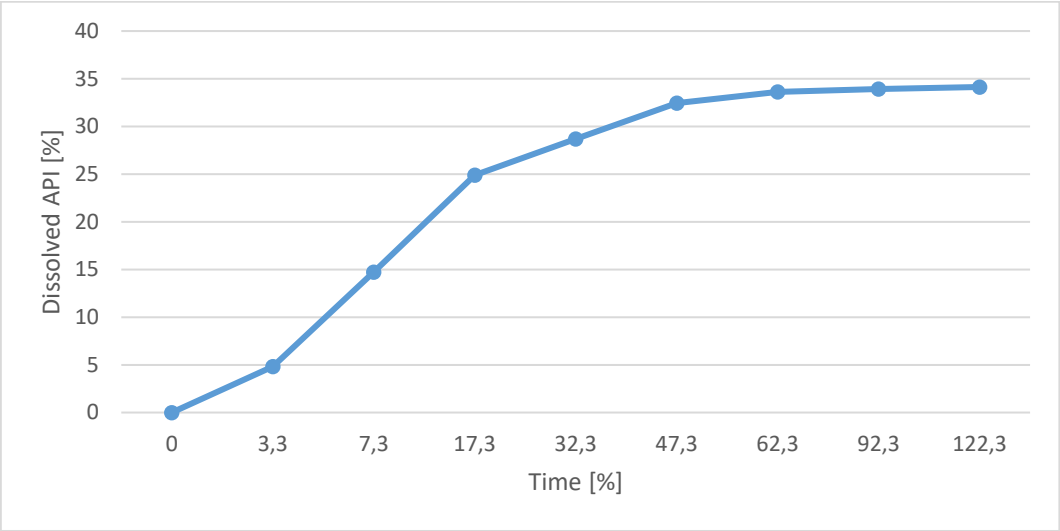

Figure 35: API release profile of ibuprofen sodium from coated granules, 42,5% coating amount containing 10% Tween® 65 and 90% Dynasan® 116

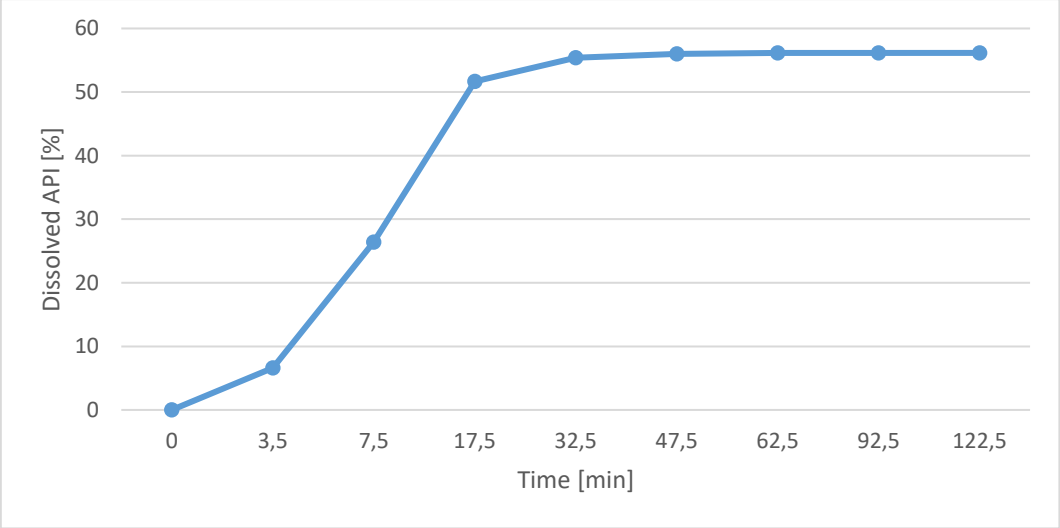

Figure 36: API release profile of ibuprofen from coated granules, 42% coating amount containing 5% Tween® 65 and 95% Dynasan® 116

The first figure (Figure 34), shows the profile of the 50% coating amount, 5% Tween® 65 with 95% Dynasan® 116 ibuprofen sodium granules. The highest measured API release was after 122.4 min. 100% API release was not achieved due to the low flow through. 10% of API was released between 17.4 minutes and 32.4 minutes. So, after five minutes less than 10% API was released, indicating sufficient taste masking of the granules.

The highest measured API release of the 42.5% coating amount, 10% Tween® 65 with 90% Dynasan® 116 samples was after 122.3 minutes (Figure 35). The 10% API release was located between 3.3 minutes and 7.3 minutes. So, after five minutes approximately 9% API was released, indicating sufficient taste masking of the granules.

In the case of the last formulation with 35% coating amount, 5% Tween® 65 with 95% Dynasan® 116 (Figure 36), the highest measured API release was after 122.5 minutes. Due to the low flow through, the 100% API release could not be determined. 10% API was released between 3.5 minutes and 7.5 minutes. Judging from the fact that after 3.5 minutes 6.6% API and after 7.5 minutes 26.4% API was released, we conclude that this formulation was not sufficiently taste-masked.

4.3 *In vitro* simulated mouth study

The objective of the method is to simulate the API release in the human mouth.

4.3.1 Coated paracetamol pellets

The following Figures 37, 38 and, 39 show the API release profiles of the *in vitro* simulated mouth study.

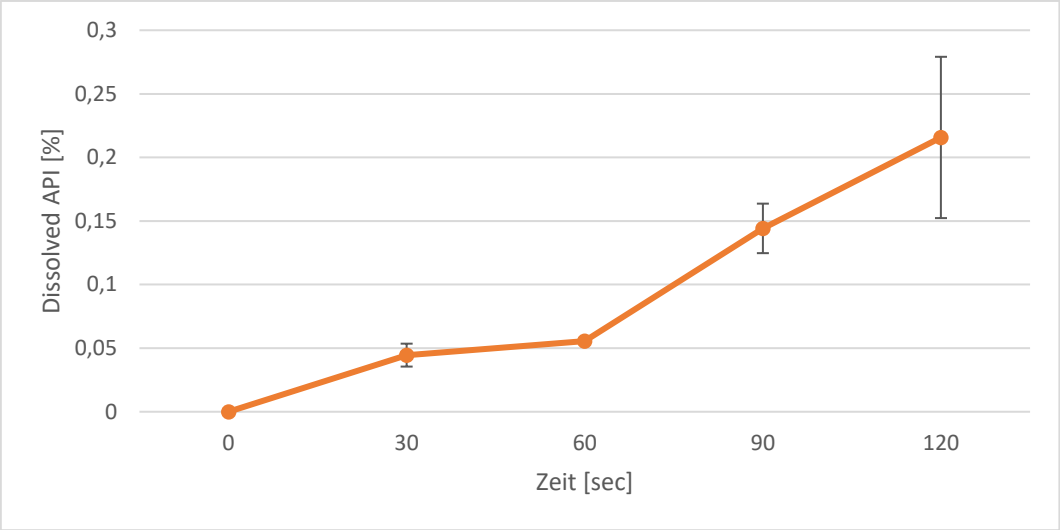

Figure 37: API release profile of coated paracetamol pellets, 35% coating amount containing 20% Tween® 65 and 80% Dynasan® 116, in vitro simulated mouth study

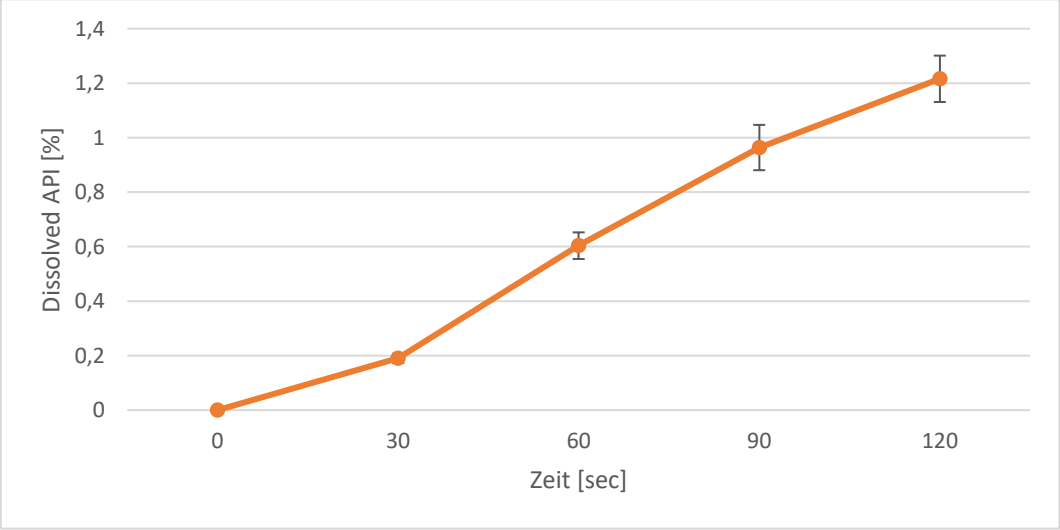

Figure 38: API release profile of coated paracetamol pellets, 20% coating amount containing 30% Tween® 65 and 70% Dynasan® 116, in vitro simulated mouth study

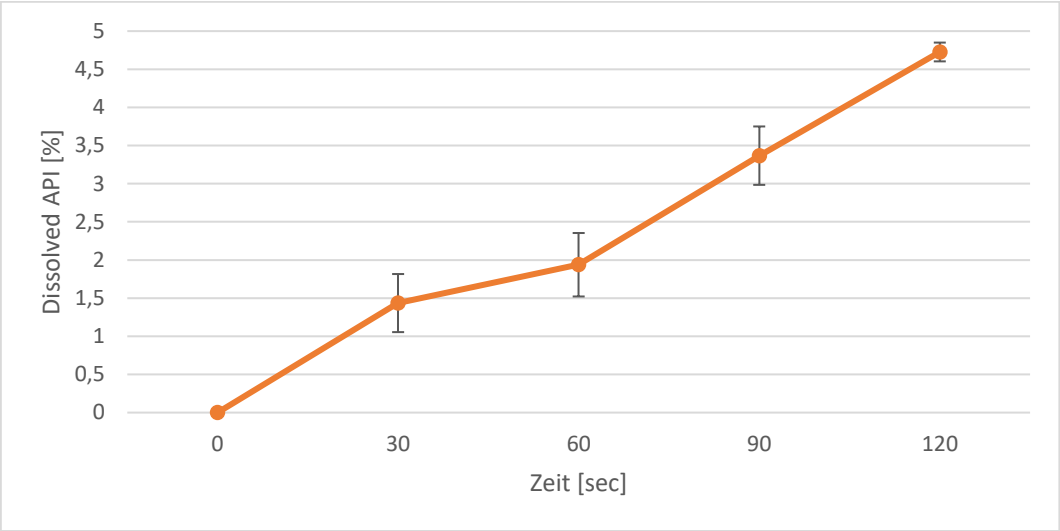

Figure 39: API release profile of coated paracetamol pellets, 10% coating amount containing 30% Tween® 65 and 70% Dynasan® 116, in vitro simulated mouth study

The samples were taken at 30 s, 60 s, 90 s, and 120 s. Using 35% coating containing 80% Dynasan 116 and 20% Tween® 65, 0.04% of API was released after 30 s. The concentration of paracetamol was increased to 0.2% after 2 minutes (Figure 37). In the case of samples coated with 20% coating, containing 70% Dynasan® 116 and 30% Tween® 65, the release of API increased from 0.2% after 30 s to 1.2% after two minutes (Figure 38). The last Figure 39 shows a release profile of 1.4% after 30 s to 4.7% after two minutes.

4.3.2 Coated ibuprofen sodium granules

The next three Figures 40, 41 and 42 demonstrate the API release of the coated ibuprofen sodium granules.

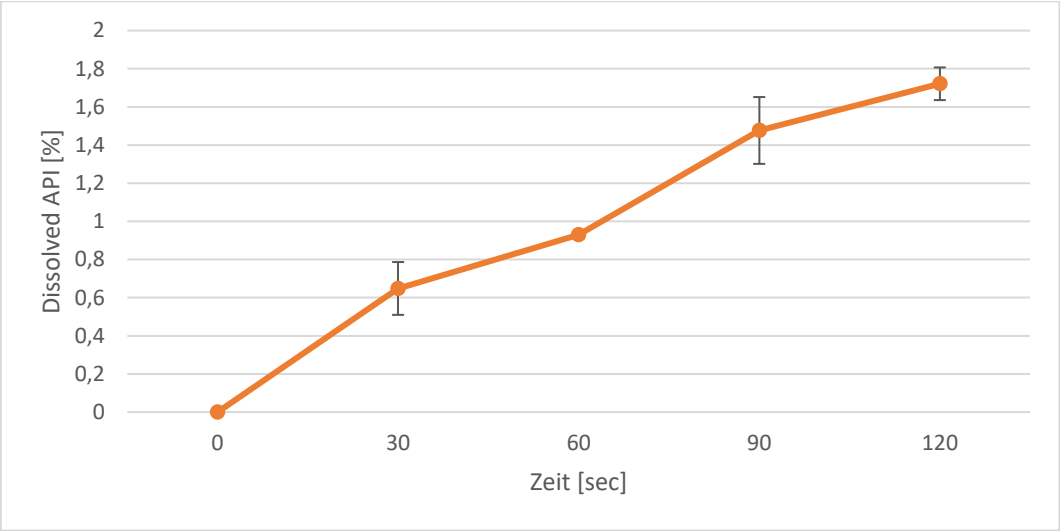

Figure 40: API release profile of coated ibuprofen sodium granules, 50% coating amount containing 5% Tween® 65 and 95% Dynasan® 116, in vitro simulated mouth study

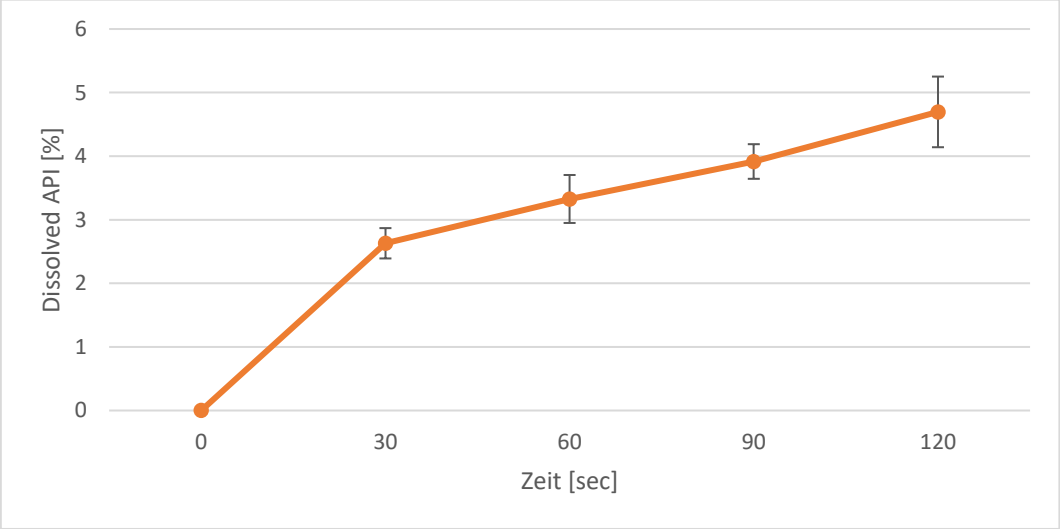

Figure 41: API release profile of coated ibuprofen sodium granules, 42,5% coating amount containing 10% Tween® 65 and 90% Dynasan® 116in vitro simulated mouth study

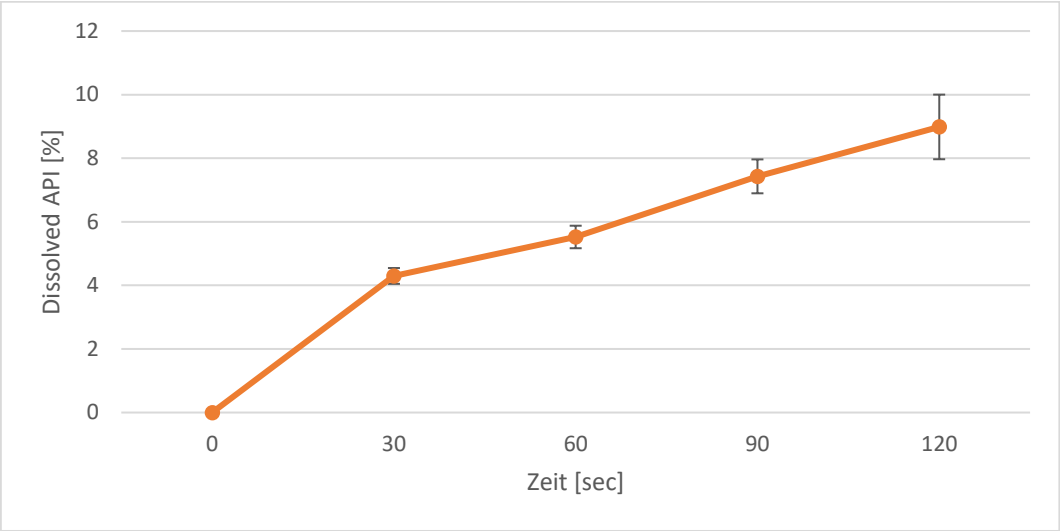

Figure 42: API release profile of coated ibuprofen sodium granules, 35% coating amount containing 5% Tween® 65 and 95% Dynasan® 116, in vitro simulated mouth study

The samples were also taken at 30 s, 60 s, 90 s, and 120 s. By using 50% coating containing 95% Dynasan® 116 and 5% Tween® 65, 0.6% of API was released after 30 s. The concentration of ibuprofen sodium was increased after two minutes up to 1.7%. (Figure 40). Samples coated with 42.5% coating, containing 90% Dynasan® 116 and 10% Tween® 65, the release of API increased from 2.6% after 30 s to 4.7% after two minutes (Figure 41). The last Figure 42 (35% coating amount containing 5% Tween® 65 and 95% Dynasan® 116) shows a release profile of 4.3% after 30 s to 9.0% after two minutes.

4.4 *In vivo* taste masking study

The *in vivo* taste masking study was carried out with 11 human volunteers, 6 women and 5 men. Their age ranges from 24 years to 48 years; two participants were smoker.

4.4.1 Preparing the volunteers

The first part of the study was to prepare the volunteers. All eleven volunteers received solutions with different concentrations. The taste of solutions was then rated on a scale from 1 - 5, selecting 1 for “no bitter taste” and 5 for “very unpleasant taste”.

4.4.2 Paracetamol

The concentration of the solutions was selected based on the API concentrations of the *in vitro* simulated mouth study of paracetamol.

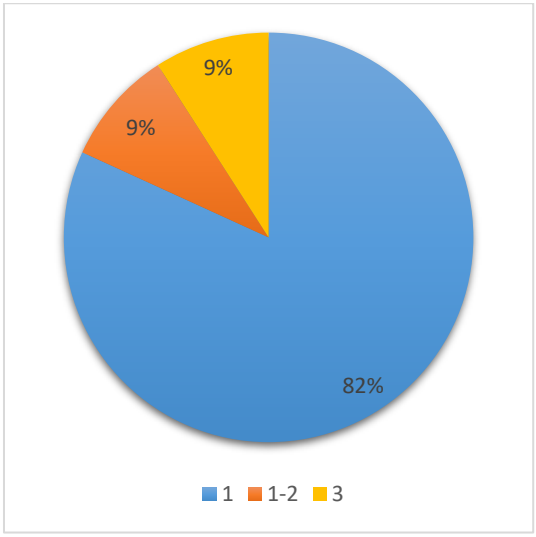

Figure 43: Frequency of 1_P solution

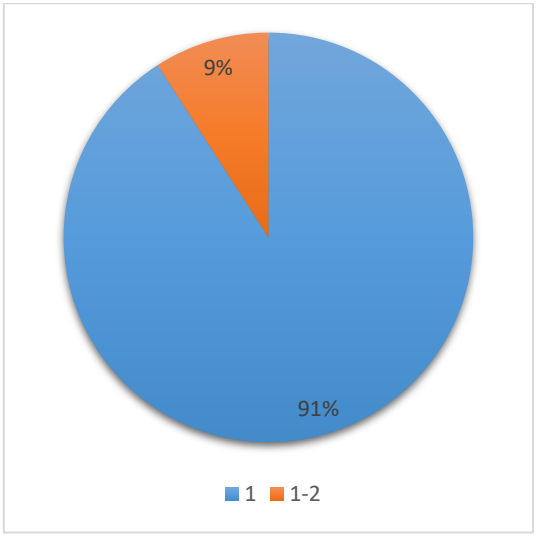

Figure 44: Frequency of 2_P solution

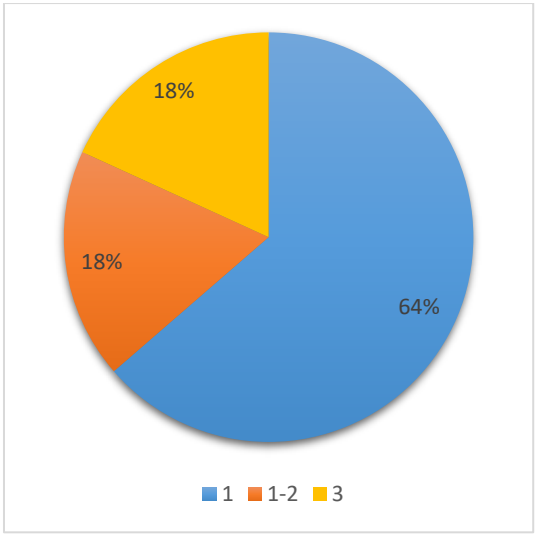

Figure 45: Frequency of 3_P solution

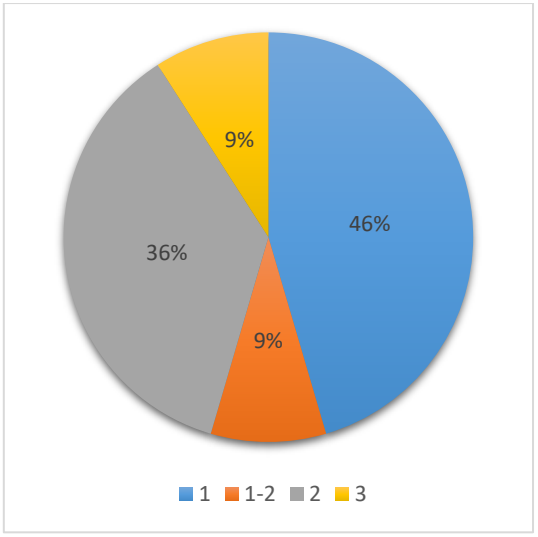

Figure 46: Frequency of 4_P solution

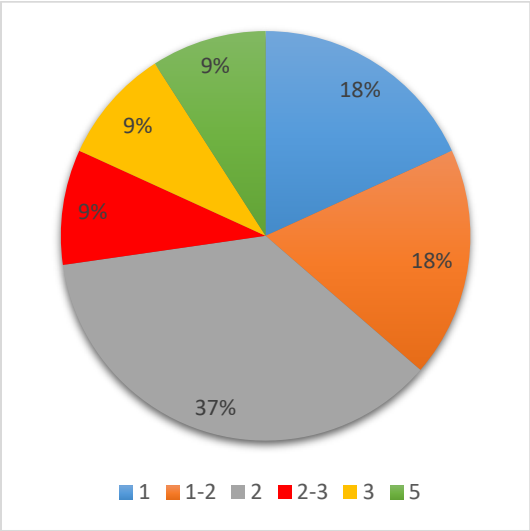

Figure 47: Frequency of 6_P solution

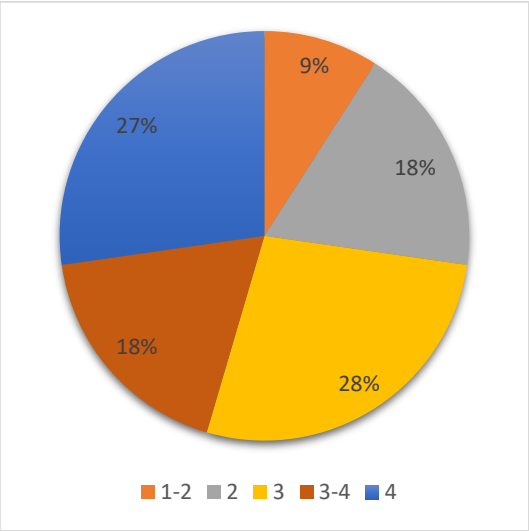

Figure 48: Frequency of 8_P solution

In the Figures (43 – 48) it can be seen, that with an increasing concentration of paracetamol in solutions from 0.4 mg/ml to 4.5 mg/ml, the rate of bitterness also increases from 1 to 5. Codes 1_P to 8_P are described in Table 12.

4.4.3 Ibuprofen sodium

The concentrations of the solution were selected based on the API concentrations of the *in vitro* simulated mouth study of ibuprofen sodium.

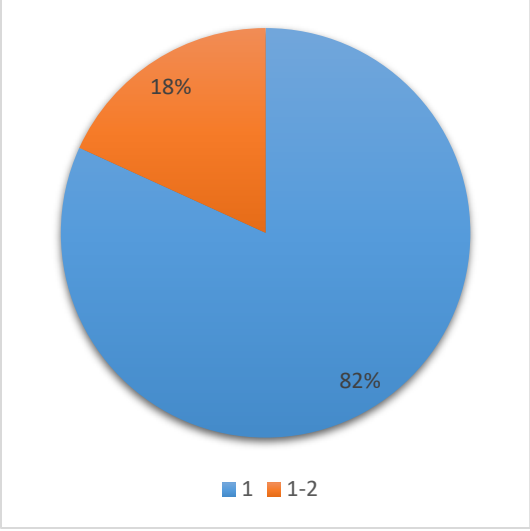

Figure 49: Frequency of 1_I solution

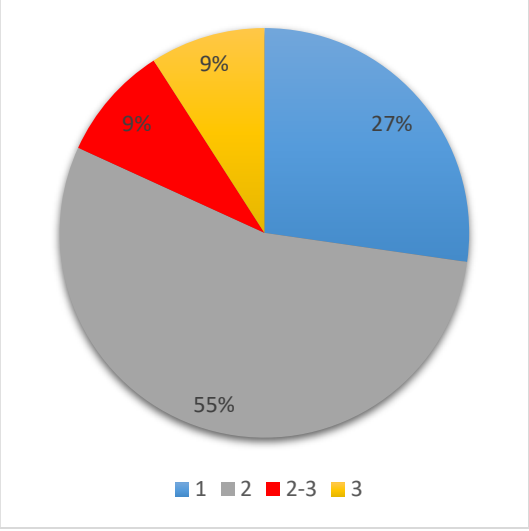

Figure 50: Frequency of 2_I solution

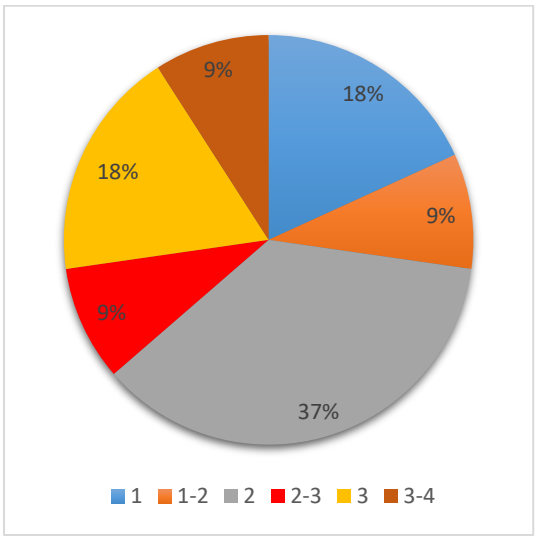

Figure 51: Frequency of 3_I solution

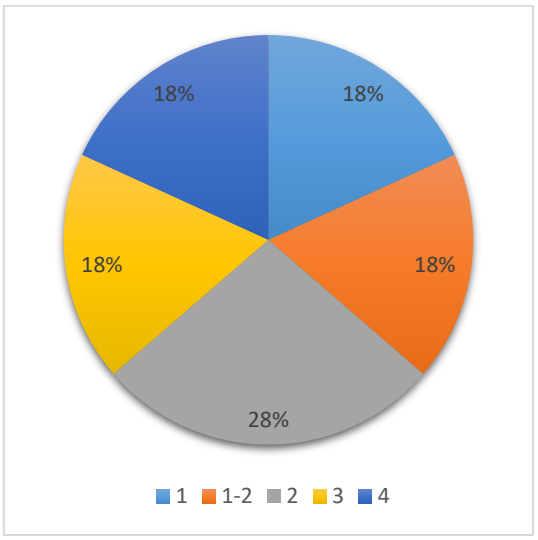

Figure 52: Frequency of 4_I solution

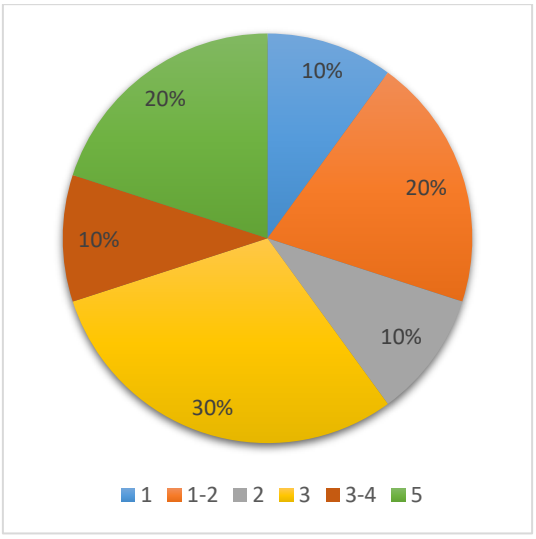

Figure 53: Frequency of 6_I solution

Figures (49 - 53) show, that the concentration of ibuprofen sodium in solutions increases from 0.02 mg/ml to 1.1 mg/mL, the rate of bitterness also increases from 1 to 5. Codes 1_I to 6_I are described in Table 13.

4.5 Taste masking study of coated particles

The human volunteers received three samples with coated ibuprofen sodium and three samples with coated paracetamol. For each API, three samples with different coating amounts were taken. The characterizations of these samples are listed in Table 16. The volunteers washed out their mouth with water and swallowed the saliva. Afterwards they received 1 mL of pure water, which they kept in the mouth for the whole test. Then they received a single dose of coated ibuprofen sodium 600 mg or paracetamol 500 mg particles. The taste was evaluated by volunteers at two steps: the first step was marked by the sensation of the first unpleasant taste, the second step by the sensation of a taste so unpleasant, that it caused the volunteer to spit the sample out.

Sample	**Dissolution test: Concentration [mg/L] after 5 min**	***In vitro* simulated mouth: Release [%] after 2 min**	**Taste masking quality**
Paracetamol			
35% coating amount, 30% Tween® 65 and 70% Dynasan® 116	2.5	0.2	sufficient
20% coating amount, 30% Tween® 65 and 70% Dynasan® 116	5.6	1.2	moderate
10% coating amount, 30% Tween® 65 and 70% Dynasan® 116	13.1	4.7	insufficient

Ibuprofen sodium			
50% coating amount, 5% Tween® 65 with 95% Dynasan® 116	4.2	1.7	sufficient
42,5% coating amount, 10% Tween® 65 with 90% Dynasan® 116	10.7	4.7	moderate
35% coating amount, 5% Tween® 65 with 95% Dynasan® 116	44.1	9.0	insufficient

Table 16: Characterization of different particles

The three paracetamol and ibuprofen sodium samples were tested by the volunteers in the following sequence: first, the sufficiently taste-masked samples; then, the moderately-taste masked samples; finally, the insufficiently taste-masked samples. The average times for the sensation of the taste of paracetamol is shown in Figure 54, and for ibuprofen sodium in Figure 55.

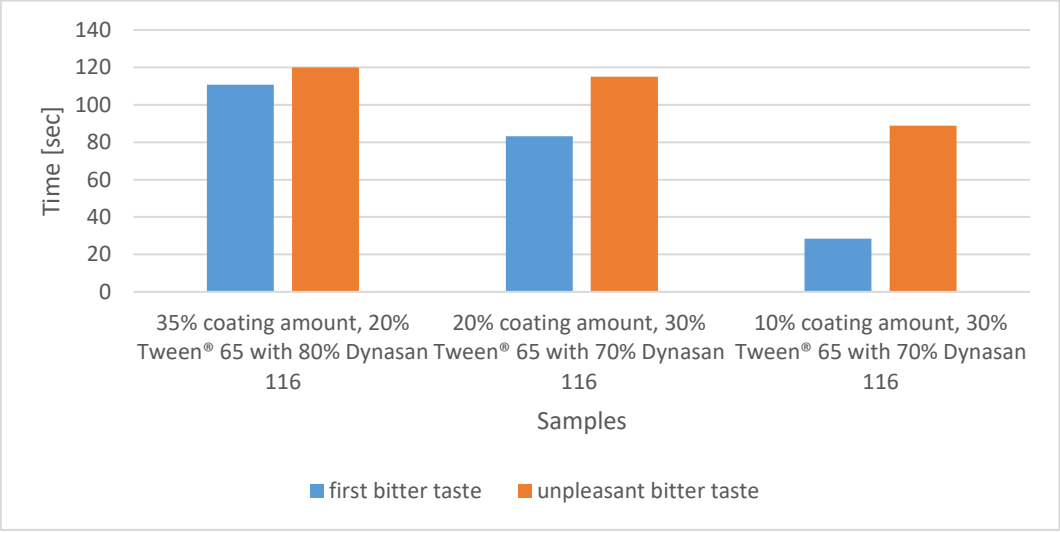

Figure 54: Average time for the sensation of bitter taste of paracetamol pellets

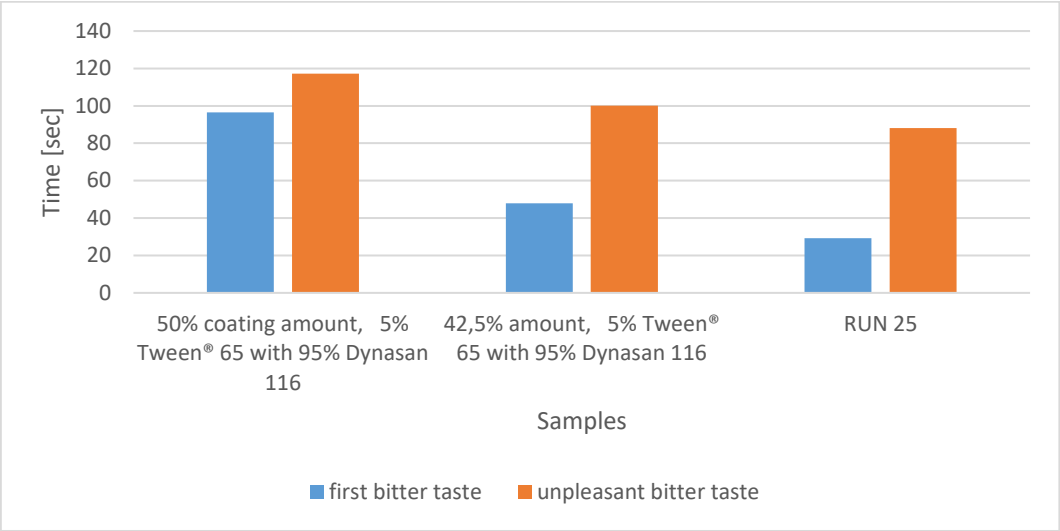

Figure 55: Average time for sensation of bitter taste of ibuprofen sodium granules

The data shown in Figures 54 and 55 confirms the pre-assessment using the *in vitro* taste masking evaluation method: the samples of paracetamol pellets with 35% coating, containing 20% Tween® 65 with 80% Dynasan® 116 and ibuprofen sodium granules with 50% coating, containing 5% Tween® 65 with 95% Dynasan® 116 are the samples with sufficient taste masking. The first bitter taste was detected by the volunteers after 110.7 seconds and 96.5 seconds, respectively. The unpleasant bitter taste was not detected for paracetamol samples with 35% coating (every experiment was stopped after 120 seconds), but for ibuprofen sodium granules with 50% coating, containing 5% Tween® 65 with 95% Dynasan® 116, it was detected after 117.3 seconds. The moderate taste masked samples were the paracetamol samples with 20% coating, containing 30% Tween® 65 with 70% Dynasan® 116 and the ibuprofen sodium granules with 42.5% coating, containing 10% Tween® 65 with 90% Dynasan® 116. The average time when the bitter taste was detected was 83.2 seconds and 47.8, for paracetamol and ibuprofen sodium, respectively; the unpleasant bitter taste was detected after 115 seconds and 100 seconds for paracetamol and ibuprofen sodium, respectively. The insufficient taste masked samples were the paracetamol samples with 10% coating, containing 80% Dynasan® 116 and 20% Tween® 65 and the ibuprofen sodium granules with 35% coating, containing 5% Tween® 65 with 95% Dynasan® 116.

The first bitter taste was detected after 28.3 second and 29.2 seconds for paracetamol and ibuprofen sodium, respectively. The unpleasant bitter taste was detected after 88.8 seconds and 88.1 seconds for paracetamol and ibuprofen sodium, respectively.

4.5.1 Evaluation of the coated samples

4.5.2 Paracetamol

The average time when the first bitter taste was detected, was 74.1 seconds (deviation ± 44.6 seconds) of all three paracetamol samples. This average time (± SD) was taken as the threshold for the evaluation of taste masking and the samples were identified as moderately taste masked. If the time for detection of the first unpleasant bitter taste of a sample was less than this threshold, the sample was identified as insufficiently taste masked. If the time for detection of the first unpleasant bitter taste was longer than the threshold, the samples were identified as sufficiently taste masked. Table 17 shows the classification of taste masking for the paracetamol samples.

Time (sec)	average time - standard deviation: 0 - 29.4	average time ± standard deviation: 29.4 - 118.7	average time + standard deviation: ≥ 118,7
Taste masking quality	insufficient	moderate	sufficient

Table 17: Classification of taste masking of paracetamol pellets

Figures (56 – 58) show the application of the characterization of taste masking to the paracetamol samples.

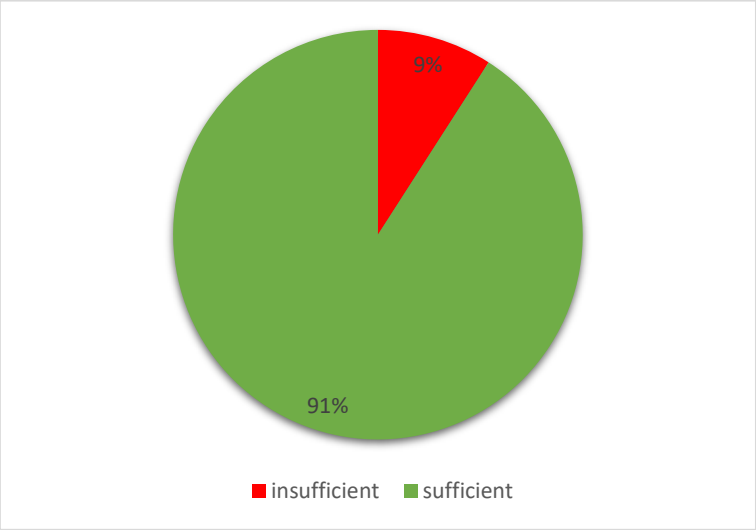

Figure 56: Evaluation of sufficient taste masking of paracetamol pellets with 35% coating amount, 20% Tween® 65 and 80% Dynasan® 116

Figure 56 shows the taste masking evaluation of paracetamol samples using 35% coating amount with 20% Tween® 65 and 80% Dynasan® 116 particles, which was declared as sufficiently taste masked. 91% of the volunteers confirmed this as sufficient taste masked and 9% as insufficient taste masked.

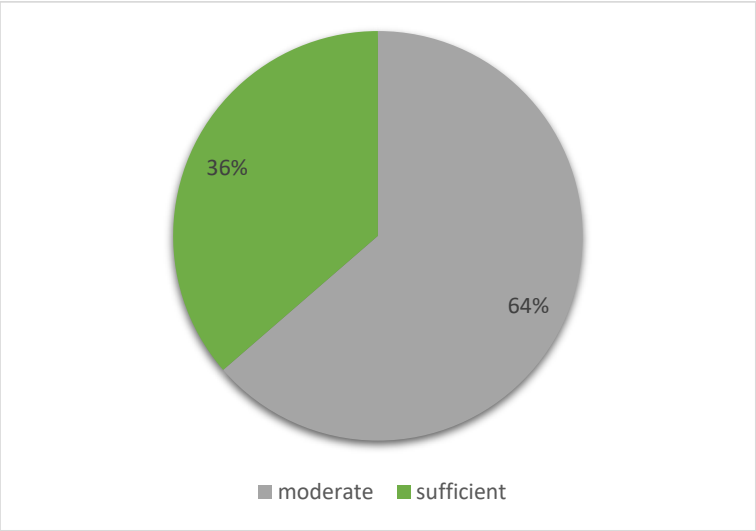

Figure 57 Evaluation of sufficient taste masking of paracetamol pellets with 20% coating amount, 30% Tween® 65 and 70% Dynasan® 116

The moderately taste masked sample was the one with 20% coating amount, 30% Tween® 65 and 70% Dynasan® 116. Figure 57 demonstrates the *in vivo* evaluation of the taste masking of this sample. As can be seen, 64% of the volunteers voted for the moderate taste masking and even 36% assessed the taste masking as sufficient.

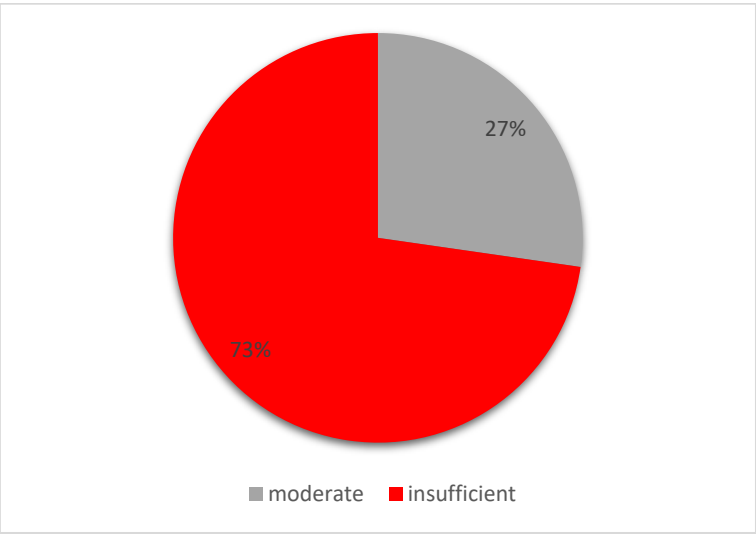

Figure 58: Evaluation of sufficient taste masking of paracetamol pellets with 10% coating amount, 30% Tween® 65 and 70% Dynasan® 116

The last Figure (Figure 58) shows the results of the *in vivo* evaluation of the taste masking of samples with 10% coating amount, 30% Tween® 65 and 70% Dynasan® 116 particles. The *in vitro* characterizations show the insufficient taste masking of this samples, which was confirmed by 73% of the volunteers. The sample was identified as moderately taste masked by 27% of the volunteers.

4.5.3 Ibuprofen sodium

The average time for the detection of the first unpleasant taste of coated ibuprofen sodium samples was 57.8 (± 46.1) seconds. Samples detected within this time were identified as moderately taste masked. If the time for detection of the first unpleasant bitter taste of a sample was less than this threshold, the sample was identified as insufficiently taste masked. If the time for detection of the first unpleasant bitter taste was longer than the threshold, the samples were identified as sufficiently taste masked. Table 18 shows the classification of taste masking for the ibuprofen sodium samples.

Time (sec)	average time - standard deviation: 0 - 11.8	average time ± standard deviation: 11.8 - 104	average time + standard deviation: ≥ 104
Taste masking quality	insufficient	moderate	sufficient

Table 18: Classification of taste masking of ibuprofen sodium granules

In the following Figures (59 – 61) we can see the *in vivo* taste masking evaluation of coated ibuprofen sodium granules.

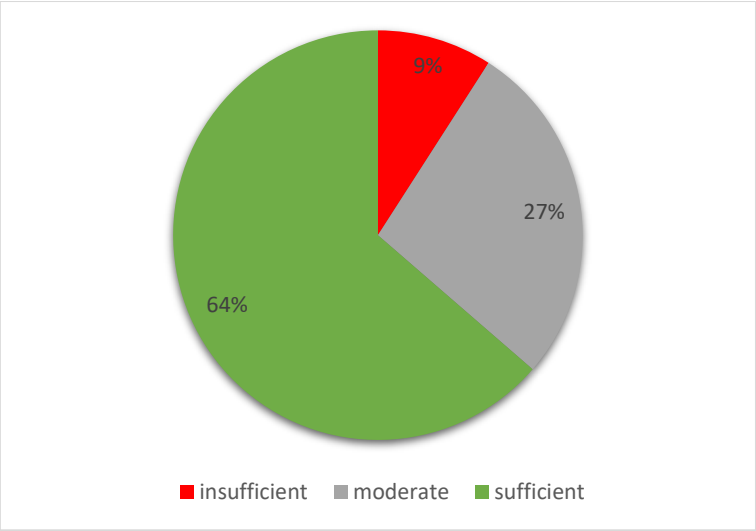

Figure 59: Evaluation of sufficient taste masking of ibuprofen sodium granules with 50% coating amount, 5% Tween® 65 and 95% Dynasan® 116

Figure 59 shows the result of the *in vivo* study of the ibuprofen sodium granules with 50% coating amount, 5% Tween® 65 and 95% Dynasan® 116. The sample was defined as sufficiently taste masked by 64% of the volunteers. 27% of volunteers found the taste as moderately masked and 9% identified the taste masking as insufficient. This values confirm our rating in the pre-assessment (Table 16) that this sample is sufficiently taste masked.

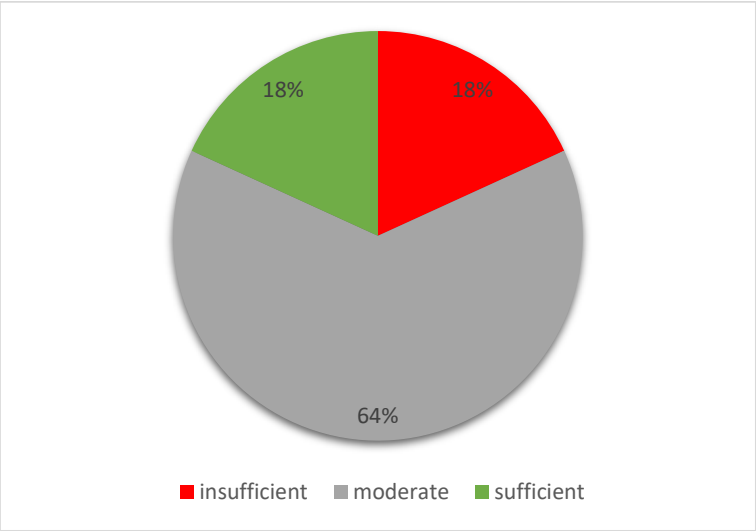

Figure 60: Evaluation of moderate taste masking of ibuprofen sodium granules with 42,5% coating amount, 10% Tween® 65 and 90% Dynasan® 116

The ibuprofen sodium granules with 42.5% coating amount, 10% Tween® 65 with 90% Dynasan® 116 (Figure 60) was declared as moderately taste masked in the pre-assessment (Table 16). Sixty-four percent (64%) of the volunteers confirm this statement. The taste masking was identified as sufficient by 18% of volunteers. The other 18% ranked the taste masking as insufficient.

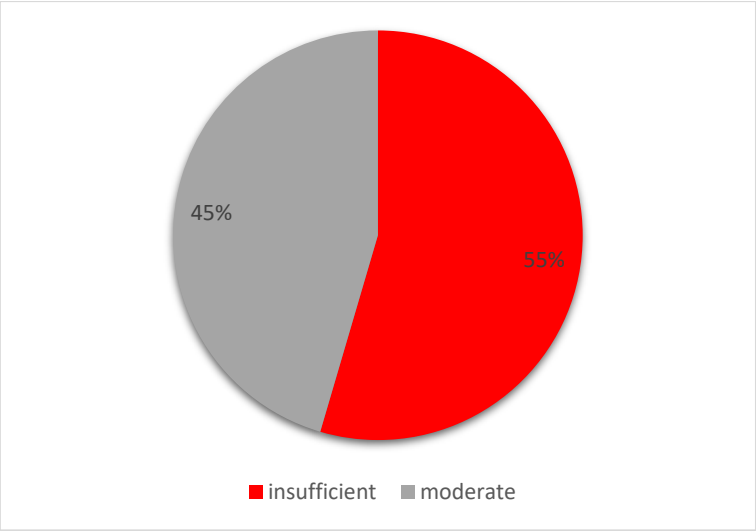

Figure 61: Evaluation of sufficient taste masking of ibuprofen sodium granules with 35% coating amount, 5% Tween® 65 and 95% Dynasan® 116

The insufficiently taste masked sample characterized in the pre-assessment (Table 16) was the ibuprofen sodium granules with 35% coating amount, 5% Tween® 65 with 95% Dynasan® 116 (Figure 61). This finding was confirmed by 55% of the volunteers. The other 45% declared the sample as moderately taste masked.

The *in vivo* test shows very good correlations to the *in vitro* studies. So, it is possible to evaluate API's that have a bitter taste with the help of concentration measurements.

4.6 Correlation between *in vitro* simulated mouth study and *in vivo* study.

The results of the *in vitro* simulated mouth study and the results of the *in vivo* study were compared so as to find a correlation between these two methods.

4.6.1 Paracetamol

In the *in vivo* study, when evaluating the samples with 35% coating amount, 20% Tween® 65 and 80% Dynasan® 116 particles, the average time when the first bitter taste occurred was 110.7 seconds. Due to the API release profile of the *in vitro* simulated mouth study, the percentage of API release after 120 seconds was 0.2% (± 0.06). So, with this value and with the declaration, that these particles are the sufficiently taste masked particles, we can say that from 0% - 0.2% (± 0.06) API release, the particles are sufficient taste masked.

In case of samples with 20% coating amount, 30% Tween® 65 and 70% Dynasan® 116 particles, the first bitter taste was detected after at 83.2 seconds, according to the *in vivo* study. The API release of the *in vitro* simulated mouth study after 90 seconds was 1.0% (± 0.08). Consequently, the area in which the particles were declared as moderate taste masked is from 0.2% (± 0,06) to 1.0% (± 0.08) API release.

The first bitter taste of samples with 10% coating amount, 30% Tween® 65 and 70% Dynasan® 116 particles was detected after 28.3 seconds. Using the *in vitro* simulated mouth study, 1.4% (± 0.4) of API was released after 30 seconds. If the API release is ≥ 1.4% (± 0.4), the particles are insufficiently taste masked.

This area between 1% (± 0.08%) and 1.4% (± 0.4%) API release was described as a mixture of moderately and insufficiently taste masked, depending on the sensitivity of volunteers to the bitter taste.

4.6.2 Ibuprofen sodium

The average time of the *in vivo* study of the 50% coating amount, 5% Tween® 65 with 95% Dynasan® 116 when the first bitter taste occurs, was 96.5 seconds. The API release of the *in vitro* simulated mouth study was 1.5% (± 0.2%) after 90 seconds. So, with this value and with the declaration, that these particles are sufficient taste masked, we can say that if particles have a release between 0% - 1.5% (± 0.2%), they are declared as sufficient taste masked.

In the case of the 42.5% coating amount, 10% Tween® 65 with 90% Dynasan® 116 samples, the first bitter taste was detected after 47.8 seconds, according to the *in vivo* study. The API release of the *in vitro* simulated mouth study after 60 seconds was 3.3% (± 0.4%). According to this, we can say that if we have an API release between 1.5% (± 0.2%) and 3.3% (± 0.4%), the particles can be declared as moderate taste masked.

The first bitter taste of samples with 35% coating amount, 5% Tween® 65 with 95% Dynasan® 116 was detected after 29.6 seconds. According to the *in vitro* simulated mouth study, 4.3% (± 0.2%) of API are released after 30 seconds. Thus, if the particles have an API release ≥ 4.3% (± 0.2%), they are insufficiently taste masked.

The Area between 3.3% (± 0.4%) and 4.3% (± 0.2%) API release was described as a mixture of moderately and insufficiently taste masked, depending on the sensitivity of volunteer to the bitter taste.

5.0 Conclusion

Taste masking is an important topic in the pharmaceutical industry, especially for the improvement of patient compliance in the pediatric and geriatric fields. The evaluation of the taste masking quality however is very difficult, due to ethical concerns, time-, and cost aspects. Also, to find enough human volunteers for testing the drugs is not always possible.

This thesis demonstrates the suitability of hot-melt coating for taste-masking of an unpleasant bitter taste of drugs.

The results of this thesis further show the development of laboratory methods for evaluation taste masking quality. To this end, *in vitro* results (dissolution test, flow-through-cell, simulated mouth study) were correlated to the results of an *in vivo* taste study: The simulated mouth study shows sufficient results in correlation with the results of the human *in vivo* study; the dissolution test and the flow through cell are suitable methods to verify at which time 10% and 85% of the API is released. All in all, these *in vitro* methods have been shown to give adequate results for preliminary assessments of taste masking quality, distinguishing between, sufficient, moderate, and insufficient taste masking.

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List of Abbrevation

IP_3: Inositol trisphosphate

DAG: Diacylglycerol

PKA: Protein kinase A

cAMP: Cyclic adenosine monophosphate

GPCR: G protein-coupled receptors

HME: Hot-melt coating

FCP: Free choice profiling

GPA: General Procrustes Analysis

CYP: Cytochrome P

HLB-Value: Hydrophilic-lipophilic balance value

ADI-Value: Acceptable daily intake value

MDS: Multidimensional Scaling

PCA: Principal Component Analysis

CATA: Check-all-that-apply

COX: Cyclooxygenase

WHO: World Health Organization

PLC: Phospholipase C

GRAS: Generally recognized as safe

LSLR: Least squares logarithmic regression

ChemFET: Chemical field-effect transistor

CYP's: Cytochrome P450