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DEVELOPMENT OF HOT-MELT EXTRUDED PELLETS WITH ALCOHOL-RESISTANT AND ABUSE-DETERRENT PROPERTIES

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ABSTRACT

The objective of this thesis was the development of hot-melt extruded pellets that feature a i) controlled drug release, ii) minimal risk of alcohol-induced dose dumping and iii) drug abuse deterrence.

The concomitant intake of alcoholic beverages together with controlled-release formulations, containing opioid and non-opioid drugs with a narrow therapeutic index poses a serious safety concern. Alcohol has the potential to alter the release-rate-controlling mechanism of the formulation, which may result in an immediate and uncontrolled drug release. So far, only a limited number of dosage forms that withstand the impact of alcohol are available. Thus, for the design of alcohol-resistant dosage forms, it is vital to consider the physico-chemical key factors of the drug, the excipients and the properties of the final dosage form. There are promising technological strategies, such as hot-melt extrusion (HME) that are helpful in minimizing the risk of dose dumping by producing robust/compact dosage forms. Thus, pellets comprising pure calcium stearate (CaSt) or CaSt with either Compritol® or Precirol® (matrix carriers) and paracetamol or codeine phosphate (model drugs) were prepared via HME and the impact of alcohol on their drug release characteristics was investigated. It was found that the drug release behavior of the pellets was a strong function of the drug solubility, the addition of Compritol® and Precirol®, the dissolution media composition and hence, the pellet wettability. All pellet formulations comprising Compritol® or Precirol® showed accelerated drug release with increasing alcohol levels due to increased media uptake and enhanced wetting. In contrast, pellets containing pure CaSt as matrix carrier showed robustness in alcoholic media. Neither the wetting nor the media uptake of pure CaSt was altered by alcoholic media, making hydrophobic CaSt a suitable matrix material to impede alcohol-induced dose dumping.

To aggravate intentional drug tampering, deformable pellets with high compression strength composed of cornstarch, gum arabic or xanthan (matrix carriers) and antipyrine or codeine phosphate (model drugs) were prepared via an innovative continuous one-step HME process. Here, the drug was fed as an aqueous solution into the molten matrix material. To ensure a controlled drug release and avoid dose dumping pellet formulations that had suitable mechanical characteristics were coated with Aquacoat® ARC. The results indicated that coated cornstarch-based pellets are a promising formulation that makes tampering difficult due to a high compression strength combined with robustness in alcoholic media.

KURZFASSUNG

Das Ziel dieser Dissertation war die Entwicklung schmelzextrudierter Pellets mit kontrolliertem Freisetzungsprofil, die Resistenz gegenüber möglichem Alkoholeinfluss aufweisen und Arzneimittelmissbrauch erschweren.

Werden Arzneiformen mit kontrollierter Freisetzung gleichzeitig mit Alkohol eingenommen, kann es zu einem Verlust der Retard-Mechanismen kommen, mit der Gefahr einer schlagartigen Liberation großer Arzneistoffmengen. Besonders im Fall von Opioidanalgetika und Arzneistoffen mit geringer therapeutischer Breite kann Alkohol-Dose-Dumping zu schweren Nebenwirkungen führen. Bisher sind nur wenige Darreichungsformen mit Alkoholresistenz erhältlich. Um solche Arzneiformulierungen herzustellen, sind die physikalisch-chemischen Eigenschaften des Arzneistoffs, der Additiva sowie der Arzneiformulierung selbst, zu beachten. Die Schmelzextrusion eignet sich für die Herstellung alkoholresistenter Arzneiformen. Dementsprechend wurden schmelzextrudierte Pellets auf ihr Freisetzungsverhalten im alkoholischen Medium untersucht. Reines Calciumstearat (CaSt) bzw. CaSt/Precirol® oder CaSt/Compritol® dienten als Matrixmaterialien und Paracetamol oder Codeinphosphat als Arzneistoff. Es zeigte sich, dass die Arzneistofffliberation der Pellets stark von der Arzneistofflöslichkeit, der Zugabe von Compritol® und Precirol®, der Alkoholkonzentration des Freisetzungsmediums und der Benetzbarkeit der Pellets abhängt. Formulierungen, die Compritol® oder Precirol® enthielten, wiesen eine beschleunigte Arzneistofffreisetzung mit zunehmendem Alkoholgehalt auf. Dies war auf eine hohe Benetzbarkeit von Compritol® und Precirol® mit Alkohol zurückzuführen, wodurch es auch zu einer gesteigerten Flüssigkeitsaufnahme kam. Freisetzungsversuche der Pellets mit reinem CaSt zeigten, dass Alkohol keinen Einfluss auf das Liberationsverhalten der Pellets hat. Weder das Benetzungsverhalten noch die Flüssigkeitsaufnahme von reinem CaSt wurden durch den Zusatz von Alkohol beeinflusst. Demzufolge kann CaSt als geeignetes Matrixmaterial um alkoholresistente Darreichungsformen herzustellen, herangezogen werden. Um Arzneimittelmissbrauch zu erschweren, wurden verformbare Pellets mit hoher mechanischer Belastbarkeit mittels eines innovativen kontinuierlichen Schmelzextrusions-prozess hergestellt. Dabei dienten Maisstärke, Gummi arabicum oder Xanthan als Matrixmaterial und Antipyrine oder Codeinphosphat als Arzneistoff. Pellets, die geeignete mechanische Eigenschaften aufwiesen wurden mit Aquacoat® ARC überzogen, um sie alkoholresistent zu machen. Die Ergebnisse zeigten, dass überzogene Maisstärkepellets eine vielversprechende Formulierung darstellen, um eine missbrauchssichere Darreichungsform, welche dem Einfluss von Alkohol standhält, herzustellen.

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1 Introduction

1.1 Multiple-unit dosage forms (Pellets)

The concept of multiple-unit dosage forms was established in the 1950s [1]. A multiple-unit dosage form is defined as *an oral pharmaceutical formulation composed of a unit which disintegrates in the stomach into a variety of small discrete units* (e.g. hard gelatin capsule filled with pellets, tablets compressed from pellets) [2]. These units are spherical or semispherical with a size of 0.5 and 1.5 mm [1] made up of fine powders or granules, also referred to as pellets. Due to their unique properties they offer several therapeutic and technological benefits compared to conventional single-unit dosage forms (e.g. powder-filled capsules, directly compressed tablets), which are often associated with the risk of dose dumping [3].

Pellets are distributed uniformly throughout the gastro-intestinal (GI) tract, thereby enhancing drug absorption, increasing bioavailability, offering less gastric irritation and lowering the risk of dose dumping and side effects [2, 3]. From a technological point of view the benefits of pellets are i) good flow properties due to their uniform size and spherical shape, ii) low friability and iii) a narrow particle size distribution [4]. Hence, pellets are suitable for further processing steps such as capsule filling, tabletting and coating in order to obtain a controlled drug release formulation. Apart from technological advantages, pellets show an improved patient compliance [1] because of individually dosing and, flexibility to body weight dose adaptation for pediatric formulations [5]. Moreover, pellets with different release patterns can be combined to achieve unique release profiles [6].

Pellets are mainly prepared via the wet mass extrusion/spheronization technique [7]. In general, this process involves the following steps: granulation, extrusion, spheronization and drying [7]. The main drawback of this technology is the extensive use of solvents, which are needed to prepare the wet mass by mixing the powder blend and the granulation liquid. Most commonly water is used as the granulation liquid, but also ethanol, water/ethanol mixtures and other organic solvents [1, 4], which often require specialized equipment due to flammability and residue of organic solvents have been reported [8]. Furthermore, time consuming drying phases are needed to remove residual water/solvents. Compared to the well established wet mass extrusion/spheronization process, the technology of hot-melt extrusion (HME) offers some distinct advantages and a promising alternative for pellet manufacturing.

1.2 Hot-melt extrusion

HME is one of the most widely applied processing technologies in the plastic industry since the 1930s, including the production of plastic bags, pipes and sheets [9]. Due to the fact that HME offers several benefits over other traditional pharmaceutical production processes, HME found its place in the pharmaceutical industry for the manufacturing of a variety of dosage forms, such as tablets, granules, pellets, implants, films and patches [10]. As a continuous and solvent-free manufacturing method, HME does not require subsequent drying steps thus, the process is fast, efficient, environmental friendly and cost-effective [9, 11]. In addition to these aspects, HME has the potential to improve the dissolution behavior of poorly soluble drugs and hence their bioavailability, by forming drug/polymer solid dispersions [12]. Since at least 50% of the new chemical entities under development are associated with poor solubility and bioavailability [9, 10, 13], HME is a potent technique to overcome this obstacle.

A formulation for a hot-melt extruded dosage form typically comprises a drug which is embedded into a matrix carrier, as well as other components, such as plasticizers, anti-tacking agents, pore formers, disintegrants and others [8]. The selection of an appropriate carrier system is crucial in the formulation and design of a hot melt-extruded dosage form. Carrier systems that are generally used are thermoplastic polymers, low-melting waxes and lipids [8, 9].

Basically, HME transfers a powder mix with a rotating screw through an orifice at elevated temperatures to obtain a product of uniform shape and density [9, 14]. A typical continuous HME process comprises i) feeding of the formulation via one or more feeders (volumetrically or gravimetrically), ii) conveying of the feedstock along the barrels via a rotating screw, where melting, plasticizing, mixing and homogenization takes place, iii) downstream processing and iv) monitoring with on-line and in-line control tools to ensure an appropriate product quality [10, 15, 16].

In the pharmaceutical industry co-rotating intermeshing twin-screw extruders are the most important type of extruders [9]. The screw is located inside a cylindrical barrel and can be designed individually with the help of various screw elements like conveying and kneading elements to meet particular requirements such as high or low shear. The barrels are composed of individually-controllable heating-sections, which are bolted together.

Based on the desired final dosage form various downstream systems, like calandering, injection molding and strand cutting are available [16]. To form almost spherical pellets a hot die-face pelletizer can be used as downstream unit [8, 16-18]. The hot die-face pelletizer is directly connected to the extrusion die, where the emerging extruded strands are cut immediately at the orifice using rotating knives [16].

In summary, HME represents an innovative approach for the production of several types of dosage forms and drug delivery systems. Various studies have demonstrated that HME has been used successfully for improving the dissolution rate and bioavailability of the drug by forming a solid dispersion, masking the bitter taste of a drug, and providing controlled, modified, and targeted drug release [9, 10, 14, 19]. Furthermore, due to the dense structure and hardness of melt extruded solid dosage forms it is suggested that HME is a promising manufacturing process for the development of robust dosage forms that minimize the risk of drug abuse and alcohol-induced dose dumping [11, 18, 20, 21].

1.3 Drug abuse

The issue of prescription drug abuse outlines a major public health challenge and growing problem associated with considerable social and human costs in USA and Europe [22]. Results from the International Narcotics Control Board reported that emergency room visits and drug overdose deaths related to prescription opioid drugs in the US are increasing outnumber road accident fatalities [22]. Also in Europe the number of deaths remains high and is increasing in some countries [22]. Moreover, frequent abuse of opioid drugs might lead to serious consequences such as negative health effects (HIV, hepatitis C), social concerns (unemployment) and drug-related crime [23].

The phrase “prescription drug abuse” encompass the term “drug abuse” as well as “drug misuse” [24]. Drug abuse can be referred to *the use of medication for its mind-altering effects, whether or not one also has pain or has been prescribed the medication (nonmedical use)* [25], whereas drug misuse can be defined as *inappropriate use of a medication but for a medical purpose rather than for mind-altering effects* [25].
Especially, oral opioids and non-opioid drugs with a narrow therapeutic range, such as benzodiazepines (central nervous system depressants) and amphetamines (stimulants) show a high potential for abuse [24]. Primarily, controlled-release opioid dosage forms that are first-choice formulations for (chronic) pain treatment [26-28] are particularly popular among drug abusers due to their high drug loading and euphoric effects [24]. Tampering of the dosage form, which describes a chemical or physical manipulation that alters or damages the integrity of the dosage form, is usually done to achieve euphoric and mind-altering effects [24]. In the early stages, persons open to drug abuse prefer to take an overdose orally by simple chewing or swallowing. As abuse progresses, the route of administration tends from oral use to snorting and finally to intravenous injection [25, 29]. However, almost all forms of tampering start with the dosage form being grounded into fine powder to make nasal insufflation and intravenous administration feasible [24]. Alternatively, smoking or inhalation, and extracting the dosage form with water or alcohol

are further possibilities for tampering [24]. In addition, the simultaneous intake of alcoholic beverages together with oral opioid controlled-release formulations is another common tampering method [24, 28, 30]. Here, alcohol has the potential to alter the release-rate-controlling mechanism of the dosage form which may result in a premature and exaggerated drug release of the complete dose, leading to drastically increased peak plasma concentrations (i.e., an opioid overdose, which may lead to respiratory depression followed by hypoxia and even death [31]) [32]. This phenomenon is known as alcohol-induced dose dumping and poses a serious safety concern [11, 28, 32-34].

Overall, there is a growing need to develop new flexible technologies for producing safe drug formulations that impede/minimize both (i) drug abuse and (ii) alcohol-induced dose dumping.

1.3.1 Approaches to counteract drug abuse (Abuse-deterrent formulations ADFs)

To counteract drug abuse a number of novel formulation types and strategies, with the aim to prevent the abuser from achieving a rapid euphoric effect, have been introduced over the last few years. In general, two formulation approaches exist which can be classified into abuse-deterrent formulations (ADFs) and tamper-resistant formulations [35]. The former approach is designed to decrease the desirability of the formulation to the abuser, while the latter one prevents tampering and stops alteration of the formulation altogether. However, it has to be noticed that, according to Katz et al. [36], the term “abuse-deterrent” is used rather than “tamper-resistant” since “resistant” may imply a degree of infallibility of these formulations that cannot be supported by current data. Also the US Food and Drug Administration (FDA) prefers to use the term “abuse-deterrent” because “tamper-resistant” refers to packaging requirements regarding certain classes of drugs, devices, and cosmetics [37].

In April 2015 the FDA, who considers the development of ADFs a high public health priority, issued the final guidance document covering the evaluation and labeling of abuse deterrent opioids [37] to provide a general framework for the categorization of ADFs. This suggested framework includes several approaches that impede drug abuse:

- *Physical and chemical barriers*

Physical and chemical barriers can prevent common methods of mechanical tampering. While physical barriers hinder destruction of the dosage form (e.g., due to increased hardness), chemical barriers (e.g., gelling agents) impede extraction using common solvents.

- *Agonist/antagonist combinations*

An opioid antagonist is incorporated to counteract the physiological effects of the drug, therefore reduces euphoria if the drug product is manipulated. The drug product can be

designed such that the antagonist is not clinically active if the medication is used as prescribed, but becomes active if the product is manipulated.

- *Aversion*

Aversive agents can be added to the formulation to create unpleasant temporary side effects (e.g., warmth, flushing, itching, sweating) if the product is manipulated or overdosed.

- *Certain delivery systems*

It is recommended to use unattractive delivery systems (e.g., subcutaneous implants and depot injectable formulations), which may be difficult to manipulate.

- *New molecular entities (NME) and prodrugs*

Prodrugs are biologically inactive substances that hinder opioid activity and the associated euphoric effects until they are metabolized in vivo to their active form can minimize abuse.

- *Combinations of the previous categories*
- *Novel approaches/technologies that are not covered by the previous categories*

Based on this framework table 1 provides a comprehensive overview of both approved and non-approved products having abuse deterrent properties. However, it has to be noticed that the table not solely includes opioids but also other drugs with abuse potential such as central nervous system (cns)-stimulants (i.e., methylphenidate HCl, lisdexamfetamine dimesylate).

Table 1
Categorization of ADFs approaches and associated products with suitable abuse-deterrent technologies.

Physical/chemical barriers				
Product	**Dosage form/API**	**Technology**	**FDA approval**	**References**
Remoxy (Pain Therapeutics Inc.)	SR capsule Oxycodone HCl	*ORADUR* (DURECT Corp.) – gelatin capsule consists of a highly viscous base material (sucrose acetate isobutyrate) to provide controlled drug release and a barrier against extraction, crushing, chewing and dissolution in alcohol.	No, denied 2011 due to concerns in the chemistry, manufacturing and controls section.	[38-40]
Opana ER (Endo Pharmaceuticals Inc.)	ER tablet Oxymorphone HCl	*Intac* (Grünenthal GmbH) – HME process using high molecular weight PEO-based mixtures offering a final product with extensive mechanical strength, which is hard to chew, crush and snort. Additionally, the tablet forms a viscous gel when placed in fluids.	Yes, 2011	[21, 41]
Oxycontin (Purdue Pharma L.P.)	CR tablet Oxycodone HCl		Yes, 2010	[41-43]
Nucynta ER (Janssen Pharmaceuticals Inc.)	ER tablet Tapentadol		Yes, 2011	[44, 45]
Exalgo (Mallinckrodt, Inc.)	ER tablet Hydromorphone HCl	*OROS* Push-Pull osmotic delivery system (Alza Corp.) – tablet is surrounded by a drug release rate-controlling semipermeable and non-erodible rigid cellulose acetate membrane which is resistant to physical tampering and extraction.	Yes, 2010	[46-48]
Concerta (Janssen Pharmaceuticals Inc.)	ER tablet Methylphenidate HCl		Yes, 2000	[48, 49]
Xartemis XR (Mallinckrodt Pharmaceuticals)	ER tablet Oxycodone HCl/acetaminophen	*Acuform* (Depomed) – polymer-based gastric retentive platform (not intended as ADF, but high amount of PEO makes the tablets harder to crush, snort or inject).	Yes, 2014	[48, 50, 51]

Continuation of Table 1
Categorization of ADFs approaches and associated products with suitable abuse-deterrent technologies.

Physical/chemical barriers				
Product	**Dosage form/API**	**Technology**	**FDA approval**	**References**
Rexista (Intelliphamaceutics Inc.)	ER tablet Oxycodone HCl	*PODRAS* Paradoxical OverDose Resistance Activating System (Intelliphamaceutics Inc.) - is intended to decrease the likelihood of oral abuse. Product is difficult to chew, crush, grind, snort or inject. Additionally, the product claims to be dose-dumping resistant.	Not yet, but FDA grants *Fast Track* designation in May 2015	[29, 52, 53]
Xtampza ER (Collegium Pharmaceutical Inc.)	ER capsule Oxycodone HCl	*DETERx* (Collegium Pharmaceutical Inc.) – microsphere-in-capsule formulation consists of hydrophobic waxes and drug-fatty acid ionic complexes, designed to resist tampering and dose dumping without compromising the drug release profile. Additionally, the product can be administered as a sprinkle or through feeding tubes, which offer a benefit for chronic pain patients with dysphagia.	Not yet, but FDA grants *Fast Track* designation in February 2015	[48, 54-57]
ATLP-02 (Atlantic Pharmaceuticals Inc.)	IR oral dosage form Oxycodone HCl	*SMART/Script technology* (SMART/Simple, Controllable, Resistant, Insoluble, Physical Trap) (Atlantic Pharmaceuticals Inc.) – uses a physical/chemical component system. Upon tampering inactive ingredients are released which can be used to soften the impact of crushing and to agglomerate with and may sequester the drug thereby slowing drug release and hinder dose dumping.	Not yet, has finished preclinical testing	[48, 58]

Continuation of Table 1
Categorization of ADFs approaches and associated products with suitable abuse-deterrent technologies.

Physical/chemical barriers				
Product	**Dosage form/API**	**Technology**	**FDA approval**	**References**
Egalet-001; Egalet-002 (Egalet Corp.)	ER tablet Morphine HCl/ Oxycodone HCl	*Guardian technology* (Egalet Corp.) – uses injection molding to create mechanically strong matrix tablets combined of an outer non-erodible shell (ethyl cellulose or polylactic acid) that is filled with an erodible drug matrix core (primarily made of PEO and plasticizer). Resistant to physical tamping and exhibits a precision zero-order delivery profile.	Not yet, in late-stage clinical development (phase III)	[48, 59, 60]
-	IR/CR oral dosage form	*Nobuse* (Tris Pharma) – a drug-ion exchange resin complex is formed and coated with a flexible non-breakable film (PVA, plasticizer, enteric polymers).	No, under development	[48, 61]
-	IR/ER oral dosage form	*OptiGel Lock technology* (Catalent Inc.) – softgel formulation that can be used for both IR and ER oral products and offers multi-level abuse deterrence. Softgels cannot easily be crushed or ground into fine powders, thereby impede nasal administration and inhalation. May also include bubbling agents that foam when the product is aspirated which prevent injection abuse by decreasing syringeability.	No, under development	[48, 62]
-	CR oral dosage form	*IntelliPASTE* (Intelliphamaceutics Inc.) – novel technology described as "paste in a capsule" and is composed of hydrophobic fatty materials (e.g., oil, wax) mixed with clay (e.g., bentonite). The paste behaves like toothpaste and has abuse-deterrent properties.	No, under development	[48, 63]

Continuation of Table 1
Categorization of ADFs approaches and associated products with suitable abuse-deterrent technologies.

Physical/chemical barriers				
Product	**Dosage form/API**	**Technology**	**FDA approval**	**References**
CEP-33237 (Teva Pharmaceutical Industries Ltd.)	ER tablet Hydrocodone bitartrate	*OraGuard technology* (Cima Labs Inc.) – tamper- and dose dumping-resistant properties achieved due to a multistep process: drug is wet granulated with appropriate polymers; subsequently, granules are coated with strong polymer film, mixed with gel-forming polymers and compressed into tablets.	Not yet, FDA has accepted for review the NDA for CEP-33237 in February 2015	[48, 64–66]
-	CR solid oral dosage form (capsules or tablets) -	*Trigger Lock platform* (Flamel Technologies) – drug loaded coated *Microprism*®microparticles which are resistant to all usual crushing tools retaining its coating integrity even after crushing) and extraction.	No	[67, 68]
Moxduo (ORxPharma)	IR/CR solid oral dosage form (capsules or tablets) Morphine HCl/Oxycodone HCl	*Stealth Beadlets* (ORxPharma) – beadlets (i.e., group of pellets, granules or beads) consists of both hydrophilic and hydrophobic substances and mixed with an alkalizing agent (i.e., meglumine). Forming a barrier to product tampering and provide resistance against extraction and dose dumping.	No	[48, 69]
LevoCap ER (Relmada Therapeutics Inc.)	ER capsule Levorphanol	*SECUREL* (Relmada Therapeutics Inc.) – the formulation is composed of drug, HPMC (delays extraction by gel forming when heated above 40 °C), fumed silica (enhances thickening of HPMC in aqueous environment), coconut oil (produces stickiness to waxes and makes organic extraction difficult) and thermo-softening waxes.	Not yet, end of phase II expected to take place before the end of 2015	[48, 70]

Continuation of Table 1
Categorization of ADFs approaches and associated products with suitable abuse-deterrent technologies.

Physical/chemical barriers

Product	Dosage form/API	Technology	FDA approval	References
-	IR/CR/SR capsule	*ABUSOLVE* (Ensap Drug Delivery, a division of Capsugel) – hard shell capsules filled with various materials to provide the desired release profile (IR, CR, SR) and deter abuse by snorting, heating, injecting and dose dumping (high melting point excipients, highly viscous, or water/ethanol insoluble materials).	No, under development	[71, 72]
-	ER tablet Oxycodone HCl	*LockTab* (Ethypharm) – high mechanical strength tablets which limit the abuse via crushing, chewing and extraction. In addition, the formulation prevents dose dumping.	No, under development	[48, 73-75]
-	ER tablets	*INTELLITAB* (Altus Formulation) – mechanically strong tablets that resist common drug tampering. Tablets immediately form hard, stable gels upon extracting in common solvents.	No. under development	[76]
Hysingla ER (Purdue Pharma L.P.)	ER tablets Hydrocodone bitartrate	*RESISTEC* (Purdue Pharma L.P.) – unique combination of polymer and processing to ensure a high tablet hardness. When dissolved in aqueous environment, the tablet instantly forms a viscous hydrogel.	Yes. 2014	[77]
Zohydro ER (Pemix Therapeutics)	ER capsule Hydrocodone bitartrate	*BeadTek technology* (Pemix Therapeutics) – a capsule formulation technology comprises an indistinguishable blend of inactive beads, active IR drug beads and active ER drug beads. If the capsule is crushed and dissolved in liquids, a viscous gel is immediately formed.	Yes. 2015	[78, 79]
MorphaBond ER (Inspirion delivery technologies, LLC)	ER tablet Morphine sulfate	Unnamed (Inspirion delivery technologies, LLC) – solid tablet consists of central core (e.g., gelling agents) covered by protective coating barrier that provides mechanical strength. Core is surrounded by a diffusion-controlled drug layer. Upon crushing/extracting the central core starts to gel and entraps the drug.	No, under development	[48, 80, 81]

Continuation of Table 1
Categorization of ADFs approaches and associated products with suitable abuse-deterrent technologies.

Agonist/antagonist combinations				
Product	**Dosage form/API**	**Technology**	**FDA approval**	**References**
Talwin NX (Sanofi-Aventis)	Tablets Pentazocine	Co-formulated with a *small amount of naloxone* to block euphoric effects of pentazocine when injected.	Yes, 1967 (reformulation in 1982)	[24, 48]
Embeda CII (Pfizer)	ER capsule Morphine sulfate	Gelatin capsule containing pellets of morphine sulfate surrounding an *inner core of sequestered naltrexone HCl (antagonist)*. When tampered the antagonist is released to counteract the addictive effects of the opioid.	Yes, 2009	[48, 82]
ALO-02 (Pfizer)	ER capsule Oxycodone HCl	Gelatin capsule containing pellets of morphine sulfate surrounding an *inner core of sequestered naltrexone HCl (antagonist)*. When tampered the antagonist is released to counteract the addictive effects of the opioid.	No. FDA has accepted for review the NDA for ALO-02 in February 2015	[83]
ELI-200 (Elite Pharmaceuticals Inc.)	SR capsule	*ART technology* (Elite Pharmaceuticals Inc.) –capsule filled with small beads each containing an opioid and an opioid antagonist (naltrexone HCl).	Not yet, in phase III	[48, 84]
Suboxone (Reckitt Benckiser Pharmaceuticals Inc.)	Sublingual film Buprenorphine	*Fast dissolving sublingual combination product* containing an opioid and an opioid antagonist (naloxone) was introduced as an alternative to tablets due to greater patient acceptance and better abuse deterrence.	Yes, 2010	[48, 85]
Targiniq ER (Purdue Pharma L.P.)	ER tablets Oxycodone HCl	Formulation contains a *combination of oxycodone and naloxone in a 2:1 ratio*. The antagonist is added to block euphoric effects of the opioid if tablet is manipulated.	Yes, 2014	[48, 86]

Continuation of Table 1
Categorization of ADFs approaches and associated products with suitable abuse-deterrent technologies.

Aversion				
Product	**Dosage form/API**	**Technology**	**FDA approval**	**References**
Lomotil (Pfizer US Pharmaceuticals)	Tablet Diphenoxylate HCl	Formulation includes *atropine sulfate* as aversive agent to discourage deliberate overdosage Atropine can cause dry mouth, weakness, blurred vision, fatigue and tachycardia when taken in large doses	Yes, 1960	[48]
Acurox (Acura Pharmaceuticals)	IR tablet Oxycodone HCl	Formulation contains the aversive agent *niacin* to cause unpleasant side effects (flushing, warmth and tingling of skin) if an overdose is taken. This product is now marketed under the trade name Oxaydo (see *Combinations*) without the niacin.	No, rejected 2010	[85, 86]
Certain delivery systems				
Product	**Dosage form/API**	**Technology**	**FDA approval**	**References**
Probuphine (Titan Pharmaceuticals Inc.)	Subdermal implant Buprenorphine HCl	*ProNeura technology* (Titan Pharmaceuticals Inc.) the long acting implant delivers a constant low level of the drug for up to six months without the possibility of tampering. Because of the matrix technology of the implant (small solid rod comprising a mixture of drug and ethylene vinyl acetate) it is difficult to retrieve the drug from the rod and discourages patients' attempts to remove them.	Not yet, end of phase III expected by mid 2015	[87, 88]
-	ER oral dosage form	*Geopolymer matrix* (Emplicure AB) – Geopolymer is a porous ceramic material composed of the three dimensional polysialate framework containing SiO_4 and AlO_4. The geopolymer matrix offers high mechanical strength, adjustable porosity and good resistance against extraction in different solvents.	No.	[89, 90]
-	Transdermal patch	*Geopolymer matrix* (Emplicure AB) – tamper resistant transdermal patch based on a geopolymer formulation where the drug is incorporated in a geopolymer matrix.	No, under development	[90, 91]

Continuation of Table 1
Categorization of ADFs approaches and associated products with suitable abuse-deterrent technologies.

New molecular entities (NME) and prodrugs

Product	Dosage form/API	Technology	FDA approval	References
Vyvanse (Shire US Inc.)	Capsule Lisdexamfetamine dimesylate	*In-vivo conversion of lisdexamfetamine dimesylate* to dextroamphetamine. The conversion is rate-limiting and occurs in the systemic circulation. The formulation has reduced potential for recreational abuse.	Yes. 2007	[48. 94. 95]
KP201/APAP (Kem Pharm Inc.)	IR oral dosage form KP201 (NME prodrug of hydrocodone)/ acetaminophen	*KP 201* combines hydrocodone with the ligand benzoic acid. Hydrocodone is not released until it is metabolized in the GI tract following oral administration (molecular-based approach to abuse-deterrence).	No, NDA filing anticipated in the second half of 2015	[96]

Combinations

Product	Dosage form/API	Technology	FDA approval	References
Oxaydo (Egalet Corp.)	IR tablet Oxycodone HCl	*AVERSION* (Acura Pharmaceuticals) – incorporates a gelling agent (i.e., PEO) to impede injection and a nasal tissue irritant (i.e., sodium lauryl sulfate) to limit nasal insufflations.	Yes. 2011	[48. 97]

From table 1 it is obvious that there are some products, which are resistant to multiple routes of drug tampering and alcohol-induced dose dumping. However, the majority of these products are single-unit dosage formulations (i.e., tablets) like Exalgo®, a hydromorphone once daily controlled-release formulation. Exalgo® was brought into the market after Palladone™ was withdrawn from the market in 2005 due to concerns relating to alcohol interfering with the release-rate-controlling mechanism and causing lethal episodes of dose dumping [29, 98]. To date, only two multiple-unit preparations (i.e., Xtampza ER capsule, Moxduo), which are currently not yet approved by the FDA, have been designed to resist drug tampering and dose dumping without compromising the drug release profile.

However, beside the above mentioned technologies (see Table 1) there are further approaches described [11], which may help to overcome the problems of alcohol-induced dose dumping. It is suggested, to consider the physico-chemical key factors (i.e., solubility, wettability, swellability) of the drug, the excipients and the final dosage form. Moreover, the selection of appropriate polymers (i.e., polyethylene oxide, cross-linked high amylose starch, carbomer, hypromellose) in combination with alcohol resistant coatings (i.e., Aquacoat ARC®) and/or promising technologies, such as HME, are beneficial for the preparation of multiple-unit alcohol-robust formulations. For detailed information, please refer to chapter 2.

1.4 Objective

Prescription opioid abuse is a worldwide growing significant health problem. The best strategy to address this problem would be the development of new molecular entities that are able to relieve pain without possessing euphoric and physical dependence effects, which is not possible up to date. Thus, the manufacturing of abuse-deterrent dosage forms is highly important. Furthermore, it is known that patients who suffer from (chronic) pain, and who are frequently treated with controlled-release opioid analgesics as first choice medications, often consume alcoholic beverages together with their medications to manage pain [99]. Alcohol is likely to interact with the drug product and causes a sudden drug liberation (i.e., dose dumping), which possibly results in dangerous side effects and poses a serious safety concern. Hence, to tackle the problem of alcohol-induced dose dumping, robust dosage forms that withstand the influence of alcohol need to be designed. So far, publications regarding safe multiple-unit drug products that prevent both drug abuse and alcohol-induced dose dumping remain limited, thus this thesis focused on the development of multiple-unit pellets via HME that feature a controlled drug release, drug abuse deterrence and a minimal risk of alcohol dose dumping.

First of all, this work deals with physico-chemical key factors, which have to be considered, as well as suitable matrix systems and promising technological approaches, which are appropriate to prevent alcohol-induced dose dumping. Moreover, this work encompasses investigations of the interactions between alcohol and a lipophilic hot-melt extruded pellet formulation. In-vitro drug release studies in alcoholic and non-alcoholic media were performed and the pellet surface properties and internal morphology were studied. Moreover, media uptake and wetting behavior upon exposure to alcoholic media were examined. To additionally impede intentional drug tampering with common household devices, deformable pellets with high compression strength were prepared via an innovative continuous one-step HME technique, with the drug fed as an aqueous solution into the molten matrix material. Subsequent coating of the pellets ensured a controlled drug release and avoids alcohol-induced dose dumping. Again, the in-vitro drug release behavior of the pellets in alcoholic and non-alcoholic media was examined and characterization of the pellets regarding their mechanical properties was conducted.

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2 The design of controlled-release formulations resistant to alcohol-induced dose dumping – A review

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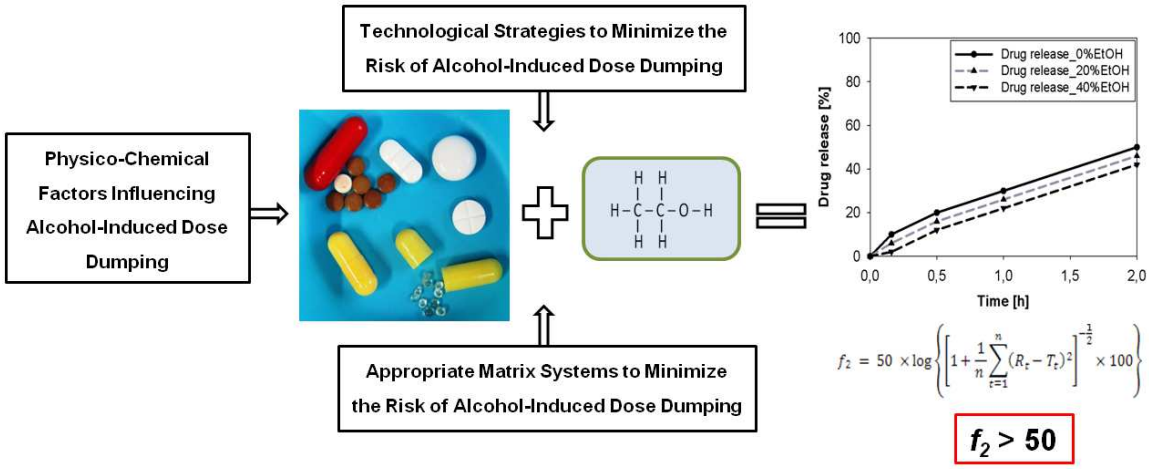
2.1 Graphical abstract



2.2 Abstract

The concomitant intake of alcoholic beverages together with oral controlled-release opioid formulations poses a serious safety concern since alcohol has the potential to alter the release rate controlling mechanism of the dosage form which may result in an uncontrolled and immediate drug release. This effect, known as alcohol-induced dose dumping, has drawn attention of the regulatory authorities. Thus, the Food and Drug Administration (FDA) recommends that in vitro drug release studies of controlled-release dosage forms containing drugs with narrow therapeutic range should be conducted in ethanolic media up to 40%. So far, only a limited number of robust dosage forms that withstand the impact of alcohol are available and the development of such dosage forms is still a challenge. This review deals with the physico-chemical key factors which have to be considered for the preparation of alcohol-resistant controlling dosage forms. Furthermore, appropriate matrix systems and promising technological strategies, which are suitable to prevent alcohol-induced dose dumping, are discussed.

2.3 Introduction

Alcohol-induced dose dumping effects in controlled-release oral dosage forms have received increased attention in recent years. Dose dumping, which is defined as *"unintended, rapid drug release in a short period of time of the entire amount or a significant fraction of the drug contained in a modified release dosage form"* [1], can have

dangerous effects. For example, in 2005 the FDA withdrew a hydromorphone-modified release drug formulation, Palladone™, from the US market, since taking it together with alcohol fatally increased the peak plasma concentrations of hydromorphone [2]. Currently, the FDA recommends to assess the risk of alcohol-induced dose dumping for opioid and non-opioid drugs with a narrow therapeutic index, such as metoprolol succinate (ß-blocker) and venlafaxine HCl (antidepressant) [3-5]. Especially, prolonged-release formulations, which offer a reduced dosing frequency and a prolonged therapeutic effect due to higher drug amounts, are of specific interest. For example, in the treatment of (chronic) pain controlled-release opioid dosage forms have been used as first choice formulations [6-8]. However, if patients suffer from pain, they often turn to alcohol to cope with the pain-related stress and to reduce the pain perception [9]. A study examining the relationship between pain and alcohol reported that both problem drinkers and non-problem drinkers consume alcohol to manage pain [10]. If patients are treated with opioid analgesics numerous side effects, including respiratory depression, nausea and/or urinary retention might occur [11]. The most deleterious effect is the first one which may arise due to rapid dose escalation. Thus, if the dosage form is consumed with ethanol, the drug release can increase immediately, resulting in an overdose and leading to respiratory depression followed by hypoxia and even death [12]. Regarding non-opioid drugs, alcohol might enhance sedation (through synergistic interactions), decrease of motoric skills and may lead to orthostatic hypotension [13].

Apart from side effects associated with ethanol, the mechanistic understanding of the oro-gastrointestinal absorption and hepatic metabolism is important. After oral administration of a dose-dumping susceptible formulation co-ingested with ethanol, a major part of the drug is dissolved in the stomach immediately. After a sufficient gastric retention time, the entire amount of the dissolved drug is uncontrollably emptied into the small intestine. Thus, absorption occurs which may result in high plasma concentrations [14]. Generally, the onset of intestinal drug absorption mainly depends on the gastric emptying rate which can individually vary in normal healthy subjects from 120 to 180 min in the fasted state [15]. Lennernäs et al. showed that for in vitro studies an experimental duration of 2 h is necessary to mimic gastric physiology (emptying) and rationally screen possible ethanol-drug interactions under physiological conditions [14].

Moreover, it is known that the consumption of alcoholic beverages may prolong the gastric emptying rate and therefore the onset of drug absorption due to the caloric content of alcohol, which is comparable with the lightly-fed state after the consumption of a meal [15-17]. For example, carbohydrate-rich and fermented beverages, such as beer and red wine, induce a prolonged gastric emptying rate in comparison with strong alcoholic drinks (whiskey, gin, etc.) [16]. Thus, several FDA guidelines for drugs with narrow therapeutic

window suggest to test possible alcohol dose dumping effects over a period of at least 2 h in ethanolic media with different ethanol concentrations [3].

Frömming et al. were the pioneers who studied the influence of ethanol on the in vitro and in vivo drug liberation from acetylsalicylic acid sustained-release tablets. The authors reported faster drug release from tablets if co-ingested with 120 ml commercial brandy, which was proved by urinary excretion data [18]. Because of the ethical issues associated with in vivo-testing in human volunteers, mostly in vitro studies have been performed [19, 20]. The in vitro approach requires drug release studies to be conducted in acidic media to simulate the stomach with alcohol concentrations of 5%, 20% and 40% (*v/v*) over a period of 2 h [21]. The different ethanol contents in the dissolution media represent different alcoholic beverages: 5% ethanol for beer, 20% for mixed drinks and 40% for hard liquor [21]. Quantification of the dose-dumping effect of a drug formulation is still an open issue without a regulatory decisional framework. One suggestion is to classify whether the drug formulation is “rugged” or “vulnerable” [22]. Here, the drug release of the formulation is investigated in ethanolic media and standard media (without ethanol) and a f_2 similarity test to distinguish between these categories [22, 23] is performed. The similarity factor f_2 is a logarithmic reciprocal square root transformation of the sum of the squared error. According to Moore and Flanner [24] the f_2 value is calculated by the following expression (1):

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-\frac{1}{2}} \times 100\right\} \quad (1)$$

where n corresponds to the number of dissolution time points considered and R_t and T_t are the percent drug dissolved of the reference and test formulations at time point t. It is a simple and effective tool to assess the similarity of two dissolution profiles: the value of f_2 ranges from 0 to 100 and dissolution profiles are considered similar when the f_2 value exceeds 50 [25]. Values below 50 indicate that the formulation is not alcohol-resistant. The aim is to mitigate the potential dose-dumping risk at the early stages of development of a controlled-release drug formulation [26]. Note, that low f_2 values are also obtained, if drug release is significantly slower in ethanolic media.

A second strategy to assess alcohol resistance of drug formulations is to calculate the relative change in amount of dissolution ($D_{A/N}$) in ethanolic media compared to pure media [27] as given in Eq. (2):

$$D_{A/N} = \frac{100 \times (D_A - D_N)}{D_N} \quad (2)$$

where D_A is the percent drug dissolved in ethanolic medium and D_N corresponds to the percent drug dissolved in pure media [27]. Positive values indicate that ethanol increases dissolution, whereas negative data indicate decreased dissolution in ethanol. However, compared to calculation of f_2 values, no critical values are given. Thus, no classification can be carried out.

Another challenge in the development of safe drug products is tampering with oral controlled-release formulations, which often occurs through chewing or crushing to subsequently snort the drug or to dissolve it in water or ethanol for intravenous injections [28-30]. Many novel drug formulations are under development to counteract these practices, by making the dosage form less prone to abuse. According to Webster et al., formulations can be classified into abuse-deterrent formulations and abuse-resistant formulations [29]. Abuse-deterrent formulations comprise an opioid drug and an opioid antagonist (i.e., naltrexone, naloxone). If the dosage form is applied as suggested in the prescribing information, only the opioid is released. However, if the tablet or capsule is manipulated due to breaking or milling, the antagonist is released and blocks the opioid actions. Thus, opioid euphoria is diminished or even reversed [29]. On the contrary, abuse resistant formulations use physical barriers and mechanical properties, such as increased hardness. Thus, crushing or milling is made impossible and no extraction of the drug is feasible [29].

The aim of this review is to indicate, which physico-chemical parameters must be defined for the rational design of alcohol-resistant controlling dosage forms. Furthermore, we discuss the additives that meet the physico-chemical requirements and describe promising technological strategies for minimizing the risk of dose-dumping.

2.4 Physico-chemical factors influencing alcohol-induced dose dumping

To develop an alcohol-resistant controlled-release dosage form, key physical and chemical factors of the formulation components must be considered, such as (i) solubility, (ii) wettability, (iii) swellability, and (iv) mechanical properties of the active pharmaceutical ingredient (API) and the excipient(s) in the final dosage form.

2.4.1 Effect of solubility

Generally, polar molecules are most soluble in polar solvents and non-polar molecules in non-polar solvents. Therefore, the ratio of hydrophilic and hydrophobic groups of the drug plays a crucial role for the solubility behavior in various solvents (Fig. 1). In principal, the aqueous solubility depends on the ability of the drug molecules to form hydrogen bonds with water molecules. Hence, the greater the hydrophilic part of a molecule relative to the hydrophobic part is, the greater the aqueous solubility becomes. In alcohol, which has

lower hydrogen bonding capacity than pure water, solubility decreases [31, 32]. Moreover, ethanol is less polar compared to pure water, which is reflected by the differences in the dielectric constants (25 and 80 for ethanol and water at 20 °C, respectively) [33]. If ethanol is added to water, a decrease in the dielectric constant in relation to pure water occurs, and thus, the solubility of an in-water poorly soluble drug increases [34]. In contrast, for highly soluble drugs in water the addition of ethanol will reduce the solubility [35]. If the drug shows high solubility in ethanol, it has to be protected by integrating/embedding it in a matrix system.

Generally, drug release from matrix systems is governed by various effects, depending on the drug-product design. These effects include medium penetration into the matrix, hydration, swelling, and drug diffusion and/or matrix erosion [36]. This implies that the drug release rate is influenced to a great extent by the medium to which the matrix system is exposed to [37]. If the matrix system is freely soluble in alcohol, the matrix will immediately start to disintegrate/dissolve in alcoholic environment resulting in an early and uncontrollable drug release. Therefore, a matrix system that withstands the influence of alcohol and remains intact during the course of the drug release process is required.

The EDACS™ technology, just to mention one example, provides a matrix that is insoluble in water and only slightly soluble in ethanol [38, 39]. Also the novel Egalet® matrix system works on this principle. Hence, its robust behavior in the presence of ethanolic media is owed to the fact that the matrix offers a higher solubility in aqueous media compared to ethanol [40, 41]. Both matrix systems will be described in more detail in chapter 4.3.

Since there is a limited amount of literature available dealing with the matrix solubility behavior in ethanolic media, there is need for further studies on the effects of alcohol on the matrix system. However, to overcome solubility concerns of drugs in ethanolic media it is necessary to use a robust matrix system with high solubility in aqueous media and/or insolubility in ethanol.

Water (wt.%)	Ethanol (wt.%)	Dielectric constant (ε_r) of water-ethanol mixtures at 20 °C (*)	Solubility behavior of drugs with greater hydrophilic parts	Solubility behavior of drugs with greater hydrophobic parts
100%	0%	80.37	++++	+
80%	20%	68.66	+++	++
60%	40%	56.49	++	+++
0%	100%	25.00	+	++++

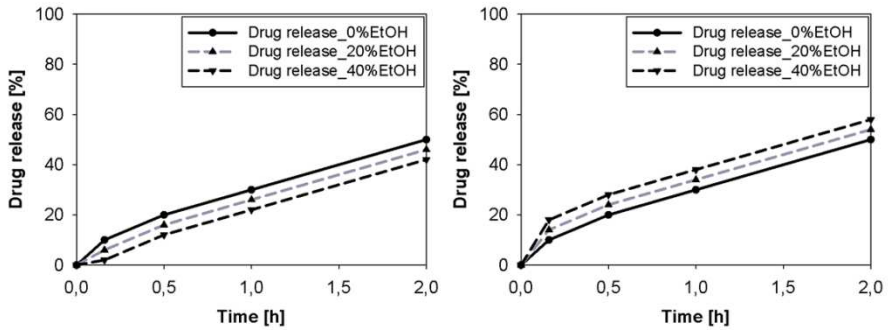


Fig. 1. Schematic illustration of the solubility behavior of drugs with increased hydrophilic/hydrophobic ratio in various media and the supposed resulting in vitro drug release profiles. (*) The dielectric constant values are based on Akerlof et al. [33].

2.4.2 Effect of wettability

Wettability is another parameter that influences dose dumping. Wettability of a substance depends on its chemical structure and hydrophilic/hydrophobic nature. Generally, wettability can be determined by measuring the static contact angle of a liquid on a given surface: a contact angle smaller than 90° indicates wettability and above 90° poor wettability [42]. Angles close to 0° correspond to excellent wettability. Lippold et al. reported a correlation between the wetting behavior of a substance and the drug dissolution rate [43], probably because wetting establishes solute-solvent contacts necessary for the solvent to penetrate the matrix system and release the drug [44]. The solvent penetration into the matrix system can follow both dissolution of drug particles and capillary forces acting along the pores within the matrix [45]. Capillary forces occur because of intermolecular forces between the solvent and the matrix surface and draw the solvent into the matrix. In general, the better the wettability of the matrix surface, the higher the penetration rate [46]. It is assumed that for low contact angles (<90°) drug release would occur due to solvent penetration by capillary forces and high contact angles (>90°) are representing a negative capillary pressure, which would hinder the solvent from penetrating the matrix [45] resulting in slower drug release. If wettability of a matrix system is improved when in contact with alcoholic components, accelerated media uptake and, faster drug release will occur. Therefore, materials appropriate for the design of alcohol-

resistant formulations should have wetting angles that do not significantly decrease in the presence of ethanol.

2.4.3 Effect of swellability

Another phenomenon which affects alcohol-induced dose dumping is swellability of a polymeric matrix material. Polymers that swell in contact with aqueous media can be generally divided into two categories: (i) swellable polymers that are insoluble in water, also referred as hydrogels, and (ii) swellable polymers that are soluble in water, termed hydrophilic polymers [47]. Hydrogels form a three-dimensional crosslinked polymeric network in the presence of water. These polymeric networks are insoluble due to their chemical or physical crosslinks, such as entanglements, crystallites, or hydrogen bonds. The thermodynamic compatibility of the polymer chains with the molecules of the surrounding fluid is responsible for the swelling [48]. However, in this review we particularly focus on hydrophilic polymers, since they are widely used for the preparation of oral controlled-release dosage forms.

In general, hydrophilic matrix formulations comprise a compressed mixture of a hydrophilic polymer and a drug. On contact with aqueous media a gel layer is formed due to the polymer transition from the glassy state to a hydrated rubbery state [49]. The formation of this gel layer on the matrix surface occurs via simple entanglement of adjacent polymer chains without proper crosslinking [50, 51]. Again, the thermodynamic interactions of the polymer chains and the surrounding media are responsible for the swelling [51]. The composition and physical properties of the gel layer controls the water transport into the matrix system, the drug diffusion (release rate, kinetics) and finally, the erosion of the matrix [52, 53]. According to Missaghi et al. the presence of ethanol in the dissolution media may affect the formation of the gel layer and the integrity of the matrix [53]. Roberts et al. observed an initial rapid release of aspirin from hypromellose matrices with high standard deviations in 40% ethanolic media [19]. This behavior might be attributed to the slower initial interaction between the ethanol and hypromellose, forming a non-uniform gel layer with inconsistent drug release [51]. Thus, if the formation of a gel layer occurs fast enough, which implies that the hydrophilic polymer and the surrounding media immediately reach thermodynamic equilibrium, fast diffusion of ethanol into the matrix is prevented and an alcohol-resistant formulation is obtained (Fig. 2a). If the equilibrium is not reached fast enough, formation of the gel layer is hindered and ethanol may diffuse into the system (Fig. 2b). As a consequence, rapid drug release occurs due to the absence of the protecting gel layer.

Therefore, the rapid formation of a strong and stable gel layer upon swelling in ethanolic media is crucial in designing alcohol-resistant drug formulations.

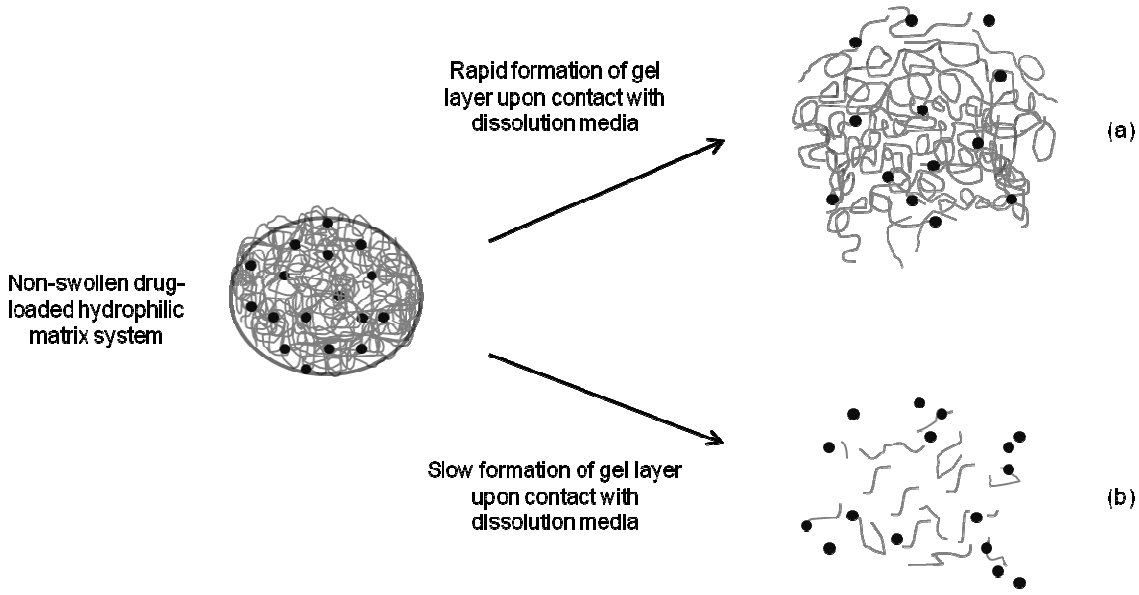


Fig. 2. Schematic illustration of a drug-loaded hydrophilic matrix system in the non-swollen state and upon contact with dissolution media. (a) If the hydrophilic polymer and the surrounding media immediately reach thermodynamic equilibrium the polymer gels fast. The drug molecules dissolve and diffuse consistent through the gel layer into the dissolution media. (b) If the thermodynamic equilibrium is not reached fast enough, the formation of the gel layer is hindered. Therefore, the dissolution media can penetrate deep into the matrix, rapidly dissolve the drug and disintegrate the matrix.

2.4.4 Effect of mechanical properties

The mechanical strength (hardness) of the final dosage form is yet another factor that must be considered in formulation development. It strongly depends on porosity and compactness of the formulation and on the technology used for production. It is known that the compression force strongly affects hardness of matrix systems [49, 54]. This phenomenon can also be achieved by applying elevated temperatures and high shear forces, e.g., during hot-melt extrusion. Moreover, depending on the matrix system, also the number of pores may decrease resulting in an increased compactness of the dosage form [55]. Additionally, high shear forces lead to disentangled chains. Upon cooling the polymer chain-drug complex entangles again, resulting in strong solid bridges between the drug and the polymer particles, again increasing the compactness of the system [56, 57].

Furthermore, mechanical strength may prevent drug abuse by making the dosage difficult to crush, chew, dissolve and draw into needles for intravenous injections.

2.5 Appropriate matrix systems to minimize the risk of alcohol-induced dose dumping

Hydrophilic polymers are widely used as excipients for the preparation of hydrophilic matrix systems with controlled-release profiles. Insoluble in ethanol, they are expected to be unaffected when consumed together with alcohol. Due to their hydrophilic nature, the

polymers begin to swell upon contact with water, forming a gel layer. The drug release is controlled by the diffusion through the layer and/or erosion mechanisms [54]. In this review we particularly focuses on hydrophilic polymers (polyethylene oxide, cross-linked high amylose starch, Carbopol® and hypromellose) since we consider them the most interesting candidates with regard to alcohol-resistant dosage forms. A short list of some important polymers is presented in Table 1.

Table 1
Polymers that may be suitable for the preparation of alcohol-resistant dosage forms and their properties.

Polymer	Molecular weight (kg/kmol)	Solubility	References
Polyethylene oxide	100,000-7,000,000	Soluble in water; insoluble in most alcohols	[58]
Cross linked high amylose starch (Contramid®)	No data available	Soluble in water; insoluble in ethanol	[59]
Carbomer (Carbopol®)	$1.0\text{-}4.0 \cdot 10^6$	Not soluble, only swellable in water and ethanol	[20, 60]
Hypromellose	10,000-1,500,000	Soluble in cold water; practically insoluble in ethanol and hot water	[19, 52, 53, 61, 62]

2.5.1 Polyethylene oxide

Polyethylene oxide (PEO) is a nonionic homopolymer of ethylene oxide that is commercially available in a wide range of molecular weights (from 100,000 to 7,000,000 Da) [58]. PEO is soluble in water due to hydration of the ether oxygen and insoluble in alcohol [58]. It has been shown that high-molecular-weight PEO can be used as a matrix-forming polymer for solid dosage forms featuring controlled drug release [63-66]. These polymers are also suitable for sustained-release matrix tablets prepared via hot-melt extrusion [67, 68]. When PEO comes in contact with water, it hydrates rapidly, swells to a significant extent and forms a hydrogel layer on the matrix surface [65]. Drug release from the PEO matrix is controlled by erosion of the matrix and diffusion of the drug through the swollen hydrogel layer at the tablet surface [67].

Recently, Palmer et al. investigated the influence of hydro-alcoholic media on the drug release from PEO extended-release matrix tablets using freely water-soluble metformin HCl and water insoluble gliclazide as model APIs with different solubility behavior [69]. Robust matrix tablets with a mechanical strength of 2.32 MPa for gliclazide and 0.70 MPa

for metformin HCl were manufactured using a rotary tablet press. The in vitro drug release studies indicated that the PEO matrices remained intact, and no dose dumping effect was observed after exposure to 5% and 40% hydro-alcoholic media for up to 12 hours. To compare the drug release profiles from PEO matrices in hydro-alcoholic media with those in purified water, a f_2 similarity test was conducted. The obtained f_2 values were acceptable ($f_2 > 50$) for gliclazide release profiles in both tested alcoholic media. For the metformin HCl matrix tablets a f_2 value below 50 ($f_2 = 42$) was calculated after 12-h exposure to 40% hydro-alcoholic media. Due to a higher solubility of metformin HCl in water (compared with ethanol) [69], the drug release significantly decreased in 40% hydro-alcoholic media. Although this yields good alcohol resistance, the difference between the dissolution profiles from metformin HCl matrix tablets in hydro-alcoholic media compared to purified water is too high, resulting in low f_2 values. Thus, we state that once the drug release decreases in alcoholic media (i.e., no dose dumping will occur) the similarity factor is not an appropriate tool to evaluate alcohol-induced dose dumping. Furthermore, we suppose that if drug liberation in alcoholic media is reduced this may prevent drug abuse.

In addition, the authors examined the effect of hydro-alcoholic media on the hydration and swelling properties of pure, mechanically strong (i.e., 3.3 MPa) PEO compacts, which were prepared using three viscosity grades of commercially available PEO (Polyox™). The results demonstrated that all compacts exhibited consistent swelling and gelation without compromising the matrix's integrity in water and in hydro-alcoholic media [69]. As such, PEO may be a suitable hydrophilic polymer for controlled-release matrix tablets, providing resistance to alcohol-induced dose dumping. To our knowledge, there is no literature addressing alcohol-resistant multiple-unit dosage forms with PEO as a matrix system.

2.5.2 Starches and starch derivatives

Starch is composed of two polysaccharids, linear amylose and branched amylopectin and is widely used for food and non-food applications [70]. In the pharmaceutical industry modified and pregelatinized starches serve as excipients in hydrophilic matrix systems for orally-administered solid dosage forms with controlled drug release [58, 71-74]. In the past few years cross-linked high-amylose starch (CLA), or Contramid®, emerged as a promising excipient for the preparation of controlled-release matrix tablets manufactured mainly via direct compression [75-79].

For the production of Contramid®, a high-amylose corn starch containing 70% amylose and 30% amylopectin is used. When placed into water, a Contramid® tablet begins to swell and a sponge-like gel is formed [77]. Due to a self-assembly process of amylose and amylopectin chains into double helices, a tri-dimensional network is formed which swells

to reach a final thickness. [80]. The swelling process of Contramid® tablets is anisotropic, meaning that the tablets swell more in the axial direction (70-80%) than in the radial (25-35%) which can be explained by the flattening of the particles in the axial direction during direct compression of the tablet [76, 80]. Upon swelling, a dense membrane is formed at the external tablet surface, while the core maintains a coarse porous texture. The outer membrane acts as the diffusion rate-limiting barrier for drug delivery. If the outer membrane has a smaller diffusion coefficient than the inner core a quasi-zero-order-release kinetic from a Contramid® matrix tablet can be obtained [80].

Traynor et al. examined the influence of ethanol on the in vitro release behavior of extended-release tablets with a controlled-release core based on tramadol hydrochloride (HCl) and Contramid® (Tridural™; Labopharm, Canada) [59]. This core is coated with a release-controlling matrix composed of polyvinylpyrrolidone-polyvinyl acetate copolymer, xanthan gum and tramadol HCl to allow an early onset of the drug [59]. Tramadol HCl is a centrally-acting analgesic with weak opioid agonist properties [81]. Its high solubility in water requires a careful choice of retarding additives to ensure a desirable release profile [82]. Moreover, since tramadol HCl is an opioid analgesic, it is particularly important to prevent uncontrolled drug release. Drug release of Tridural™ extended-release tablets was evaluated in phosphate buffer (pH 6.8), with and without ethanol [59]. In phosphate buffer the API release followed a zero-order-release kinetics for 4 to 16 h [59], which was attributed to the core component, Contramid®. However, the presence of ethanol in the dissolution media caused a significant decrease in the release rate of tramadol HCl [59]. Because pregelatinized starches (e.g., Contramid®) are insoluble and not swellable in alcohol [58, 59], ethanolic media prevented the formation of the release-controlling membrane, resulting in a 25% reduction in the drug release rate [59].

Since other non-pregelatinized starches, including corn, rice and potato starch, are insoluble in ethanol and have Contramid®-like properties, they may be suitable as additives to an alcohol-resistant formulation. To our knowledge, no data are available concerning these excipients in combination with alcohol-induced dose dumping.

2.5.3 Carbomer

Carbomers are synthetic polymers of acrylic acid with high molecular weight that are crosslinked with either allyl sucrose or allyl ethers of pentaerythritol [58]. Marketed under the trade name “Carbopol®,” they are available in a number of different grades, which vary in molecular weight and polymer type [83]. Due to their hydrophilic nature and tightly cross-linked structure, Carbopol® resins are widely used in oral controlled-release dosage forms [60, 84-86]. Being highly cross-linked, rather than dissolving in water and polar solvents (e.g., alcohol) these polymers readily swell upon hydration, producing a gel layer. Unlike other hydrophilic polymers, such as HPMC whose swelling is due to the relaxation

of polymer chains and their subsequent entanglement or physical cross-linking, chemically cross-linked Carbopol® polymers form a hydrogel upon hydration. This hydrogel is not a simple, entangled chains of polymer, but consists of discrete microgels composed of many polymer particles, into which the drug is dispersed [83]. Since the gel layer is water-insoluble and not erodible, drug release from Carbopol® dosage forms is not controlled by erosion. If the gel layer is fully hydrated osmotic pressure from within the network might break up the structure by sloughing off discrete pieces of the hydrogel followed by drug diffusion through water-filled interstitial spaces between the microgels [83, 87]. This mechanism results in much slower drug liberation from Carbopol® matrices. Due to the pK_a of 6 of the polymer, the mechanism of drug release may be affected by the dissolution medium, as the formation of the gel layer is pH-dependent. It was observed that at lower pH values the polymer is not fully swollen, providing a faster drug release. However, when the pH increased above the pK_a of 6, the maximum swelling up to 1000 times of the original volume and 10 times of the original diameter occurred, leading to retardation of the drug liberation [83, 88-90].

Rahim et al. determined the influence of ethanol on the swelling and release behavior of Carbopol® matrix tablets [91]. The matrix systems were a lightly cross-linked Carbopol® 971P and highly cross-linked Carbopol® 974P. Freely-soluble metformin HCl, moderately-soluble caffeine and slightly-soluble theophylline were used as model drugs to represent different degrees of aqueous solubility. The swelling and dissolution studies were conducted separately in acidic (pH 1.2) and buffered (pH 6.8) media, each with 0%, 20% and 40% (*v/v*) ethanol. During the swelling studies the media uptake (non-alcoholic versus alcoholic) was determined and after drying the mass loss was calculated. The results revealed that the interaction between the ethanol concentration and the dissolution medium pH affects both the dissolution media uptake and the mass loss of drug-free polymer compacts. The dissolution media uptake and mass loss decreased with increasing amount of ethanol in buffered media. Conversely, the increasing ethanol concentration in acidic media caused an increase in dissolution media uptake and mass loss from compacts.

In addition, the presence of ethanol affected the in vitro release behavior of Carbopol® matrix tablets. In the case of metformin HCl, the release rate decreased with the increasing ethanol concentration due to the solubility of metformin HCl decreasing with the increasing amount of ethanol in the dissolution media [91]. As for the effect of hydro-alcoholic media on the drug release rate for caffeine and theophylline, the release was the slowest at 20% ethanol concentration and increased at the ethanol concentration of 40%. This effect can be attributed to the higher solubility of these APIs in ethanol. Although the

drug release rate and mechanism were significantly influenced by the presence of ethanol in the dissolution media, no dose dumping from Carbopol® matrices was observed [91].

These results show that the influence of alcohol on Carbopol®-based tablets is due to the drug solubility, the polymer grade and the interplay between the ethanol concentration and the medium pH. Therefore, it can be concluded that the characteristics of Carbopol®, including its cross-linked structure and swelling behavior in water and ethanol, makes it suitable for the development of controlled-release dosage forms, reducing the risk of alcohol-induced dose dumping [20].

2.5.4 Cellulose ethers

Cellulose derivatives are the most widely-used excipients for hydrophilic matrix systems. In particular, hypromellose, formerly known as hydroxypropyl methylcellulose (HPMC), is the polymer of choice for the preparation of oral-controlled drug delivery systems [49, 58]. Hypromellose is a non-inonic water soluble polymer with a pH-independent drug release profile. If hypromellose comes into contact with water, it hydrates rapidly, which leads to the relaxation of polymer chains and subsequent entanglement. The cross-linking of the polymer chains forms a viscous gel layer [92]. The mechanism of drug release through the gel layer is based on several processes: on the one hand, drug diffusion through the swelling gel layer and, on the other hand, the matrix erosion of the swollen layer [49]. To effectively control and prevent premature drug release from hypromellose matrix systems, it is crucial that the hydration of the polymer and the gel layer formation occur fast to ensure complete swelling of the matrix.

There are several reports available dealing with the effect of ethanol on hypromellose matrices [19, 52, 53, 61, 62]. Asare-Addo et al. studied the impact of ethanol on drug release for direct-compressed hypromellose matrix tablets containing theophylline as model drug and the polyol maltitol as diluent [62]. The dissolution results revealed that there was no failure of the formulation in 5-40% ethanolic-acidic media (pH 1.2) up to 12 h. The obtained f_2 values ranged from 57 to 74 [62]. The drug release was slightly increased in 5 and 20% ethanolic media. In the 40% ethanolic media the drug release decreased after 2 h, despite a twofold increase in theophylline's solubility in the presence of 40% ethanol (*v/v*). This phenomenon might be due to the lower solubility of maltitol in ethanol, which could account for the decreased drug release in 40% ethanolic media [62].

Gohel et al. formulated venlafaxine-HCl-coated and triple-layered matrix tablets using water-soluble hypromellose and water-insoluble ethyl cellulose to obtain the controlled-release profile and to prevent burst release of the highly aqueous-soluble drug [61]. In response to the FDA's suggestion to examine the in vitro release behavior of modified-release dosage forms in dissolution media containing ethanol, drug liberation studies were conducted in distilled water with 10% ethanol. Since the tested batches showed unaltered

dissolution profiles in the presence of 10% ethanolic media, the authors concluded that the formulations are alcohol-resistant and that the hypromellose matrix remains intact in a 10% ethanolic solution. As the used ethyl cellulose comprises more than 46.5% of ethoxyl groups, it is freely soluble in ethanol but insoluble in aqueous media [58]. Therefore, it was suggested that ethyl cellulose is also insoluble in a 10% ethanolic solution [61]. Despite the fact that the drug release of the formulation was not affected in 10% ethanolic media, it is presumed, that dose dumping will occur in higher concentrated ethanolic media (40%) due to the high solubility of ethyl cellulose in ethanol.

Roberts et al. investigated the influence of ethanol on aspirin's release rate and the mechanism in hypromellose-matrix-based controlled-release tablets [19]. It was found that the presence of ethanol in the dissolution media had an impact on the drug release kinetics and the mechanism in matrix tablets, the magnitude of which depended on the used ethanol concentration (0%, 10%, 20%, 30%, 40%). The in-vitro release of aspirin increased proportionally to the increasing ethanol levels due to higher solubility of aspirin in hydro-ethanolic media. The obtained release profiles showed a near-zero-order release profile and drug release was considered to be erosion dominated, with the exception of 40% ethanolic medium in which an initial rapid erosion- and diffusion-controlled drug release was observed. The swelling behavior showed a slower initial interaction between 40% ethanolic medium and hypromellose, which was responsible for the initial rapid release during the first 30 min [19]. This slower initial interaction can be ascribed to the practically insolubility of hypromellose in alcohol, and hence a delayed formation of the strong gel layer. Image analysis of the matrix swelling behavior in 40% ethanolic medium showed that the formation of a less porous and stronger gel layer, which limits the medium uptake, occurred after 75 min. In the 0% ethanolic medium this was already observed after 25 min. However, no alcohol-induced dose dumping occurred [19].

Levina et al. studied the effect of 5% and 40% (*v/v*) ethanol solutions on hydration, gel formation and drug liberation in hypromellose matrix systems comprising three model drugs: felodipine (freely soluble in alcohol), gliclazide (slightly soluble in alcohol) and metformin HCl (slightly soluble in alcohol) [52]. The obtained drug release profiles in the ethanolic medium differed from those in the aqueous medium and had an increase in standard deviation. However, the f_2 values used for establishing a similarity between the two dissolution profiles indicated conformity and confirmed that no dose dumping effect occurred [93]. The observed discrepancies in the dissolution profiles of the hypromellose matrix tablets were ascribed to the drug solubility changes in ethanol solutions [52]. Furthermore, it was recorded that all tested hypromellose matrix tablets consistently retained their matrix integrity when placed in ethanol solutions. Moreover, the consistent swelling and gel layer formation of the hypromellose compacts did not disrupt the matrix

integrity [52]. These results are consistent with Missaghi et al. [53] who stated that the presence of up to 40% ethanolic media had little effect on the textural behavior of hypromellose compacts. The rheological analysis of various viscosity grades of hypromellose in hydro-ethanolic solutions/dispersions demonstrated a pseudoplastic behavior for all tested hypromellose grades whereas the measured viscosity revealed dependency on the ethanol contents of the solutions and increased with the increasing ethanol concentration. Regardless of the ethanol concentrations in the solution, the hypromellose matrices remained intact for up to 6 h of hydration [53].

Although all of the above studies indicate that alcohol influences the kinetics, release mechanism and rheological properties of hypromellose matrix systems, no dose dumping was observed. Therefore, hypromellose can be considered suitable for the design of alcohol- resistant dosage forms.

In general, it has to be noticed that although the above described alcohol-induced dose dumping studies were conducted with a conventional United States Pharmacopeia (USP) testing apparatus, various dissolution media (i.e., phosphate buffer, acidic media and aqueous media) and different ethanol concentrations ranging from 5% to 40% were used. Therefore, it is challenging to check the resulted data against each other. Additionally, the conventional methods only use non-physiologic buffers and do not mimic hydrodynamic conditions. Thus, physiological in vivo conditions are not accurately reflected which makes in vitro in vivo correlations difficult.

2.6 Technological strategies to minimize risk of alcohol-induced dose dumping

The available controlled-release technologies that can reduce the risk of alcohol-induced dose dumping include osmotic drug delivery devices, controlled-release matrix systems and controlled-release coated systems. However, in this section we particular focus on osmotic drug delivery devices since controlled-release matrix systems were covered in more detail in chapter 3. Methods to prepare such devices can be classified in hot-melt extrusion, wet granulation and direct compaction. Since the latter two are rather standard methods in the field of pharmaceutical technology, we particularly focus on hot-melt extrusion as promising alternative to prepare such dosage forms.

2.6.1 Osmotic drug delivery devices

A novel long-acting opioid formulation of oral hydromorphone was developed to provide continuous pain control over a 24-h period and to enhance treatment compliance [94]. For a continuous drug release over an extended period of time, the oral osmotic (OROS®) Push-Pull delivery system based on the principle of osmosis is used for OROS® hydromorphone tablets [94]. Each OROS® system comprises an osmotically-active bilayer

core tablet surrounded by a rate-controlling semipermeable coating membrane. The tablet bilayer core consists of two layers: the pull layer with hydromorphone and the push layer that contains a hydrophilic expanding compartment. After ingestion, the semipermeable membrane allows fluid from the gastrointestinal tract to enter in the core tablet. The push layer expands and forces the suspended drug out of the tablet through a small delivery orifice in the membrane. The osmotically-controlled system is designed such that the drug release rate is actively controlled by the dosage form regardless of the environmental factors, such as the gastrointestinal motility, the surrounding pH or the presence of food and alcohol [95]. Sathyan et al. investigated the pharmacokinetic profile of OROS® hydromorphone in the presence of alcohol [94] and concluded that the pharmacokinetics of the dosage form was only minimally affected by alcohol. Moreover, it was reported that the controlled-release properties and functionality of the delivery system remained unchanged in the presence of alcohol due to the specific OROS® technology and that no dose dumping of hydromorphone occurred [94]. The findings are consistent with those of Koziara et al., who determined the influence of ethanol on semipermeable cellulose acetate-based membranes used as osmotic drug delivery systems [96]. It was found that ethanol increased the permeability, elasticity and swelling of cellulose acetate membranes. Although increasing ethanol concentrations up to 60% caused a slight increase in the drug release from OROS® systems, the drug delivery system maintained the controlled-release properties and no dose-dumping was observed [96].

2.6.2 Controlled-release matrix/coated systems

Ethypharm developed a flexible and well-adapted formulation (LockTab®) to minimize risks associated with drug abuse [97, 98]. Oxycodone HCl and selected excipients were compressed into tablets using conventional manufacturing methods that involve high-compression forces. The tablets had a high tensile strength of 8.2 MPa and could not be destroyed by a mortar and a pestle [98], which in addition may limit the abuse via snorting, chewing and extraction. In-vitro release tests of the LockTab® tablets were conducted in acidic media (0.1N HCl) with up to 40% ethanol. Since drug release from the tablets occurred even slower in the presence of ethanol, it can be concluded that no dose dumping effect would occur if the tablets were co-ingested with alcoholic beverages [97, 98].

Another promising technology is the OraGuard™ extended-release technology, developed by CIMA Labs, which provides resistance against alcohol-induced dose dumping, mechanical crushing and extraction with aqueous and organic solvents [99]. The tamper- and dose dumping-resistant properties were achieved due to a multistep process, in which the API is granulated with appropriate polymers that were chosen according to their solubility behavior in water and ethanol. Subsequently, the granules were coated with a

strong film-forming polymer followed by compression into tablets with gel-forming polymers [100].

Regarding controlled-release coated systems, Traynor et al. reported that the release profile of capsules containing controlled-release coated tramadol pellets markedly increased in ethanolic media [59]. This can be attributed to coating the pellets with Eudragit® NE30D, an alcohol soluble polymer that immediately dissolved in the dissolution media resulting in an immediate drug release [59]. Similar results were obtained by Walden et al. [8] who investigated the effect of high ethanol concentrations (up to 40%) on the in vitro release properties of various prolonged-release opioid formulations and who reported that a major effect of ethanol on the drug release was only observed in Palladone™ SR capsules produced via a coated bead technology [8]. This could be due to the coating excipients, i.e., ethyl cellulose and dibutyl sebacate, which are both soluble in ethanol [8]. Sundari et al. studied the influence of 5% and 10% alcoholic media on the in vitro drug release of diclofenac pellets prepared by wet-extrusion/spheronisation technique. The extruded pellets were coated with Eudragit® RSPO/RLPO and cellulose acetate butyrate, respectively. The observed drug release in 5% and 10% alcoholic media was slower from the prepared pellet formulations compared to marketed diclofenac formulations. However, in 5% and 10% alcoholic media the drug release was markedly increased after 2 h from both pellet formulations [101].

So far, to our knowledge there is only one coating material available that is robust in ethanolic media. FMC BioPolymer has developed Aquacoat® ARC (Alcohol Resistant Coating) which consists of guar gum that is blended with Aquacoat® ECD (Ethylcellulose Aqueous Dispersion) [102]. These two components possess contrary solubility properties. Therefore, in ethanolic media the insoluble guar gum acts as a protecting layer for the alcohol soluble ethylcellulose resulting in an intact controlled-release film. In-vitro dissolution studies of theophylline pellets coated with Aquacoat® ARC were conducted in ethanolic media with ethanol concentrations of 10%, 20% and 40%. Similar controlled-release drug rates were obtained at all tested ethanol concentrations levels, revealing the robustness of the coating system [102].

2.6.3 Hot-melt extruded systems

Hot-melt extrusion (HME) and injection molding are innovative technologies for the production of a variety of dosage forms. As continuous and solvent-free manufacturing methods, they do not require subsequent drying steps and make the process fast, efficient and cost-effective. HME converts a powder mix into a product of uniform shape and density by forcing it through an orifice at high temperatures [103, 104]. Also injection molding is a process which transfers thermoplastic polymers with the aid of heat and pressure into a shape-specific mold [105].

For example, the innovative Meltrex® technology developed by Roth et al. based on poorly soluble verapamil embedded into hypromellose and hydroxypropylcellulose matrices results in hard tablets that cannot be crushed into a fine powder [106], which may minimize the chance of physical tampering. In-vitro studies showed that ethanol concentrations of up to 40% over 8 h had no effect on the dissolution profiles of the Meltrex® formulation. This implies that the melt-extruded tablets were robust in the in-vitro environment and that no dose dumping occurred [106].

In another study, the aim was to prepare polyethylenoxide (PEO)-based matrix (INTAC® formulation technology, developed by Grünenthal GmbH) tablets with extended opioid release, which resist crushing and withstand dissolution and chemical extraction in different solvents [107]. The tablets were manufactured via HME followed by compression of the extrudates in an eccentric tablet press. The obtained tablets had extensive mechanical strength due the high-molecular-weight PEO and the HME technology. The tablets could not be crushed by a mortar, a pestle and a 500-g hammer and did not break in a hardness tester that applied a force of 500 N. In-vitro drug dissolution tests that were conducted in 40% ethanolic media showed a decrease in the drug release rate compared with that in 0.1N HCl media. Furthermore, intact tablets and tampered tablets were subjected to a standard operating procedure to determine their robustness with regard to chemical extraction in simulated alcoholic beverages. The obtained results indicated that the extraction rate of an active drug substance from the tablets in simulated alcoholic drinks was even lower than in aqueous media. The authors concluded that the hard PEO-matrix's resistance to crushing and chemical extraction made the tablet less prone to abuse [107].

One promising patent-pending technology introduces the "Extruded Deterrence of Abusable Controlled Substances" (EDACS™) matrix developed by Akela Pharmaceuticals [38, 39] and achieved by HME. The drug molecules are dispersed into the matrix and then molded into hard tablets. Due to the insolubility of the matrix, this drug delivery platform offers several solutions to problems associated with drug abuse and alcohol dose dumping. Furthermore, because the matrix is not friable and does not break upon compression, it prevents drug tampering and alcohol-induced dose dumping [38, 39]. The EDACS™ technology is designed to deter drug abuse and can be combined with proven opioids to maintain a solid dosage form with extended-release profile [39].

The novel Egalet® controlled-release matrix tablet system is prepared via a conventional two-component injection molding process, which is based on the same process principles as HME and which shapes the material in three dimensions into the final dosage form at elevated temperatures [108]. The key technology of Egalet® involves two components: an erodible matrix, in which morphine sulfate is dispersed, and a non-erodible shell that partly

covers the cylindrical tablet. Hence, both ends of the tablet are uncoated and exposed to erosion in the dissolution media [40]. A constant drug release over 12 h is maintained through the fixed surface erosion area. Haahr et al. investigated the abuse resistance of Egalet® dosage units by conducting crush tests, melting tests, extraction and in vitro dissolution tests in ethanolic media [41]. The results showed that since Egalet® dosage units were impossible to crush (hammering led to flattened units), no fine powder of the API for injection could be obtained. Melting the Egalet® dosage units resulted in a texture similar to a highly-viscous chewing gum unsuitable for injection. Extraction with different solvents (e.g., water, ethanol and methanol) yielded highly viscous solutions that could not be used for injections. The in vitro dissolution studies that were performed in phosphate buffer media (pH 6.8), including 4%, 20% and 40% ethanol, showed that the drug release rate decreased with the increasing amount of ethanol in the dissolution media. The authors concluded that the Egalet® technology minimizes the risk of alcohol induced-dose dumping and makes these dosage units almost entirely abuse-prone, which may be due to a higher solubility of the Egalet® composition in water than in ethanol [41].

It can be concluded that HME and injection molding are promising manufacturing processes for the production of robust dosage forms with a number of advantages over standard pharmaceutical technologies. Several studies indicated that the in-vitro drug release in HME systems is slower than in those prepared via traditional methods [56, 109, 110]. This can be attributed to the dense structure of HME dosage forms, since intense mixing and melting during the process result in matrices that have lower porosity than compressed matrices [109]. Liu et al. reported that the content uniformity and the hardness of wax-based tablets and granules prepared using HME were higher than of those manufactured via a high-shear melt granulation [110]. In summary, these data demonstrate that HME and injection molding are promising technologies with regard to the development of alcohol-resistant dosage forms.

2.7 Conclusions and open remarks

Currently, alcohol-induced dose dumping of oral controlled-release dosage forms is a significant challenge in the formulation development of several different APIs, including opoids and drugs with narrow therapeutic window. To design a robust and alcohol-resistant dosage form, it is vital to systematically analyze the physico-chemical key factors, including solubility, wettability, swellability and mechanical properties of the API, the excipients and the properties of the final dosage form, including hardness, swelling and drug release characteristics. There are several technological strategies, such as HME and injection molding that are helpful in minimizing the risk of alcohol-induced dose dumping and abuse by producing dosage forms with high mechanical strength. Keeping

this in mind during the early development phases of a novel alcohol-resistant dosage form, possible later reformulation or even withdrawal of the product from the market may be avoided. Nevertheless, there is still necessity for further investigations of the alcohol-induced dose dumping phenomenon to gain better insight in how the alcohol interacts with the drug formulation and how this impacts drug dissolution and absorption. Moreover, it is known that the intake of alcoholic beverages also influences the gastrointestinal physiology and, thus, the in vivo performance of modified-release dosage forms [111]. It is likely that ethanol prolongs the gastric emptying rate, induces gastric acid secretion, increases the permeability of the intestinal mucosa and impacts the gastrointestinal motor activity and fluid composition. It should be noted that the precise mechanism through which alcohol affects the in vivo behavior and bioavailability of drugs is still not fully understood, which makes prediction of the in vivo performance of a drug from conventional in vitro dissolution studies difficult. Therefore, in vitro test methods have to be adapted to the physiological conditions in order to perform rational in vitro in vivo correlations.

2.8 References

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3 Alcohol dose dumping: The influence of ethanol on hot-melt extruded pellets comprising solid lipids

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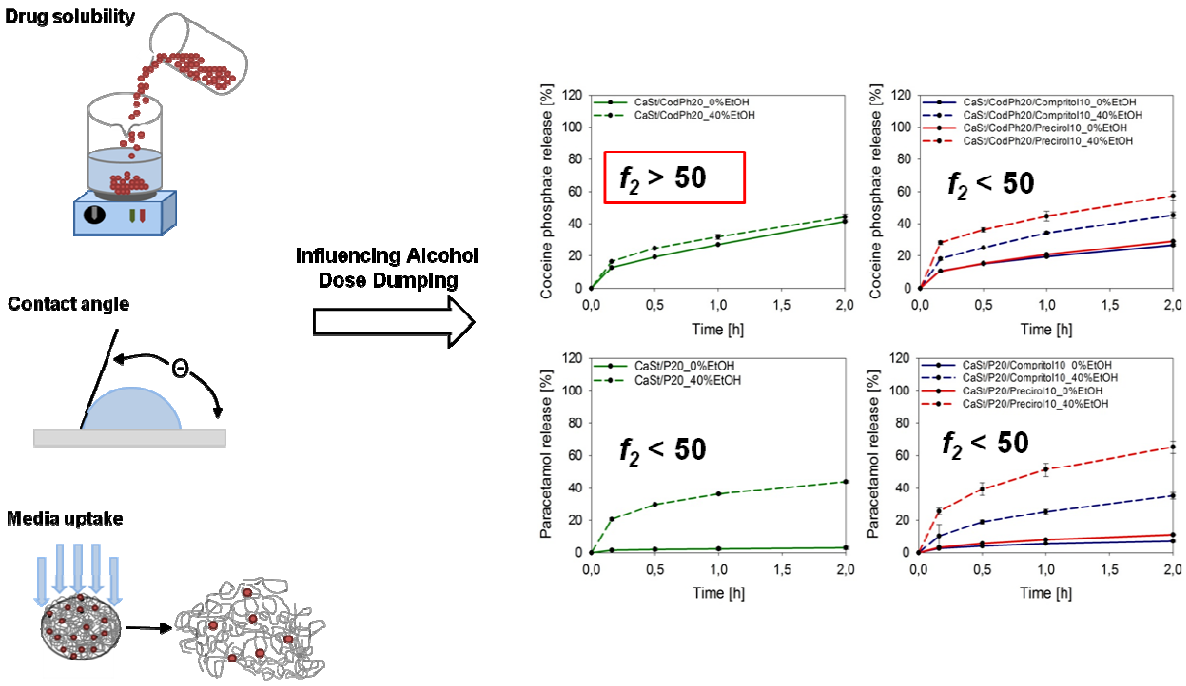
3.1 Graphical abstract



3.2 Abstract

The objective of the present study was to investigate interactions between alcohol and hot-melt extruded pellets and the resulting drug release behavior. The pellets were composed of vegetable calcium stearate as matrix carrier and paracetamol or codeine phosphate as model drugs. Two solid lipids (Compritol® and Precirol®) were incorporated into the matrix to form robust/compact pellets. The drug release characteristics were a strong function of the API solubility, the addition of solid lipids, the dissolution media composition (i.e., alcohol concentration) and correspondingly, the pellet wettability. Pellets comprising paracetamol, which is highly soluble in ethanol, showed alcohol dose dumping regardless of the matrix composition. The wettability increased with increasing ethanol concentrations due to higher paracetamol solubilities yielding increased dissolution rates. For pellets containing codeine phosphate, which has a lower solubility in ethanol than in acidic media, the wettability was a function of the matrix composition. Dose dumping occurred for formulations comprising solid lipids as they showed increased wettabilities with increasing ethanol concentrations. In contrast, pellets comprising calcium stearate as

single matrix component showed robustness in alcoholic media due to wettabilities that were not affected by the addition of ethanol.

The results clearly indicate that the physico-chemical properties of the drug and the matrix systems are crucial for the design of ethanol-resistant dosage forms. Moreover, hydrophobic calcium stearate can be considered a suitable matrix system that minimizes the risk of ethanol-induced dose dumping for certain API's.

3.3 Introduction

Alcohol-induced dose dumping of controlled-release oral dosage forms containing opioid and non-opioid drugs with narrow therapeutic ranges is a significant challenge in the formulation development. Since alcohol may alter the release-rate-controlling mechanism of the formulation, possibly resulting in an immediate and uncontrolled drug release, the concomitant intake of alcoholic beverages together with such dosage forms poses a serious safety concern. This phenomenon, known as alcohol-induced dose dumping (ADD), can have dangerous effects [1]. Particularly susceptible are controlled-release formulations that contain a high total amount of API in order to reduce the dosing frequency and prolong the therapeutic effect. In 2005, Palladone™, a hydromorphone modified-release capsule formulation, was withdrawn from the US market, since taking it together with alcohol drastically increased the peak plasma concentrations of hydromorphone by causing failure in the release-rate-controlling mechanism [2]. Such opioid-overdose may lead to respiratory depression followed by hypoxia and even death [3]. To test for possible alcohol dose dumping effects, the Food and Drug Administration (FDA) recommends to conduct *in vitro* drug release studies in ethanolic media of controlled-release dosage forms containing opioid and non-opioid drugs with a narrow therapeutic range [1, 4].

To date, only a limited number of robust single unit dosage forms [5], such as osmotic drug delivery devices [6, 7] and controlled-release matrix systems [8-15] that can withstand the effect of alcohol, are available. For the former one, a controlled-release tablet formulation of oral hydromorphone was developed using a patented oral osmotic (OROS®) Push-Pull delivery system [6]. It was shown that the controlled-release properties remained unchanged in the presence of alcohol and no dose dumping of hydromorphone occurred [6]. The same effect was reported by Koziara et al. [7]: although increasing ethanol concentrations up to 60% caused a slight increase in the drug release of OROS® systems, controlled-release properties of the drug delivery system remained unaffected and no dose dumping occurred. This could be attributed to the specific OROS® technology, which is designed such that the drug release rate is actively controlled by the dosage form, regardless of such environmental factors as gastrointestinal motility,

surrounding pH and presence of food and alcohol [16]. In the field of matrix systems and alcohol-robust controlled-release matrix tablets, hydrophilic polymers (e.g., polyethylene oxide [8], cross-linked high amylose starch [9], carbomer [10] and hypromellose [11-15]) can be used. Insoluble in EtOH, they are expected to remain unaffected when consumed together with alcohol.

Currently, only one multiple unit dosage form is available that can withstand the influence of alcohol and remain intact in the course of the drug release process. It comprises theophylline pellets coated with Aquacoat® ARC (Alcohol Resistant Coating), which consists of guar gum blended with Aquacoat® ECD (Ethylcellulose Aqueous Dispersion) [17]. Insoluble in alcohol, guar gum acts as a protective layer for the alcohol-soluble ethylcellulose, leaving the controlled-release film intact. Similar controlled-release drug rates were obtained at all tested EtOH concentrations levels (10%, 20%, 40%), confirming the robustness of the coating system [17].

However, to our knowledge, no literature exists concerning the development of uncoated alcohol-resistant multiple unit dosage forms with sustained-release. To fill this gap, in this study we investigated the influence of ethanol on the *in vitro* drug release behavior of hot-melt extruded pellets. Hot-melt extrusion (HME) is a promising technology for the preparation of alcohol-resistant controlling dosage forms. For example, Roth et al. developed the innovative sustained-release Verapamil Meltrex® formulation [18]. The *in vitro* dissolution studies indicated that ethanolic media (5%, 20% and 40% (v/v)) did not affect the drug release rate after 8 h in dissolution media. The authors concluded that the melt-extruded tablets remained intact in the *in vitro* environment and no dose dumping occurred [18].

The hot-melt extruded pellets prepared in our study were composed of the well-characterized analgesic and antipyretic drug paracetamol and the opioid analgesic drug codeine phosphate as model active pharmaceutical ingredients (APIs) and vegetable calcium stearate (CaSt) as a matrix carrier. Being a mixture of water-insoluble calcium salts of stearic and palmitic acid, CaSt is primarily used as a lubricant in tablet and capsule formulations [19]. However, Roblegg et al. demonstrated that CaSt could be used as a pelletisation matrix carrier for spherical slow-release pellets using the wet extrusion/spheronisation technique [20]. Another study by Roblegg et al. established that controlled-release spherical CaSt pellets could be produced via HME [21]. It was demonstrated that CaSt retarded the drug release to a significant extent and by adding plasticizers the *in vitro* release profile could be tailored as desired [21]. Due to its hydrophobic nature, CaSt is insoluble in water and ethanol and is a promising matrix system for alcohol-resistant formulations.

In the current study, two ethanol- and water-insoluble solid lipids (Compritol® and Precirol®), which are suitable for hot-melt extrusion [22, 23] were incorporated to form a robust/compact multiple unit dosage form resistant to ethanol. As calcium stearate shows a very high melting point, it is not expected to melt during HME. Hence, the low melting lipids Compritol® and Precirol® were incorporated which melt during the process and therefore, act as binders. All formulations were tested regarding their release characteristics in the presence of ethanol. The main goal was to achieve a better understanding of how alcohol interacts with the formulation, which is the basis for a rational formulation design. To that end, media uptake and wetting behavior upon exposure to ethanolic media were examined. Furthermore, the pellet surface properties and internal morphology were studied via scanning electron microscopy (SEM).

3.4 Materials and methods

3.4.1 Materials

Paracetamol and codeine phosphate hemihydrates donated by G.L. Pharma GmbH, Lannach, Austria were used as model APIs. The matrix carrier system was vegetable calcium stearate (stearic acid 44% and palmitic acid 54%, EP) purchased from Werba-Chem GmbH, Vienna, Austria. The solid lipids Precirol® ATO 5 (glycerol distearate) and Compritol® 888 ATO (glycerol dibehenate) were supplied by Gattefossé, Weil am Rhein, Germany. The *in vitro* drug release studies were carried out with 0.1 N hydrochloric acid (HCl) and a trisodiumphosphate-dodecahydrate buffer purchased from Merck, Darmstadt, Germany. For the dose-dumping studies, absolute ethanol (EP) was obtained from VWR International, Darmstadt, Germany. The mobile phase for the reversed phase high performance liquid chromatography (HPLC) consisted of ammonium hydrogenphosphate and ammonium dihydrogenphosphate (Fluka, Sigma Aldrich Chemicals, St. Louis, USA), phosphoric acid (85%, VWR international, Darmstadt, Germany) and methanol (LiChrosolv® Reag., EP, VWR International, Darmstadt, Germany).

3.4.2 HME process

The powder mixtures for HME were obtained by blending the matrix carrier CaSt and the model drugs paracetamol and codeine phosphate with each of the solid lipids in a turbula mixer at 60 Hz for 20 min (Turbula® TypT2F, Turbula System Schatz, Willy Bachofen AG, Muttenz, Switzerland). The powder blend was transferred into a dosing device (K-Tron, Niederlenz, Switzerland) and gravimetrically fed into a co-rotating twin-screw extruder (ZSK 18, Coperion GmbH, Stuttgart, Germany) with a length-to-diameter ratio (L/D) of 40. The screws were located inside of a cylindrical barrel composed of 10 individually-controllable heating sections. The chosen temperature profiles of all barrel zones are listed in Table 1. Pellets were made directly with our in-house developed hot-die cutter

[24]. To produce suitable extruded strands via hot die-face pelletizing, the formulations were extruded at temperatures ranging from 75 to 130 °C (depending on the formulation). The screw speed was set to 200 rpm for all experiments and the throughput of the extruder was 0.5 kg/h. The molten material was extruded through a die plate with a diameter of 1.0 mm. Subsequently, homogeneous strands were cut directly at the die face using a hot die-face pelletizer (Automatik Plastics Machinery GmbH, Großostheim, Germany) with two rotating knives and immediately air-cooled. To obtain pellets in the desired size range, the rotational speed of the knives was set manually to 1200-1300 (depending on the formulation). An overview of the formulations and the processing parameters is given in Table 1.

Table 1
Formulations (wt.%) and HME process parameters.

Formulation (wt.%)	Process parameters											
	Throughput (kg/h)	Torque (%)	Barrel-zone temperatures (°C)									Knife rotation speed (rpm)
			1	2	3	4	5	6	7	8	9	10	
CaSt/P20	0.5	16	100	110	130	130	130	130	120	110	100	110	1300
CaSt/P20/Precirol10	0.5	15	90	90	110	110	100	100	100	100	100	100	1250
CaSt/P20/Compritol10	0.5	15	100	100	110	110	100	100	100	100	100	100	1250
CaSt/CodPh20	0.5	15	85	100	100	100	100	100	100	100	100	100	1300
CaSt/CodPh20/Precirol10	0.5	15	80	85	85	85	85	85	85	85	85	85	1200
CaSt/CodPh20/Compritol10	0.5	15	75	75	75	75	75	75	75	75	75	75	1200

3.4.3 Characterization of powder substances and pellets

Differential scanning calorimetry

Thermal properties of the pure powder substances and the hot-melt extruded pellets were characterized using a differential scanning calorimeter (DSC 204F1 Phoenix®, Netzsch GmbH, Selb, Germany). Samples of about 6-9 mg were weighed into aluminium crucibles, which were sealed and pierced. The model API's and CaSt were scanned between 25 to 200 °C at a heating rate of 5 K/min, with pure nitrogen as the purge gas at a flow rate of 20 ml/min. After cooling (10 K/min) to 25 °C, a second heating run was performed. Since both solid lipids are expected to melt during HME, the samples were heated from 25 °C to 110 °C (highest applied extrusion temperature) at a heating rate of 5 K/min, hold at 110 °C for 10 min, cooled to 25 °C (10 K/min) and reheated from 25 °C to 200 °C. For hot-melt extruded pellets, only one heating cycle was performed (temperature range 25-200 °C). An empty aluminum crucible was used as a reference. The DSC data analysis was conducted with Proteus Thermal Analysis software (Netzsch GmbH, Selb, Germany).

Fourier transform infrared spectroscopy (FT-IR)

FT-IR spectroscopy using a Bruker Vertex 70 spectrometer was applied to evaluate chemical interactions between the model drugs, matrix carrier system CaSt and solid lipids. The pure substances and the hot-melt extruded pellets were placed in close contact with the diamond ATR device. Each sample was measured in triplicate with 16 scans at a resolution of 4 cm^{-1}. The spectra were collected at wavelengths ranging from 4500 to 600 cm^{-1}.

Drug solubility determination

The solubility of paracetamol and the opioid drug codeine phosphate was evaluated in ethanol and dissolution media with and without alcohol by preparing saturated solutions. The solutions were left in an incubator shaker for 48 h at 37 ± 0.5 °C. Samples of 1 ml were taken, filtered (cellulose acetate filter with a pore size of 0.2 µm) and diluted appropriately, and the concentration of the dissolved drug was quantified via UV/VIS spectrometry at a wavelength of 244 nm (paracetamol) and 284 nm (codeine phosphate), respectively. The solubility studies were performed in triplicate.

Media uptake studies

Compacts of pure CaSt, Precirol® and Compritol® and the hot-melt extruded pellets were prepared by direct compression using an electro-hydraulic press (Perkin Elmer, Überlingen, Germany) equipped with a 13 mm die assembly. In order to determine the media uptake of the compacts, the experiments were conducted similarly to the *in vitro* dissolution studies described in Section 2.3.6 using the same media. The compacts were

weighed and placed into the dissolution apparatus. After 120 min they were withdrawn from the medium and the excess surface liquid was carefully removed with tissue paper. After they were re-weighed (w_0), the compacts were transferred into an oven and dried to a constant weight (w_1) at 37 °C. The experiments were repeated three times for each time point. The media uptake capacity (%) was determined in accordance to Kreye et al. using the following equation [25]:

$$media\ uptake\ capacity\ (\%) = \frac{w_0 - w_1}{w_0} \times 100 \quad (1)$$

Contact angle measurements

Prior to the experiments, compacts of the pure powder substances (i.e., CaSt, Compritol® and Precirol®) and the hot-melt extruded pellets were prepared as described in Section 2.3.4. The contact angles of the compacts with water, ethanol, dissolution media without ethanol and dissolution media with 20% and 40% ethanol were examined using the EasyDrop System (Krüss, Hamburg, Germany). Images of the liquid drop in contact with the compacts surface were captured with a CCD camera. The contact angle values were obtained by applying the height and width (H/W) method, where the contact angle is measured optically using drop shape analysis. The contact angle values were calculated from the width of a sessile drop and its height at the apex [26]. All measurements were performed six times and the mean value was determined.

In-vitro drug release studies

All *in vitro* dissolutions tests were carried out via the USP 28 rotating basket method <711> (Pharma Test, Hainburg, Germany) at a rotational speed of 100 rpm and a release temperature of 37 ± 0.5 °C. For each formulation, 1 g of the pellets was transferred into the basket (n=3). Dissolution medium consisted of 750 ml 0.1 N HCl. After 2 h, 250 ml trisodiumphosphate-dodecahydrate buffer was added to switch the pH from 1.2 to 6.8. Samples of 1 ml were withdrawn from each vessel at predetermined time intervals (after 10 min followed by sampling at 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 h). The drug content was determined using reversed phase HPLC. A dissolution study was also performed on the pellet formulations after 12 months of storage in closed dishes at room conditions.

For the alcohol-induced dose dumping studies, additional dissolution testing was conducted in 900 mL HCl (0.1 N) with ethanol concentrations of 20% (equivalent to mixed drinks) and 40% (equivalent to hard liquor) (v/v) over a period of 2 h. To compare the drug release profiles in alcoholic and non-alcoholic media, the f_2 similarity factor was used. According to Moore and Flanner, the f_2 value was calculated using the following expression [27]:

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-\frac{1}{2}} \times 100\right\} \quad (2)$$

where n is to the number of dissolution time points considered and R_t and T_t are the percent of drug dissolved of the reference and test formulations at time point t. In general, an f_2 value in the range of 50-100 indicates that the dissolution profiles are similar.

Reversed phase HPLC analysis

The HPLC system (HP1090 liquid chromatography, Hewlett Packard, Palo Alto, USA) comprised a diode array detector (detection at 272 nm). The analysis was carried out using a reversed phase ODS silica column (125 x 4 mm, LiChrospher®, 5 µm RP-18, 100 Å pore size, VWR International, Darmstadt, Germany) as the stationary phase. An aqueous solution containing 7.6 mM ammonium hydrogenphosphate and 5.4 mM ammonium dihydrogenphosphate served as the mobile phase. This mixture was adjusted with phosphoric acid to pH 2.6. Next, the mobile phase was diluted with methanol at the ratio of 60:40 (w/w) followed by filtration through a cellulose nitrate filter (pore size 0.2 µm, Sartorius, Göttingen, Germany). Subsequently, the filtrate was degassed with helium (purity: 5.0) for 10 minutes. A volume of 5-10 µl of each sample was injected automatically with an autosampler, and the flow rate was set to 0.8 ml/min. The quantification was performed by a single-point calibration with a 100% standard solution of the API.

Pellet morphology

SEM was performed to visualize the surface morphology of the CaSt/paracetamol and CaSt/codeine phosphate pellets, with and without solid lipids before and after the *in vitro* drug release studies in dissolution media without ethanol (8 h) and ethanolic media (2 h). The pellets were mounted on stubs using a double-sided sticky band and were sputtered with chromium under vacuum. Images were obtained using a scanning electron microscope (Zeiss Ultra 55, Carl Zeiss NTS GmbH, Oberkochen, Germany) operating at an accelerating voltage of 5 kV.

Statistical analysis

All tests were performed three times, except the contact angle measurements that were conducted six times. The results were expressed as a mean ± standard deviation (SD). Statistical differences between each formulation were determined by a p-value < 0.05 (Student's unpaired t-test).

3.5 Results and discussion

3.5.1 Preparation of pellets via HME

The CaSt/paracetamol blend was extruded at a temperature ranging from 100 to 130°C, and the evaluated torque value was 16%. The temperature profile was chosen according to the softening temperature of CaSt (i.e., around 120 °C) as it was previously shown that paracetamol does not act as plasticizer in this system [21]. At this temperature range cuttable extrudates with a suitable melt viscosity were obtained. For the CaSt/codeine phosphate blend, however, the extrusion temperature had to be reduced to 85-100°C, in order to obtain a homogeneous material that can be extruded and cut at the die. The necessary reduction in the extrusion temperature suggests that codeine phosphate has a plasticizing effect on the matrix material, which is the case for a number of drugs [28, 29].

Adding Precirol® and Compritol® required a reduction in the process temperature for both model drugs, in order to obtain extrusion strands suitable for further down-streaming. For the CaSt/codeine phosphate/Compritol® formulation and for the CaSt/codeine phosphate/Precirol® formulation the extrusion temperature had to be reduced to 75 and 80-85° C, respectively (Table 1). For the CaSt/paracetamol/Compritol® formulation and for the CaSt/paracetamol/Precirol® formulation the extrusion temperature had to be reduced to 100-110 °C and 90-110° C, respectively (Table 1). These findings are in accordance with Islam et al., who observed that Compritol® acted as a plasticizer during the extrusion process [22]. Extruding a blend of paracetamol, ethylcellulose and Compritol® resulted in reduced necessary extrusion temperatures compared to the binary blend of paracetamol and ethylcellulose [22].

After cooling the melt-extruded pellets, a sieve analysis was carried out. The pellets prepared with the 1.0 mm die plate had a yield between 62.53% and 70.42% in the desired size fraction of 1.0-1.25 mm, which were used for further characterization.

3.5.2 Thermal characterization and compatibility studies

In order to determine the thermal behavior of the drug and the excipients, DSC measurements were performed on pure powder substances and hot-melt extruded pellets (Figs. 1 and 2). From the literature, it is well known that paracetamol exists in three polymorphic forms [30-33]. Form I (monoclinic paracetamol) is the commercially available and most thermodynamically stable form with a single endothermic melting peak at about 171 °C [32]. The second modification is the metastable form II (orthorhombic paracetamol), with a melting endotherm at about 157 °C [31]. The unstable form III is considered an important intermediate step in the transformation into the orthorhombic form [31]. Figure 1 illustrates the DSC signal of paracetamol used in this study. The thermogram of the first heating cycle clearly showed only one sharp endothermic event at

172.8 °C (onset = 169.4 °C), which corresponds to the characteristic melting peak of monoclinic paracetamol. No thermal events were observed during cooling, indicating an amorphous substance. Upon reheating the solidified melt, two exothermic events and one endotherm were detected. This effect was also reported in other studies [31, 33]. The exothermic signal at 82.6 °C (onset = 76.8 °C) was due to the crystallization to form III. The second exothermic event that occurred at 129.5 °C (onset at 125.8 °C) could be attributed to the transformation of form III to form II, followed by melting of form II at 160.8 °C (onset = 157.0 °C).

Codeine phosphate hemihydrate (0.5 water equivalent), which is a pseudo-polymorph of codeine phosphate [34], had a weak endothermic signal at 107.6 °C (onset = 97.1 °C), which was also reversible upon cooling (109.3 °C), and an endothermic event at 151.6 °C (onset = 146.3 °C), respectively (Fig. 2). According to the literature, these endothermic events could be attributed to the loss of water and the phase transition from the hemi-hydrate to the anhydrous form of codeine phosphate [34]. A third endothermic peak appeared at 187.7 °C (onset = 179.2 °C) as a result of internal structural rearrangements in the codeine molecule [34]. Upon reheating, this endotherm was reproducible at 180.0 °C (onset = 176.6 °C).

The thermogram of the matrix carrier CaSt showed two endothermic events during the first heating cycle (Figs. 1 and 2). The first signal outlined a broad endothermic peak in a temperature range of 113.9 °C to 123.6 °C, due to softening of the substance [35]. The endothermic peak at 189.9 °C (onset = 186.7 °C) was a result of transition of CaSt into the liquid state [21]. This thermal event was also reversible upon cooling (169 °C). Both endotherms of the first heating cycle were reproducible at repeated heating. The softening peak of CaSt occurred at 119.0 °C (onset = 111.3 °C) and the transition into the liquid state was detected at 190.3 °C (onset = 186.8 °C). The DSC scan of Compritol® was characterized by one endothermic melting peak at 75.1 °C (onset = 69.6 °C) during heating. Upon cooling, one recrystallization exotherm at 64.9 °C (onset = 58.7 °C) was obtained. Reheating of the lipid led to a slight shift of the melting endotherm towards lower temperatures (74.0 °C; onset = 67.9 °C), which indicates solid-state transitions. These findings are in agreement with the literature [36, 37]. During the first heating of Precirol®, a melting endotherm was recorded at 58.6 °C (onset = 48.5 °C). The cooling curve displayed the recrystallization exotherm of Precirol® at 52.5 °C (onset = 47.3 °C). During the second heating cycle, two melting endotherms (45.91 °C and 54.37 °C, respectively) were detected, which was reported in previous studies [36, 38-40]. The peak at lower temperatures may be due to partly melting of the lipid mass and recrystallization of lower melting crystal structures [40]. For both, Precirol® and Compritol® it is reported that the crystal structure may transform to a more stable modification during storage depending

upon the storage conditions [36]. The solid-state transformation can affect the drug release properties of the dosage form [40, 41]. However, this was not evaluated during the present study.

The obtained thermograms of the melt-extruded pellets appeared as a sum of the characteristic peaks of the individual components (Figs. 1 and 2). The pellet formulations containing paracetamol clearly indicate the presence of a crystalline drug since an endothermic event occurred during heating at 170.2 °C (onset = 168.1 °C) for CaSt/paracetamol and 170.0 °C (onset = 168.0 °C) for Cast/paracetamol/Compritol® and for Cast/paracetamol/Precirol®, respectively (Fig. 1). This endotherm corresponds well to the melting peak of monoclinic paracetamol. Additionaly, the softening of CaSt at 120 °C was evident from all thermograms.

All codeine phosphate pellet formulations had an endothermic peak at 182.4°C (onset = 179.6 °C) that was associated with the structural rearrangement within the codeine molecule, as described above (Fig. 2). Moreover, a broad endotherm was observed at around 120 °C (onset = 110 °C) due to softening of the matrix carrier, CaSt.

The melting peaks of Compritol® and Precirol® were identified in the thermograms of all pellet formulation (Figs. 1 and 2). The paracetamol formulations had melting peaks at 74.5 °C (onset = 65.7 °C) and at 57.6 °C (onset = 54.6 °C) for Compritol® and Precirol®, respectively. The thermograms of the codeine phosphate pellet formulations showed melting endotherms at 63.0 °C (onset = 58.8 °C) and at 46.0 °C (onset = 41.3 °C). The plasticizing effect of codeine phosphate led to a shift of the melting endotherms towards lower temperatures. However, the intensity of the Compritol® and Precirol® peaks was very low, which may be due to either the smaller quantity used in the pellet formulations or partial interactions of the components. To investigate chemical interactions between the drug, the matrix system and the solid lipids FT-IR measurements were conducted.

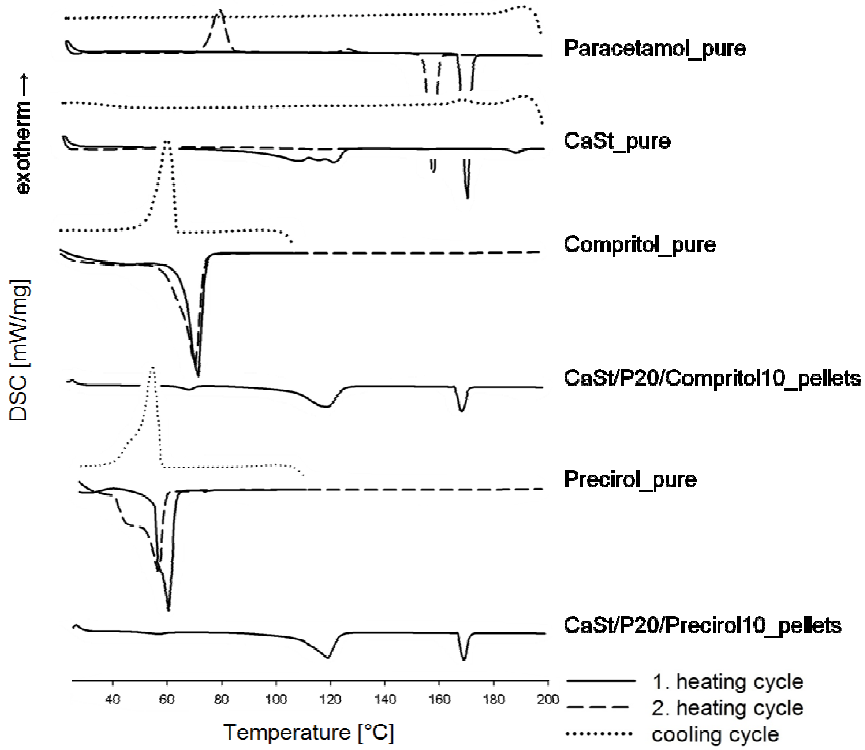


Fig. 1. DSC scans of the pure powder substances (i.e., paracetamol, CaSt, Compritol®, Precirol®) (2 heating cycles) and hot-melt extruded pellets (one heating cycle).

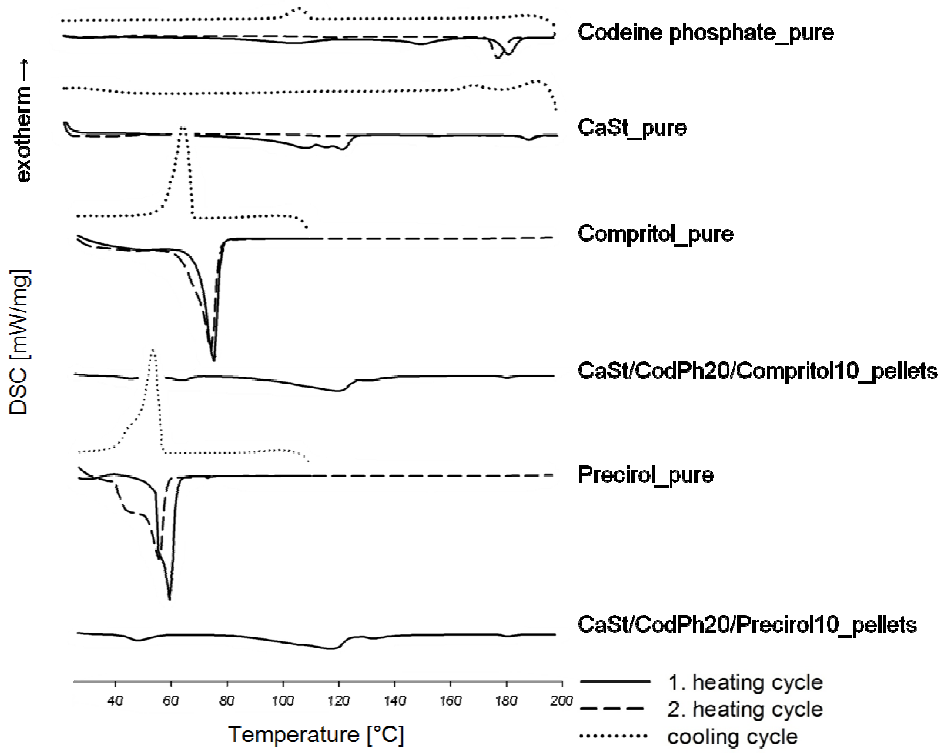


Fig. 2. DSC scans of the pure powder substances (i.e., codeine phosphate, CaSt, Compritol®, Precirol®) (2 heating cycles) and hot-melt extruded pellets (one heating cycle).

The FT-IR spectra of the pure drugs and excipients, along with the melt-extruded pellet formulations, are illustrated in Figs. 3 and 4. Characteristic peaks corresponding to the pure substances were retrieved from the infrared spectra of the melt-extruded pellets. This confirms the absence of drug-matrix interactions (for paracetamol as well as for codeine phosphate) since neither shifting of any peak nor new peaks were detected.

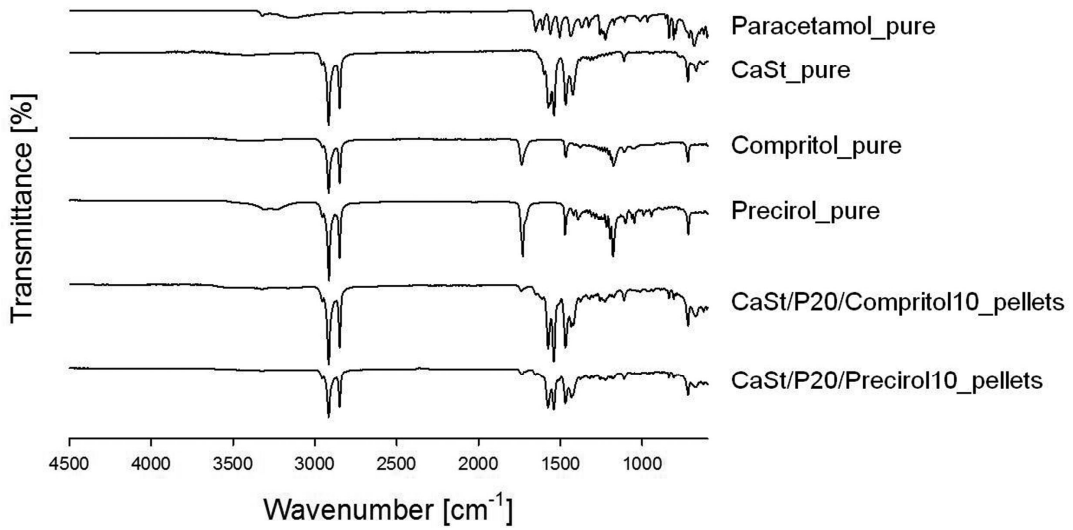


Fig. 3. FT-IR spectra of the pure powder substances (i.e., paracetamol, CaSt, Compritol®, Precirol®) and hot-melt extruded pellets.

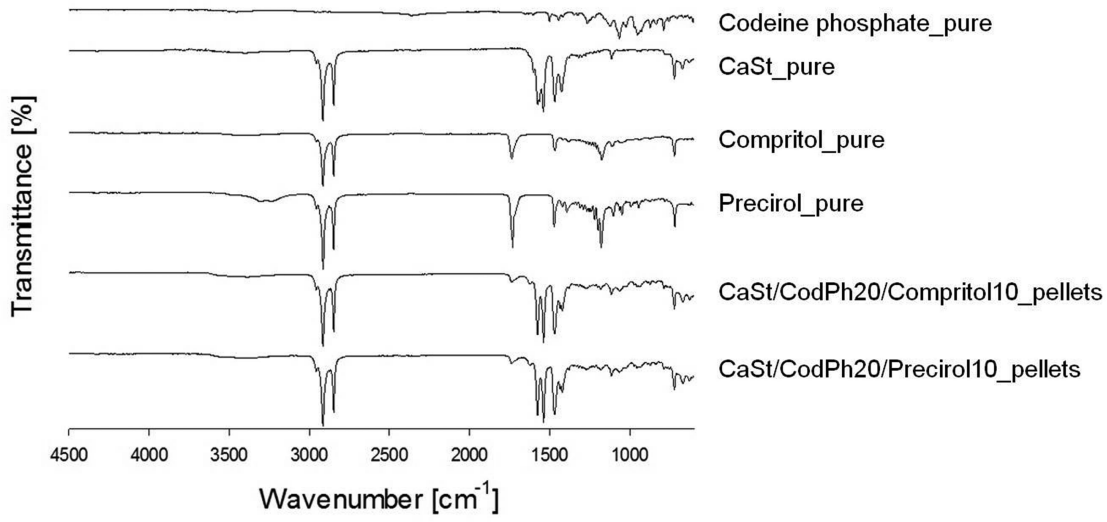


Fig. 4. FT-IR spectra of the pure powder substances (i.e., codeine phosphate, CaSt, Compritol®, Precirol®) and hot-melt extruded pellets.

3.5.3 Drug solubility

The solubility of paracetamol and codeine phosphate was determined in the hydrochloric dissolution media with and without alcohol. The data are presented in Table 2. The results demonstrate that the solubility of paracetamol is significantly affected by dissolution

media, i.e., paracetamol has a higher solubility in the presence of ethanol, i.e., a three- and ten-fold rise compared to 0.1 N HCl media was observed in 20% and 40% EtOH, respectively. These findings are consistent with the literature [42].

In contrast, the solubility of codeine phosphate markedly decreased with increasing alcohol concentration. Codeine phosphate is most soluble in polar solvents like water and the addition of ethanol will lower the dielectric constant in relation to pure water, and hence, the solubility of the drug decreases [5, 43].

Table 2
Solubility of paracetamol and codeine phosphate in various media at 37 ± 0.5 °C.

Various media tested	Paracetamol solubility [mg/ml]	Codeine phosphate solubility [mg/ml]
0.1 N HCl	14.6	518.41
0.1 N HCl/EtOH 20%	47.38	273.77
0.1 N HCl/EtOH 40%	151.44	186.09
EtOH pure	232.75[a]	3.88

[a] Based on Granberg et al. [42].

3.5.4 Media uptake and wetting studies

The media uptake of the pure matrix materials and the pellet formulations was studied. Furthermore, contact angle measurements were conducted to characterize the wetting behavior of the matrix substances and the pellet formulations in non-alcoholic media and alcoholic media.

Fig. 5 illustrates the media uptake of the compacts after 120 min of exposure to non-alcoholic and alcoholic media. The results indicate that the uptake of pure CaSt compacts was similar in 0.1 N HCl (i.e., 0.31%), in 0.1 N HCl/phosphate buffer (i.e., 0.18%) and in 20% ethanol media (i.e., 0.22%) (Fig. 5A, B, C). In 40% alcoholic media however, the media uptake was 1.02% as CaSt is swellable in ethanol (Fig. 5D) [44]. Pure Compritol® compacts showed a media uptake of 1.8% in 0.1 N HCl (Fig. 5A). The media uptake was increased in HCl/phosphate buffer (i.e., 5.5%; Fig. 5B) and was even higher when ethanol was present (i.e. 8.2% in 20% alcoholic media and 9.1% in 40% alcoholic media; Fig. 5C and 5D). In contrast, the media uptake of the pure Precirol® compacts was similar in all media (i.e., 1.2%, 0.57%, 1.2% and 1.6% in 0.1 N HCl, 0.1 N HCl/phosphate buffer, 20% and 40% alcoholic media; Fig. 5).

For the paracetamol formulations the media uptake in non-alcoholic media was independent on the pH-value (0.1 N HCl and 0.1 N HCl/phosphate buffer) and on the formulation composition (addition of Compritol® and Precirol®) (Fig. 5A and B). All media uptake values were below 1.0%. The formulation compacts increased slightly with increasing alcoholic concentration (i.e., 1.9%, 1.1%, 2.2% and 3.5%, 3.0% and 3.8% for

CaSt/paracetamol, CaSt/paracetamol/Precirol® and CaSt/paracetamol/Compritol® in 20% and 40% alcoholic media, respectively; Fig. 5C and D).

The media uptake values for the codeine phosphate formulation compacts highly exceeded those of the paracetamol formulation compacts in all tested media (Fig. 5). Most probably, this was attributed to the higher solubility of codeine phosphate. A comparatively high fraction of codeine phosphate was released during the studies leaving behind a porous matrix system. The porous system provided a higher surface area accessible to the swelling media and consequently, higher fractions of swelling media were absorbed.

The media uptake of CaSt/codeine phosphate compacts was nearly similar in 0.1 N HCl (11.4%), 0.1 N HCl/phosphate buffer (10.6%), 20% (12.9%) and 40% (12.1%) ethanolic media (Fig. 5). In non-alcoholic media the media uptake was decreased when Compritol® was added to the formulation (i.e., 9.7% and 9.9% for 0.1 N HCl and 0.1 N HCl/phosphate buffer) and was further decreased when Precirol® was added (i.e., 7.4% and 7.3% for 0.1 N HCl and 0.1 N HCl/phosphate buffer) (Fig. 5A and B). This was rather unexpected as both pure solid lipid compacts showed higher media uptake values compared to pure CaSt. It should be noted, that the pure substances were used in the pure not molten state, not reflecting the situation as present in the pellet formulation compacts, which were produced from hot-melt extruded pellets. The addition of 10% Compritol® yielded decreased media uptake compared to CaSt/codeine phosphate in 20% alcoholic media (i.e., 10.8%), whereas the addition of 10% Precirol® yielded increased media uptake (i.e., 13.2%) (Fig. 5C). In 40% ethanol however, CaSt/codeine phosphate/Compritol® and CaSt/codeine poshphate/Precirol® showed increased media uptake (i.e., 15.6% and 17.1%) compared to CaSt/codeine phosphate (Fig. 5D). Again, the observed media uptake behavior of the pure components was not reflected in the behavior of the pellet formulation compacts as pure Compritol® showed higher media uptake in 20% and 40% ethanol than pure Precirol®.

Furthermore, the wetting behavior of the compacts in alcoholic and non-alcoholic media was determined.

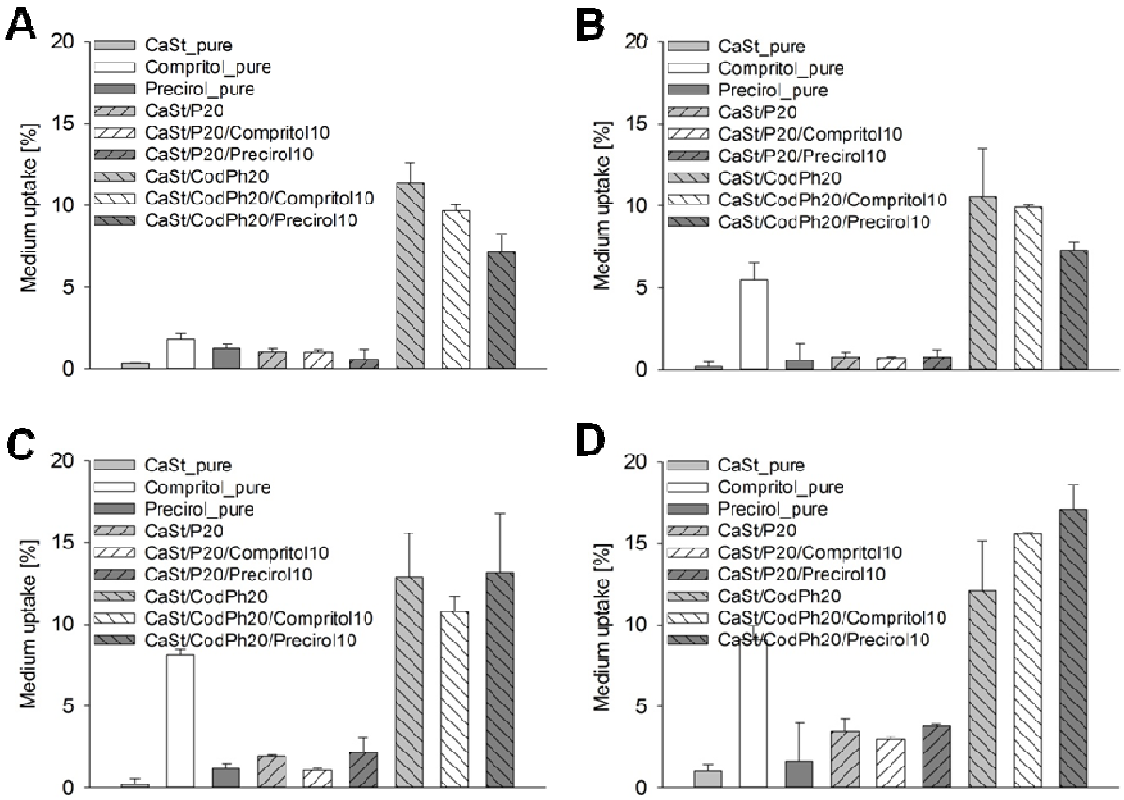


Fig. 5. Media uptake of the compacts after 120 min of exposure to (A) 0.1 N HCl, (B) 0.1 N HCl/phosphatebuffer pH 6.8, (C) 0.1 N HCl/20% EtOH and (D) 0.1 N HCl/40% EtOH; Mean values ± SD (n = 3).

The wetting behavior of a substance depends on its chemical structure and hydrophilic/hydrophobic nature. It correlates with the drug dissolution rate [45] probably because wetting establishes solute-solvent contacts that the solvent needs in order to penetrate the matrix system and release the drug [46].

Table 3 lists contact angles of the pure powder substance compacts and the hot-melt extruded pellet formulation compacts with water, ethanol, and non-alcoholic and alcoholic dissolution media. Due to the hydrophobic nature of CaSt and solid lipids, the measured contact angles in water were well above 90° (Table 3). Both solid lipids also had high contact angle values of above 90° in dissolution media. In alcoholic media, the contact angle values of CaSt slightly decreased with the increasing ethanol concentration. The obtained contact angle values of CaSt were in accordance with Schrank et al., who reported that pure water did not wet CaSt and contact angles of pure ethanol and 50% ethanol were well below 90° [44]. In the case of Compritol® and Precirol®, the contact angle values strongly decreased with increasing ethanol concentration, indicating enhanced wetting in alcoholic media. Adding 40% ethanol almost reduced the contact angle by 50%. As expected, large contact angle values (i.e., > 90°) were found for all pellet formulations in the presence of water because of the large amount of hydrophobic materials used in the formulations (i.e., CaSt, Compritol® and Precirol®). No significant

differences between the measured contact angle values in acidic media and 20% alcoholic media were found for all pellet formulations. In contrast, the obtained contact angles in 40% alcoholic media markedly decreased (i.e., < 70°), indicating enhanced wetting properties of the formulations with higher amounts of alcohol. This was supported by the contact angle values obtained in pure ethanol, which were around 30° for the codeine phosphate pellet formulations. The contact angle of the paracetamol pellet formulation compacts in pure ethanol could not be determined due to an immediate drop penetration into the compacts, proposing a total wetting of the pellet formulation compacts in pure alcohol.

Table 3
Contact angle values of the compacts with different media. Mean values ± SD (n=6).

Formulations	Contact angle (°) with:					
	Water	0.1 N HCl	0.1 N HCl/ Phosphate-buffer pH 6.8	0.1 N HCl/ EtOH 20%	0.1 N HCl/ EtOH 40%	EtOH pure
CaSt_pure	113.7±2.65	79.8±0.49	77.2±1.55	71.4±0.07	69.9±0.77	34.3±0.24
Precirol_pure	103.2±1.34	100.3±1.06	101.1±2.82	65.1±0.35	57.7±0.14	25.1±0.21
Compritol_pure	108.2±1.98	95.8±2.89	103.3±2.05	79.8±0.56	56.3±0.84	20.6±4.10
CaSt/P20	106.6±1.25	99.0±1.73	104.0±1.98	97.5±2.11	67.6±1.10	N/A[a]
CaSt/P20/Compritol10	107.7±0.84	86.3±0.28	89.9±0.21	86.1±1.84	65.8±0.14	N/A[a]
CaSt/P20/Precirol10	106.9±1.91	78.9±0.01	79.6±0.84	78.1±1.27	62.0±0.28	N/A[a]
CaSt/CodPh20	91.0±1.96	80.5±2.17	95.0±1.76	77.3±2.22	75.5±2.25	32.9±2.56
CaSt/CodPh20/Compritol10	98.1±0.45	82.0±2.30	92.2±2.55	80.6±1.79	67.4±1.54	30.9±1.08
CaSt/CodPh20/Precirol10	99.9±1.06	82.4±2.04	95.7±1.44	80.1±85.7	65.6±1.57	32.4±0.84

[a] Determination of the contact angles were impossible due to an immediate drop penetration

In summary, it is clear that alcohol affected the media uptake and wetting behavior of all compacted matrix materials, except for pure CaSt and CaSt/codeine phosphate pellet formulation, where only a small impact is seen. The media uptake of pure CaSt and CaSt/codeine phosphate was nearly similar in all tested media and the measured contact angle values decreased only slightly in alcoholic media. The media uptake of pure Compritol® and Precirol® and the pellet formulation compacts increased and the contact angle values markedly decreased with the increasing alcohol content, leading to enhanced wetting of the formulation.

3.5.5 In-vitro drug release of hot-melt extruded pellets

In a previous study, Roblegg et al. reported that melt-extruded CaSt/paracetamol pellets significantly retarded the API release, which was diffusion-controlled [21]. After 8 h, only 11.54% of paracetamol were released. Adding Compritol® and Precirol® significantly

increased the drug release rates: 18.04% (p = 0.04) and 29.55% (p = 0.005) (Fig. 6A) paracetamol, were found in the dissolution media after 8 h. The higher drug release rates were due to decreased contact angles resembling increased wettabilities (Table 3). In general, the better the wettability of the matrix surface, the higher the penetration rate and the faster the drug release [47].

The addition of Compritol® and Precirol® did not alter the release mechanism as all dissolution data obeyed the Higuchi law rather well (R^2 > 0.98, data not shown) indicating diffusion-controlled drug release. Due to the dense matrix system and due to the fact that the pellets did neither swell significantly in 0.1 N HCl and 0.1 N HCl/phosphate buffer (media uptake < 1.0%, Fig. 5) nor did the matrix materials dissolve in the dissolution media [21, 44, 48, 49], initially only paracetamol located at the pellet surface was dissolved. The dissolved paracetamol left behind pores, through which the dissolution media could enter more internal pellet regions, dissolve the drug accessible to the pores and subsequently, the API needs to diffuse through the porous system prior to entering the bulk dissolution medium [50].

The incomplete paracetamol release could be attributed, on the one hand, to the dense CaSt matrix system [21] and, on the other hand, to all the investigated formulations being rather hydrophobic (Table 3).

Fig. 6B-D illustrate the drug release profiles of the dissolution experiments carried out in alcoholic media over a period of 2 h. Clearly, the drug release depended on the alcohol concentration. The drug release rates from the CaSt/paracetamol pellets in dissolution media with 20% ethanol did not significantly differ from the 0% ethanol condition and showed a f_2-value of 71.52 (p = 0.11). Similar release profiles were obtained as the media uptake (Fig. 5) and the contact angles (Table 3) did not vary markedly in 0.1 N HCl and 0.1 N HCl/20% ethanolic media. However, in 40% alcoholic media the amount of paracetamol release increased significantly (p < 0.05; f_2-value 25.05) due to the improved pellet wettability (Table 3). The better wettability favored interactions between the pellet and the dissolution media and consequently, increased the drug release rates. The improved wettability was also reflected by the higher media uptake (Fig. 5). Additionally, the solubility of paracetamol was much higher in 40% alcoholic media compared to 0.1 N HCl (Table 2), which yielded higher drug release rates.

Similar results were observed in the case of CaSt/paracetamol/Precirol® and CaSt/paracetamol/Compritol®. Adding 20% ethanol to dissolution media did not significantly (p = 0.37 and 0.94, respectively) affect the API release from the pellets (f_2 = 79.42 and 95.58, respectively) as the wettability of the pellets was similar in 0.1 N HCl and 0.1 N HCl/20% alcoholic media (Table 3). Again the wettability increased in 40% alcoholic media yielding significantly (p < 0.05) higher release rates. After 2 h, drug release rates of

nearly 65% and 35% were observed for the CaSt/paracetamol/Precirol® and CaSt/paracetamol/Compritol® pellets, respectively. The estimated f_2-values were below 50 (19.86 and 35.98, respectively), indicating dose dumping.

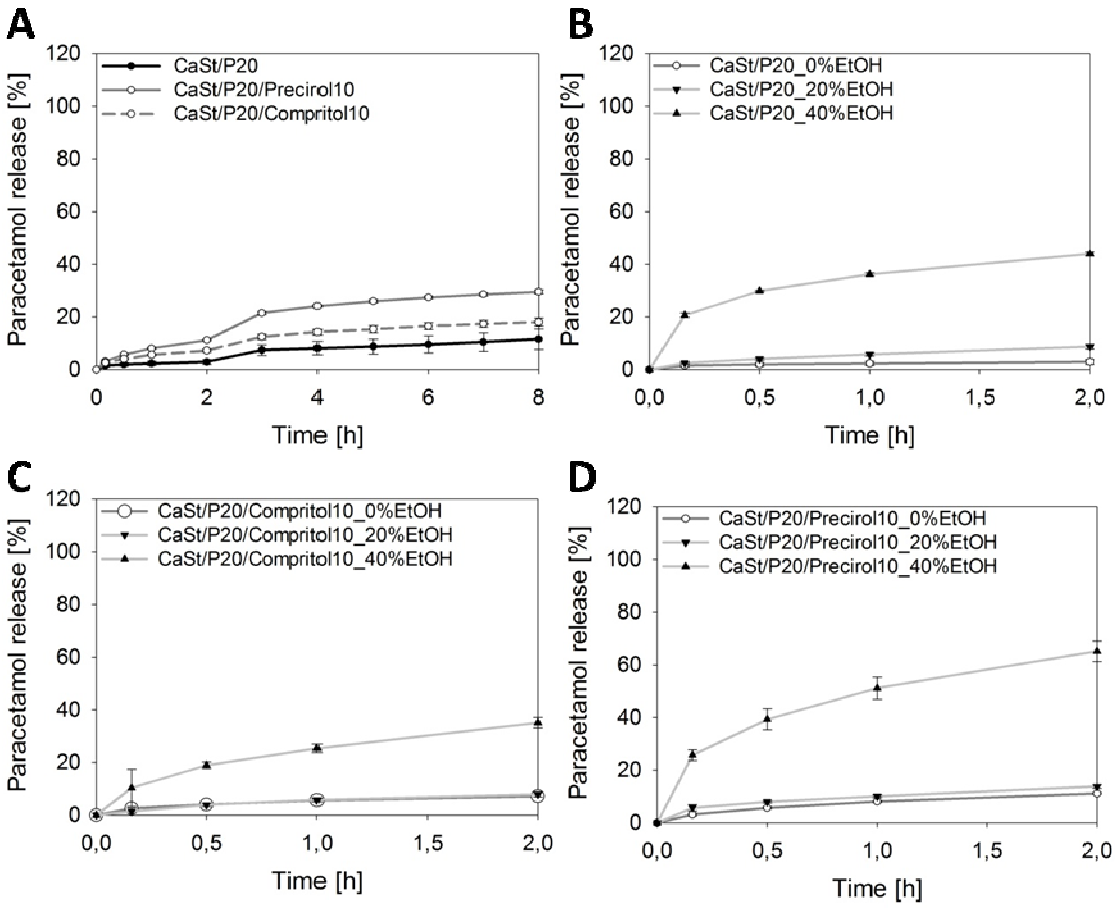


Fig. 6. Paracetamol release profiles from CaSt/P, CaSt/P/Compritol® and CaSt/P/Precirol® hot-melt extruded pellets (1-1.25 mm) in (A) non-alcoholic media over 8 h and (B, C and D, respectively) alcoholic media over 2 h; Mean values ± SD (n = 3). Release profile of pure CaSt/paracetamol pellets (Fig. 1A) is based on previous data of Roblegg et al. [21].

The drug release profiles of the CaSt/codeine phosphate pellets showed that 41.36% of the drug was detected in dissolution media without alcohol after 2 h (Fig. 7A). After 8 h, codeine phosphate was almost entirely released (i.e., 97.70%). Since the solubility of codeine phosphate is very high in the dissolution media (Table 2) the API release was rather fast even for a very dense matrix system. Incorporating Compritol® and Precirol® decreased the drug release rate to 26.83% and 29.10% (Fig. 7A), after 2 h, despite similar contact angle values (Table 3). However, fitting the dissolution data according to the Korsmeyer-Peppas approach (data not shown) revealed that CaSt/codeine phosphate/Precirol® and CaSt/codeine phosphate/Compritol® showed diffusion-controlled drug release, whereas CaSt/codeine phosphate pellets showed diffusion-controlled and case-II-transport (i.e., anomalous transport). Hence, variations in the release profiles were

attributed to different underlying release mechanisms. The drug release rate of the CaSt/codeine phosphate pellets in 20% and 40% alcoholic media increased only slightly (p = 0.44 and 0.64, respectively). The estimated f_2-values (55.85 and 67.59, respectively) confirmed that no dose dumping occurred (Fig. 7B). These results are in accordance with the findings of the media uptake and wetting studies in 20% and 40% alcoholic media, where similar contact angle values (Table 3) were obtained. This was also reflected by similar media uptake values (Fig. 5). The drug release being higher in 20% alcoholic media than in 40% one could be attributed to the lower solubility of codeine phosphate in 40% ethanol (Table 2). Although the codeine phosphate solubility was highest in non-alcoholic media (Table 2) the amount of drug release was lowest in non-alcoholic media. This might be attributed to different underlying release mechanisms; the release was diffusion-controlled in alcoholic media whereas anomalous transport was prevalent in non-alcoholic media (data not shown).

The dissolution studies of the CaSt/codeine phosphate/Precirol® and CaSt/codeine phosphate/Compritol® pellets carried out in alcoholic media demonstrated that the API liberation increased with the increasing alcohol concentration (Fig. 7C and 7D) due to improved wettabilities (Table 3) and consequently, increased media uptake values (Fig. 5). The influence of 20% and 40% alcoholic media on the drug release profile was the highest (p = 0.39 and 0.02) for the pellets containing Precirol®, and the calculated f_2-values were below 50 (47.13 and 31.87). Although the Compritol® formulation showed robustness in 20% alcoholic media (f_2 = 56.44), adding 40% ethanol to acidic media affected the drug release rate (f_2 = 43.59) and resulted in non-robust pellets compared to CaSt/codeine phosphate pellets.

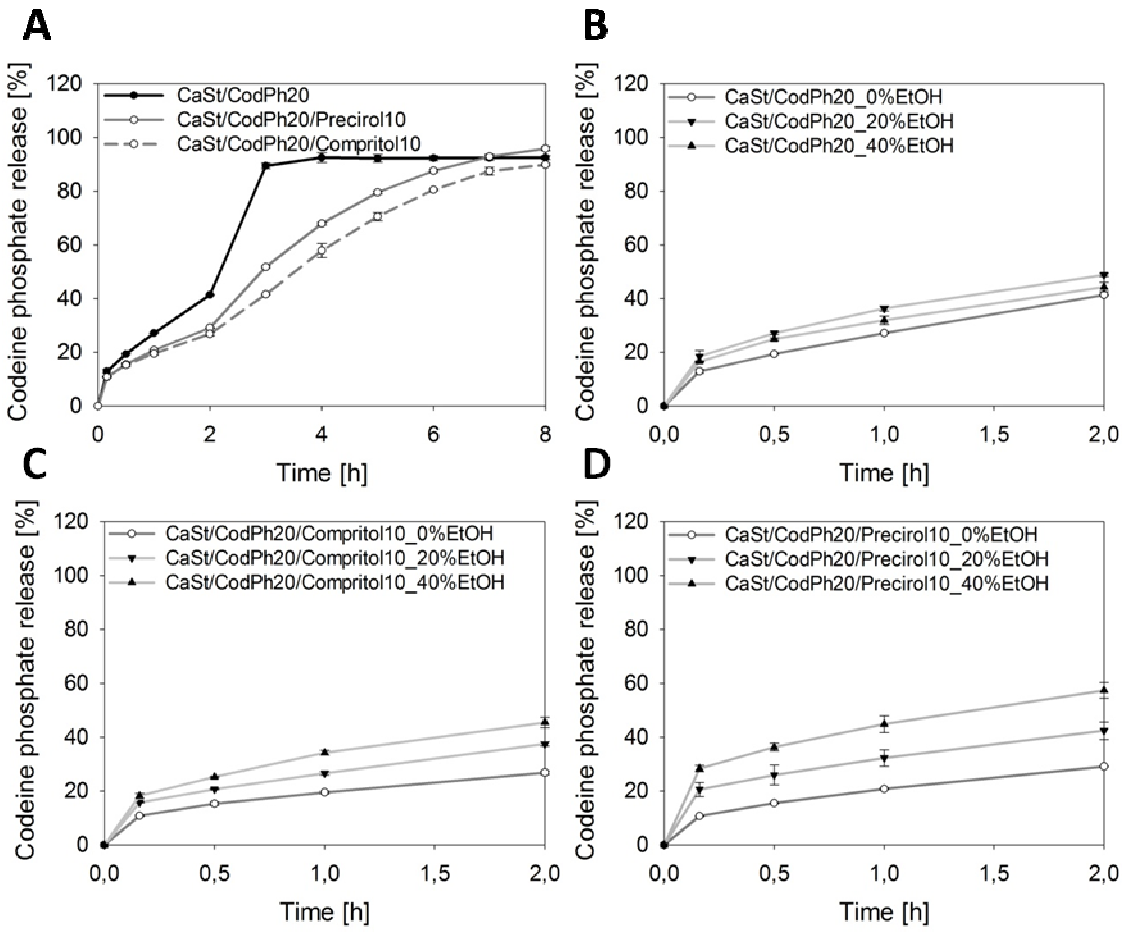


Fig. 7. Codeine phosphate release profiles from CaSt/CodPh, CaSt/CodPh/Compritol® and CaSt/CodPh/Precirol® hot-melt extruded pellets (1-1.25 mm) in (A) non-alcoholic media over 8 h and (B, C and D, respectively) alcoholic media over 2 h. Mean values ± SD (n = 3).

Although the matrix materials CaSt, Compritol® and Precirol® are reported to be insoluble in ethanol and water [19, 48, 49], and thus, expected to withstand ethanol dose dumping, the results showed that only CaSt/codeine phosphate pellets without solid lipids maintained their controlled-release mechanism, even at high ethanol concentrations. Rosiaux et al. investigated the drug release from theophylline/Compritol® and niacin/Compritol® matrix tablets in 0.1 N HCl and in 0.1 N HCl/40% alcoholic media [51]. The authors reported that the change in drug solubility in hydroalcoholic media will likely affect the release kinetics of the Compritol® matrix tablets. The results showed that the drug release rate from the theophylline/Compritol® matrix tablets in 40% alcoholic media increased significantly. The undesired rapid drug release was due to the higher solubility of theophylline in 40% ethanol compared to acidic media. In contrast, drug release from the niacin/Compritol® matrix tablets exhibited a slower release rate in 40% alcoholic media, which could be attributed to the twofold less solubility of the drug in alcoholic media compared to 0.1 N HCl [51]. These observations correlate well with the results of the dissolution studies from the CaSt/paracetamol pellet formulations. Here, the drug

release was markedly faster in 40% ethanolic media and dose dumping occurred. This could be assigned to the increased solubility of paracetamol in alcoholic media. Unexpectedly, the addition of alcohol to the dissolution media affected the drug release of the CaSt/codeine phosphate pellets with solid lipids significantly, although codeine phosphate exhibited a lower solubility in alcoholic media compared to acidic media. This clearly shows, that beside the solubility of the drug also possible interactions between the matrix system and ethanol (mixtures) has to be considered in the rational development of ethanol resistant formulations.

3.5.6 Pellet morphology

To determine the morphology of the hot-melt extruded pellets before and after the *in vitro* drug dissolution in the non-alcoholic dissolution media (8 h) and in alcoholic media (2 h), SEM images were taken. CaSt/paracetamol pellets showed a smooth surface (Fig. 8A). After the *in vitro* dissolution studies in 0.1 N HCl/phosphate buffer few pores on the pellet surface were visible due to paracetamol's dissolution in the outer layer (Fig. 8B), which is in accordance with previous studies [21]. Similarly, after dissolution in 20% alcoholic media the surface of the CaSt/paracetamol pellets exhibited a rather smooth and dense surface (Fig. 8C). In contrast, after exposure to 40% alcoholic media the surface is rough and covered by slit pores (Fig. 8D). Prior to the drug release studies, CaSt/paracetamol pellet formulations containing solid lipids had a non-porous surface (Fig. 8A1 and A2). After 8 h of dissolution in non-alcoholic media, the Compritol® pellets had a lamellar structure and a porous surface (Fig. 8B1). The Precirol® pellets had a ruptured structure with slit pores and a porous lamellar surface (Fig. 8B2). Adding 20% alcohol to dissolution media resulted in pellets with a lamellar/plate-like structure. Compared to dissolution in non-alcholic media, the pellets had an increasingly porous surface (Fig. 8C1 and C2). After dissolution in 40% alcoholic media, the lamellar and highly porous structure of the Compritol® and Precirol® pellet surface seemed to be more defined as lamellar plates increased in size (Fig. 8D1 and D2).

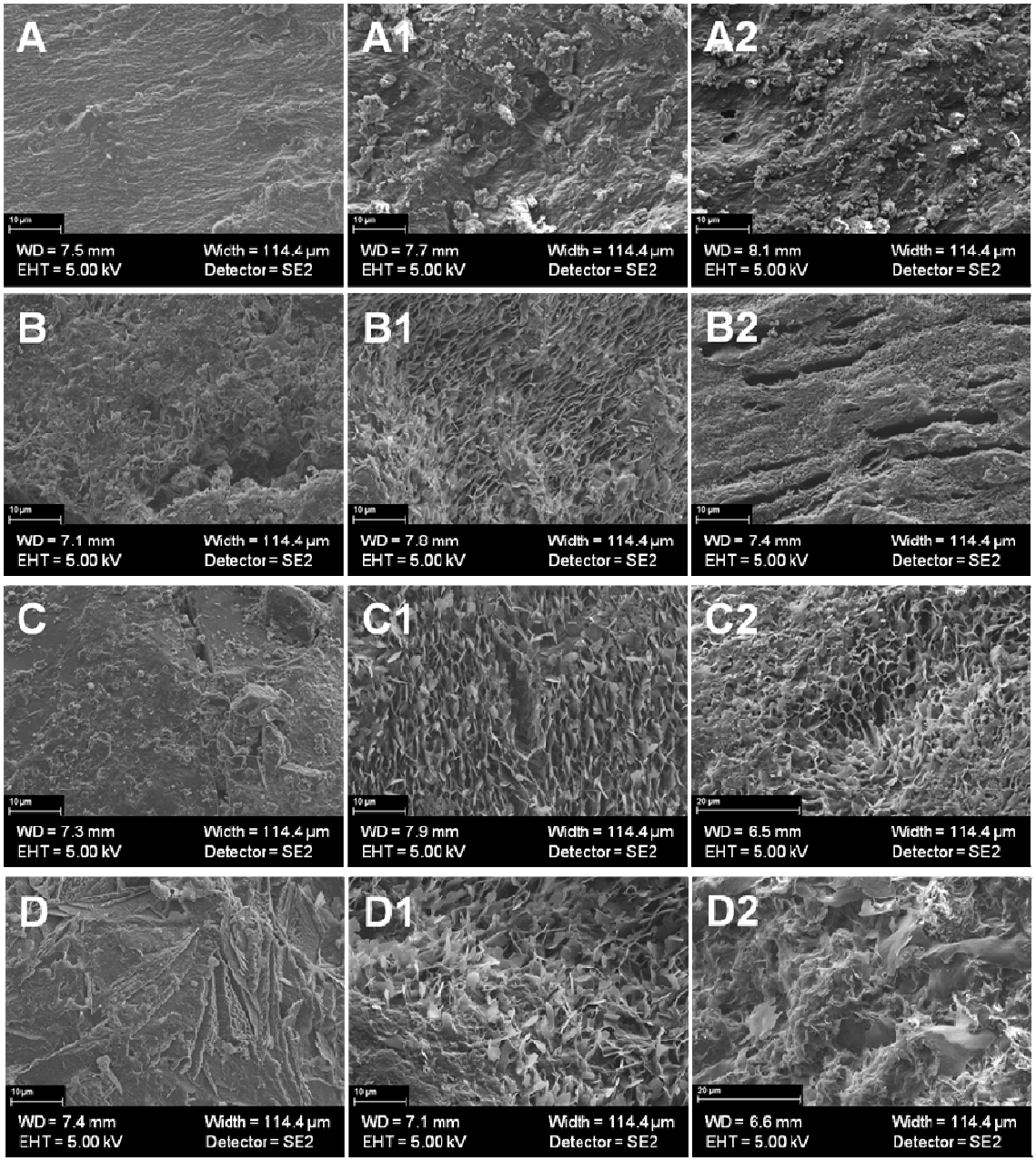


Figure 8: SEM images of: detailed internal structure of (A) a CaSt/P pellet, (A1) a CaSt/P/Compritol® pellet and (A2) a CaSt/P/Precirol® pellet before dissolution; detailed internal structure of (B) a CaSt/P pellet, (B1) a CaSt/P/Compritol® pellet and (B2) a CaSt/P/Precirol® pellet after 8 h of drug release in non-alcoholic media; detailed internal structure of (C) a CaSt/P pellet, (C1) a CaSt/P/Compritol® pellet and (C2) a CaSt/P/Precirol® pellet after 2 h of dissolution in 20% alcoholic media; detailed internal structure of (D) a CaSt/P pellet, (D1) a CaSt/P/Compritol® pellet and (D2) a CaSt/P/Precirol® pellet after 2 h of dissolution in 40% alcoholic media.

The SEM pictures of the CaSt/codeine phosphate pellets with and without solid lipids displayed dense pellet surfaces (Fig. 9A, A1 and A2). After drug release in non-alcoholic media, pores were found at the surface, indicating that the drug dissolved in the outer layer (Fig. 9B, B1 and B2). In the case of CaSt/codeine phosphate pellets, adding 20% ethanol to dissolution media did not markedly affect the pellet surface and a rather smooth surface was detected (Fig. 9C). In contrast, the surface of the CaSt/codeine phosphate

pellets containing Compritol® and Precirol® obviously changed after dissolution in alcoholic media. In 20% alcoholic media a ruptured structure with deep cracks was observed (Fig. 9C1 and C2). With the addition of 40% alcohol to dissolution media the surface of the CaSt/codeine phosphate pellets displayed a close-meshed lamellar structure (Fig. 9D). In the case of Cast/codeine phosphate pellets containing Compritol® a lamellar and porous surface was found (Fig. 9D1). After dissolution in 40% alcoholic media the surface of the Precirol® pellets is covered by well defined pores (Fig. 9D2).

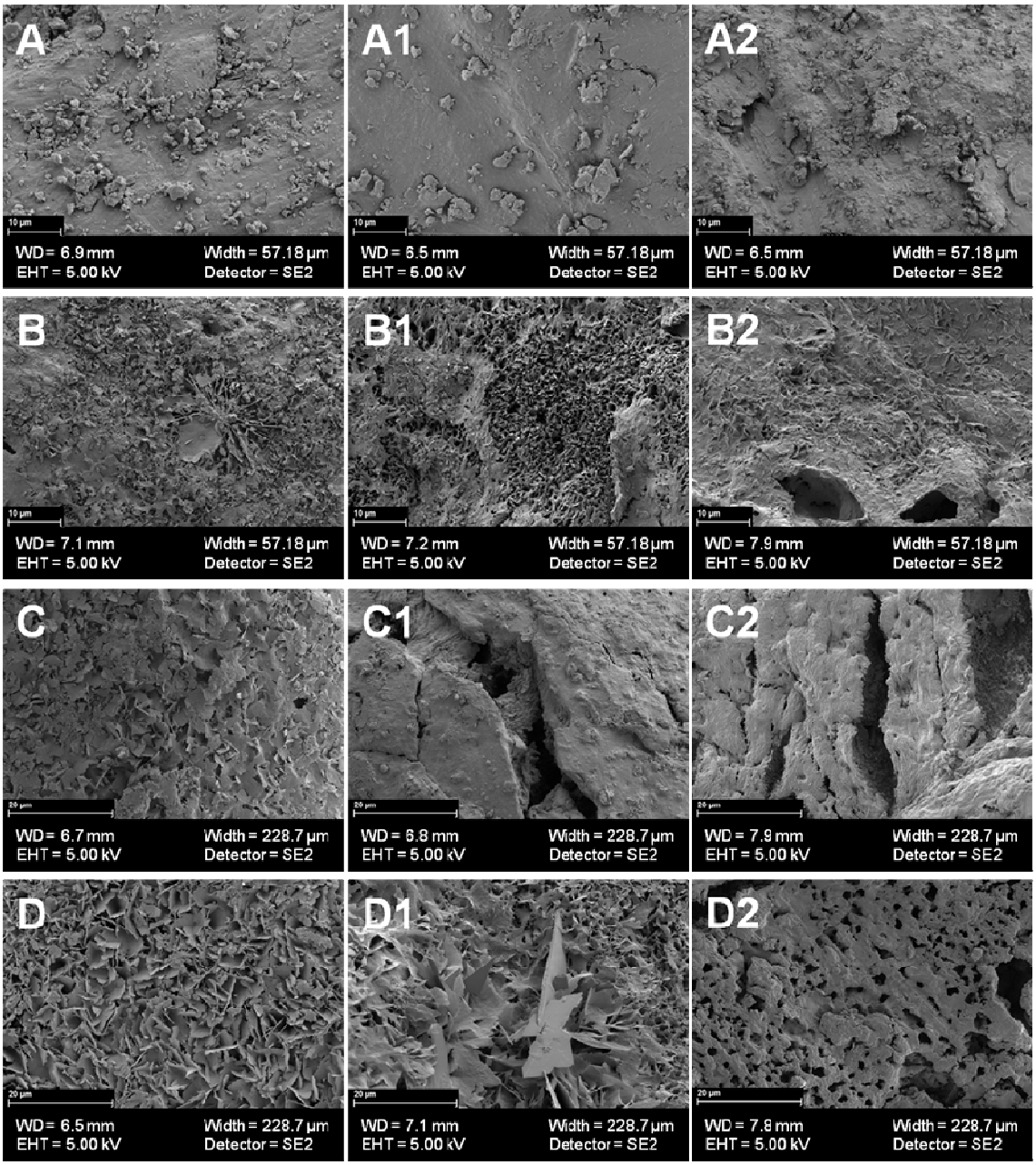


Figure 9: SEM images of: detailed internal structure of (A) a CaSt/CodPh pellet, (A1) a CaSt/CodPh/Compritol® pellet and (A2) a CaSt/CodPh/Precirol® pellet before dissolution; detailed internal structure of (B) a CaSt/CodPh® pellet, (B1) a CaSt/CodPh/Compritol® pellet and (B2) a CaSt/CodPh/Precirol® pellet after 8 h of drug release in non-alcoholic media; detailed internal structure of (C) a CaSt/CodPh pellet, (C1) a CaSt/CodPh/Compritol® pellet and (C2) a

CaSt/CodPh/Precirol® pellet after 2 h of dissolution in 20% alcoholic media; detailed internal structure of (D) a CaSt/CodPh pellet, (D1) a CaSt/CodPh/Compritol® pellet and (D2) a CaSt/CodPh/Precirol® pellet after 2 h of dissolution in 40% alcoholic media.

3.5.7 In-vitro drug release and thermal characterization of pellets after storage

Stability of the drug release profiles of the hot-melt extruded pellets was examined after 12 months of storage at room conditions. Comparing the dissolution profiles of the initial hot-melt extruded pellets and the stored hot-melt extruded pellets indicated that the obtained drug release profiles were nearly identical (data not shown) and no significant changes in the dissolution profiles were observed, compared to the initial pellet formulations ($p > 0.05$).

In addition, DSC measurements were performed of the stored hot-melt extruded pellets to evaluate their solid-state stability. The thermograms showed no changes in the solid-state behavior (data not shown). These results are considered favorable with regard to stability concerns and significant changes in drug release kinetics during long-term storage associated with solid lipids [36, 38].

3.6 Conclusions

Alcohol-induced dose dumping of controlled-release oral dosage forms is a significant challenge in formulation development. Thus, the objective of this study was to investigate the interaction between ethanol and a multiple-unit pellet formulation, using various hydrophobic lipids (i.e., pure CaSt, CaSt with either Compritol® or Precirol®) as matrix carriers for HME. Highly ethanol-soluble paracetamol and codeine phosphate, having a lower solubility in alcoholic media than in acidic media, were used as model drugs. The following results were obtained:

- The *in vitro* drug release profiles showed that pure CaSt/codeine phosphate pellets maintained their drug release behavior and dose dumping did not occur even at high ethanol concentrations.
- In contrast, pure CaSt/paracetamol pellets showed accelerated drug release in 40% alcoholic media which can be attributed to the significantly higher solubility of the drug and better wettability in alcoholic media.
- Pellets comprising Compritol® and Precirol® showed an increased drug release with increasing alcohol levels and dose dumping occurred at the highest ethanol concentrations for all APIs.

To better understand how alcohol interacts with the ethanol/water-insoluble lipids and the pellet formulations, contact angles and media uptake were studied:

- Neither the wetting nor the media uptake of pure CaSt was changed by alcoholic media, making CaSt a suitable matrix material to minimize the risk of alcohol-

induced dose dumping. However, to obtain a sustained-release profile, appropriate release modifiers need to be added. The release modifier should slow down (for codeine phosphate formulations) or increase (for paracetamol formulations) the drug release rate, while withstanding the impact of ethanol.

- The addition of alcohol to acidic media increased the media uptake and enhanced the wetting of pure Compritol® and Precirol®, and all pellet formulations comprising Compritol® or Precirol®.

Therefore, it is critical that apart from the physico-chemical properties (e.g., API solubility), the complex effects of ethanol on the media uptake and wetting properties of matrix substances are considered, even if they are reported to be insoluble in ethanol/water.

3.7 Conflict of interest

The authors report no conflicts of interest.

3.8 Acknowledgements

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4 Development of an abuse and alcohol-resistant formulation based on hot-melt extrusion and film coating

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4.1 Abstract

This study focused on the development of flexible (i.e., deformable) multiple-unit pellets that feature i) a prolonged drug release, ii) drug abuse deterrence and iii) a minimal risk of alcohol-induced dose dumping (ADD). Deformable pellets were prepared via an advanced continuous one-step hot-melt extrusion (HME) technique, with the drug (i.e., antipyrine and codeine phosphate) fed as an aqueous solution into the molten matrix material (i.e., cornstarch, gum arabic and xanthan). Formulations that had suitable mechanical characteristics (i.e., high compression strength) were coated with a flexible Aquacoat® ARC film to ensure prolonged release and to avoid ADD. The pellets were characterized in terms of their mechanical properties and in-vitro drug release behavior in alcoholic media. All formulations were abuse deterrent: they had a high compression strength and grinding the pellets into powder was impossible. Since the pellets comprising gum arabic and xanthan as a matrix did not remain intact during dissolution testing, they had a very fast drug release rate. Cornstarch-based pellets that swelled but remained intact in the dissolution media had a slower drug release. Coated cornstarch-based pellets had a prolonged release over eight hours and resistance to dose dumping in 20% and 40% ethanol.

Our results indicate that cornstarch-based pellets manufactured via the advanced HME process followed by coating are a promising formulation that makes tampering difficult due to a high compression strength combined with robustness in alcoholic media.

4.2 Introduction

Drug abuse of oral opioids and non-opioid drugs with a narrow therapeutic window, such as benzodiazepines (central nervous system depressants) and amphetamines (stimulants), has received increased public attention in recent years [1]. Drug abuse can be defined as *"the use of medication for its mind-altering effects, whether or not one also has pain or has been prescribed the medication"* [2]. Due to their high drug loading and euphoric effects, controlled-release opioid dosage forms that are first-choice formulations for (chronic) pain treatment [3-5] are especially popular among drug abusers [1]. Drugs are either chewed or crushed to subsequently snort or dissolve them in common solvents for intravenous injections in order to achieve euphoric and mind-altering effects [1, 6, 7]. To counteract these practices, the Food and Drug Administration (FDA) suggested several approaches described in the draft guidance document covering the evaluation and labeling of abuse deterrent opioids [7, 8], which include i) physical and chemical barriers, ii) agonist/antagonist combinations, iii) aversion, iv) certain delivery systems, v) prodrugs and vi) combinations thereof (Fig. 1). Physical barriers prevent destruction of the dosage form (e.g., due to increased hardness), whereas chemical barriers impede extraction using common solvents

[9]. Incorporating an antagonist reduces the euphoria if the drug product is manipulated (e.g., ground). If the drug product is swallowed (i.e., used as prescribed), the antagonist is not clinically active. Aversion is created when upon manipulation the drug product releases substances that cause unpleasant temporary side effects (e.g., warmth, flushing, itching, sweating). Furthermore, it is recommended to use unattractive delivery systems (e.g., subcutaneous implants). Prodrugs that hinder opioid activity and the associated euphoric effects until they are transformed in the gastrointestinal tract can prevent abuse via the intravenous and nasal routes [9].

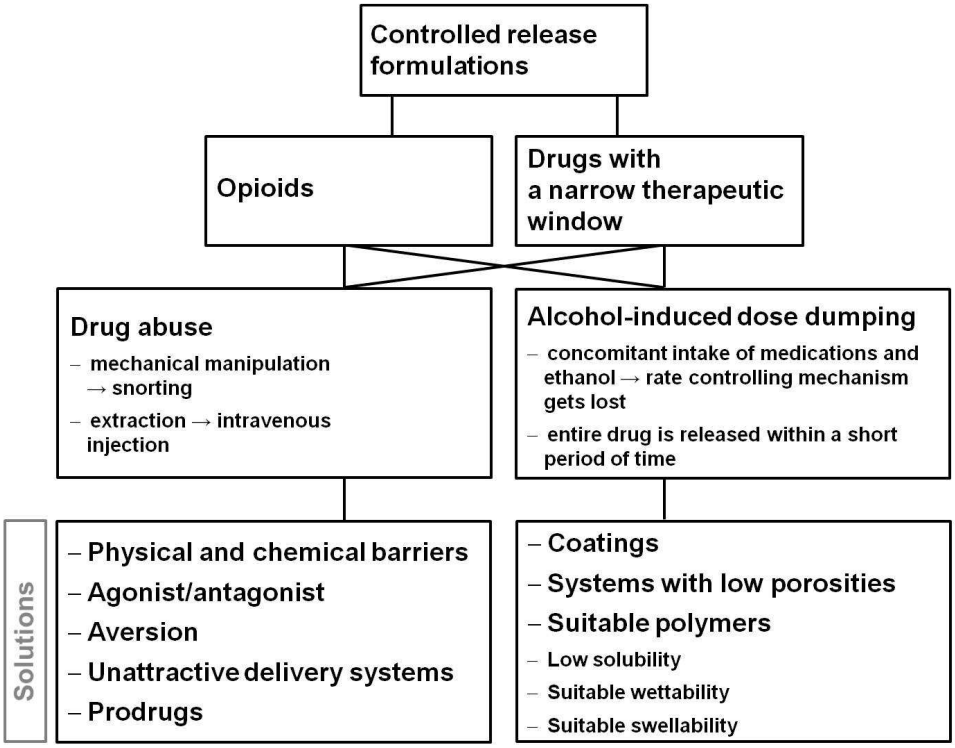

Figure 1: Systematic overview of drug abuse and alcohol-induced dose dumping.

Although these are promising tools of ensuring safe and abuse-deterrent drugs, only a few proven products are available on the market and studies in this field are scarce [10-12]. Hysingla™ ER tablets (Purdue Pharma) containing hydrocodone bitartrate provide abuse resistance via physical and chemical barriers [13]. They are formulated using RESISTEC™, which obstructs tablet crushing by applying a unique combination of polymer and processing to ensure a high tablet hardness (i.e., physical barrier). Moreover, when dissolved in aqueous environment, the tablet immediately forms a viscous hydrogel (i.e., chemical barrier) [13], making injecting it impossible. Another abuse-deterrent drug product is Zohydro® ER capsules comprising hydrocodone bitartrate and manufactured via BeadTek™ [14], a capsule formulation technology that incorporates well-known excipients and is designed to deter abuse. If the capsule is crushed and dissolved in liquids, a viscous gel is immediately formed [14].

Despite existing and hypothetical approaches to make affective abuse-deterrent formulations, tampering with drugs and subsequent drug abuse can never be eliminated entirely. Rather, formulators should focus on reducing the abuse potential by making tampering difficult and time consuming. Such formulations are less attractive to drug abusers, who are reported to spend no more than 10 minutes on tampering [15, 16].

Another challenge in the development of safe drug products is minimizing the risk of alcohol-induced dose dumping (ADD) (Fig. 1). Concomitant intake of alcoholic beverages and controlled-release oral dosage forms may alter the release-rate-controlling mechanism of the formulation, resulting in an immediate and uncontrolled drug release [17] (e.g., an opioid overdose, which may lead to respiratory depression followed by hypoxia and even death [18]). Especially those patients that suffer from (chronic) pain tend to consume alcohol to cope with the pain-related stress and reduce the pain perception [17].

Overall, there is a growing demand for new flexible technologies for producing safe drug products that prevent both (1) drug abuse and (2) ADD. Recently, Gruenenthal GmbH patented a tamper-resistant oral dosage form comprising a drug with a psychotropic action and an ethylene-vinyl acetate (EVA) polymer [19]. Manufactured via thermoforming technologies, such as hot-melt extrusion (HME), it is resistant to solvent extraction, grinding and dose dumping in aqueous ethanol [19]. However, the majority of the existing studies address either abuse-deterrence or ADD [20] but not both topics at the same time.

In this study we focus on the development of multiple unit dosage forms (i.e., pellets) that show a prolonged release and are designed to resist ADD and (due to their high compression strength) tampering with the most common household devices. For pellet preparation, an innovative manufacturing processes based on HME technique was applied. Thereby, the (visco)elastic properties of the matrix materials (i.e., cornstarch, gum arabic and xanthan) can be achieved by introducing water directly into the matrix melt. Subsequent coating of the pellets ensured a prolonged release of the model drugs (i.e., antipyrine and codeine phosphate) and ADD resistance.

4.3 Materials and methods

4.3.1 Materials

Antipyrine (Fluka, Sigma Aldrich, St. Louis, USA) and codeine phosphate hemihydrate (donated by G.L. Pharma GmbH, Lannach, Austria) were used as the model drugs. Cornstarch (Carl Roth GmbH, Karlsruhe, Germany), gum arabic (ACM Herba Chemosan AG, Vienna, Austria) and xanthan (Carl Roth GmbH, Karlsruhe, Germany) were the matrix carrier systems. Purified water was used as plasticizer.

The *in-vitro* drug release studies were carried out with 0.1 N hydrochloric acid (HCl) and a trisodiumphosphate-dodecahydrate buffer purchased from Merck, Darmstadt, Germany. For

the dose dumping studies, absolute ethanol (EP) was purchased from VWR International, Darmstadt, Germany. The mobile phase for the reversed phase (RP) high performance liquid chromatography (HPLC) consisted of MilliQ water, acetonitrile (VWR International, Darmstadt, Germany), phosphoric acid (85%, VWR international, Darmstadt, Germany) and methanol (LiChrosolv® Reag., EP, VWR International, Darmstadt, Germany). Aquacoat® ARC (Alcohol Resistant Coating, consisting of ethanol soluble Aquacoat® ECD 30 and ethanol-insoluble guar gum) from FMC BioPolymer was used for pellet coating. Talc (Carl Roth GmbH, Karlsruhe, Germany) served as anti-tacking agent and trieethyl citrate (TEC) (donated by G.L. Pharma GmbH, Lannach, Austria) was applied as a plasticizer for the coating dispersion.

4.3.2 Drug solubility determination

The drug solubility was determined in (a) water, (b) 0.1 N HCl, (c) 0.1 N HCl with ethanol concentrations of 20% and 40% (v/v) and (d) in pure ethanol (96 v%). Saturated solutions were prepared and stored in an incubator shaker at 37 ± 0.5 °C for 48 h. Samples of 1 ml were taken, filtered through a cellulose acetate filter (pore size 0.2 µm) and, if necessary, diluted. The concentration of the dissolved drug was quantified via UV/VIS spectrometry at wavelengths of 244 nm (antipyrine) and 284 nm (codeine phosphate). The solubility studies were performed in triplicate.

4.3.3 HME process

Extrusion was based on the NANEX process [21], which allows side feeding of aqueous drug suspensions and solutions directly into a molten polymer that is miscible with water [22]. The matrix material (i.e., cornstarch, xanthan and gum arabic) in the powder form was placed into the co-rotating twin screw extruder (ZSK 18, Coperion GmbH, Stuttgart, Germany). The model drugs (i.e., codeine phosphate hemihydrates and antipyrine) were dissolved in purified water (i.e., plasticizer) at concentrations of 0.5 g/ml and 1.0 g/ml for codeine phosphate and 1.0 g/ml for antipyrine. The solutions were fed from the side into the extruder containing the matrix melt. For codeine phosphate, two concentrations were used to provide different drug loadings while keeping the water content constant. Details regarding the process parameters are summarized in Table 1.

The matrix material was fed into the extruder via a gravimetric dosing device (K-Tron, Niederlenz, Switzerland) at a feeding rate of 0.5 kg/h. The screws had a length-to-diameter ratio (L/D) of 40, and the barrel consisted of 10 individually-controllable heating sections. The screw speed was 200 rpm. The drug solutions were fed via a calibrated peristaltic pump (Ismatec IP 65, IDEX Health & Science GmbH, Wertheim, Germany) into barrel 3 of the extruder. The feeding rate of the aqueous solution was adjusted to 100 g/h to yield a final drug loading of 20% for antipyrine and of 10% and 20% for codeine phosphate. The material

was extruded through a die plate with die holes of 1.0 mm in diameter. The cornstarch/antipyrine formulation was also extruded through a die plate with die holes of 1.5 mm diameter. The homogeneous strands were cut directly at the die face using a hot die-face pelletizer [23] (Automatik Plastics Machinery GmbH, Großostheim, Germany) with two rotating knives developed in-house. The rotational speed of the knives was adjusted manually to obtain pellets in the desired size range (i.e., 1.25-1.40 mm), which were immediately air-cooled [24]. An overview of the formulations and the processing parameters is provided in Table I.

Loss on drying (LOD) of the pellets was measured for 24 h at 60 °C in an oven.

Pellets were sieved according to Pharm. Eu. 7.0/2.09.38.00 using analytical DIN sieves (Retzsch GmbH, Haan, Germany). The pellet fractions between 1.25-1.4 mm were applied for further characterization studies.

Table 1
Formulations and process parameters applied during HME.

Formulation	Matrix material	Active ingredient (wt.%)	Process parameters											
			Torque (%)	Barrel zone temperatures (°C)										Knife rotational speed (rpm)
				1	2	3	4	5	6	7	8	9	10	
1	Cornstarch	without (20% H_2O)	18	65	85	85	85	85	85	85	85	85	85	1300
2	Cornstarch	Antipyrine 20% (aqueous solution)	7	65	85	85	85	85	85	85	85	85	85	1500
3	Cornstarch	Codeine phosphate 10% (aqueous solution)	22	65	85	85	85	85	85	88	88	88	87	1500
4*	Cornstarch	Codeine phosphate 20% (aqueous solution)	-	-	-	-	-	-	-	-	-	-	-	-
5	Xanthan	without (20% H_2O)	16	70	85	85	85	85	85	85	85	85	85	1600
6	Xanthan	Antipyrine 20% (aqueous solution)	2	50	50	63	85	85	85	85	85	85	83	2000
7	Gum arabic	without (20% H_2O)	25	60	65	75	75	75	75	75	75	74	74	1600
8	Gum arabic	Antipyrine 20% (aqueous solution)	11	60	60	65	65	65	65	65	65	60	65	1600

(*) Adding 20% codeine phosphate resulted in highly viscous strands that were not suitable for hot die-face pelletizing.

4.3.4 Coating process

Selected pellet formulations were coated with Aquacoat® ARC, as proposed by Rosiaux et al. [25-27]. The coating dispersion was prepared by mixing Aquacoat® ECD 30 and guar gum at a ratio of 93:7. Prior to mixing, Aquacoat® ECD 30 was plasticized with 25% TEC (w/w; based on the total polymer content) at room temperature for 30 min. Guar gum was dissolved in purified water under stirring at 65 °C for 2 h. After cooling down to room temperature, the two solutions were mixed and stirred for 30 min. To reduce the stickiness of the coating formulation, talc (50% w/w; based on the total polymer content) was added as an anti-tacking agent.

The pellets were coated in a fluidized bed coater (Mycrolab H00472, Oystar Hüttlin, Schopfheim, Germany) equipped with a bottom sprayer. The coating conditions were: inlet-air volume: 25 m^3/h; inlet-air temperature: 38 °C; spray rate: 2 g/min; spray air pressure: 1.2 bar; microclimate pressure: 0.6 bar; nozzle diameter: 1.2 mm; and coating level: 20%. After coating, the pellets were dried in the fluidized bed coater for 15 min.

4.3.5 Characterization of drug loaded pellets

Differential scanning calorimetry analysis

The solid state properties of the hot-melt extruded pellets were characterized using a differential scanning calorimeter (DSC 204F1 Phoenix®, Netzsch GmbH, Selb, Germany). For comparison reasons we evaluated the thermal behavior of the model drugs, the matrix materials and mixtures of the matrix materials with 20% purified water that acted as plasticizer during extrusion. Samples of about 5 mg were placed into hermetically sealed aluminum crucibles and scanned with pure nitrogen as the analytical gas between 25 and 200 °C at a heating rate of 50 K/min and at a flow rate of 20 ml/min. After cooling to 25 °C at 10 K/min, a second heating run was performed. An empty aluminum crucible was used as a reference. The DSC data analysis was conducted with Proteus Thermal Analysis software (Netzsch GmbH, Selb, Germany). Each sample was evaluated in triplicate.

Pellet compression strength

The pellet compression strength was determined with a conventional tablet hardness tester (PTB 111 E, Pharma Test, Hainburg, Germany) by recording the hardness values of 10 randomly picked pellets from each batch.

Additionally, the compression force of the pellets was studied using a rheometer (Physica MCR 301, Anton Paar GmbH, Graz, Austria) equipped with a parallel plate measuring system in the non-rotational mode. A single pellet was manually placed in the center of the lower plate. The upper plate was moved down at a constant velocity of 0.5 µm/s. Based on the force displacement diagrams, the maximum force of plastic deformation upon pellet

fraction (F) was determined. The crushing strength (σ) was calculated from F and the diameter of each pellet (d) according to Shipway et al. [28]:

$$\sigma = \frac{1.6\,F}{\pi d^2} \quad (1)$$

From each batch, 50 pellets were tested with the rheometer.

In-vitro dissolution studies

All *in-vitro* dissolutions tests were carried out via the USP 28 rotating basket method <711> in an USP apparatus I (Pharma Test, Hainburg, Germany). The rotational speed was 100 rpm, and the temperature was 37 ± 0.5 °C. The dissolution medium consisted of 750 ml 0.1 N HCl. After 2 h, 250 ml trisodiumphosphate-dodecahydrate buffer were added to increase the pH from 1.2 to 6.8. For the ADD studies, we used 900 mL HCl (0.1 N) with ethanol concentrations of 20% (equivalent to mixed drinks) and 40% (equivalent to hard liquor) (v/v) and tested them for 2 h. The pellet sample weight was adjusted to 1 g to ensure perfect sink conditions in all dissolution media without exceeding the maximum single dose. Samples of 1 ml were withdrawn at predetermined time intervals. Each batch was investigated in triplicate.

To compare the drug release profiles in alcoholic and non-alcoholic media, the f_2 similarity factor was used [29]:

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-\frac{1}{2}} \times 100\right\} \quad (2)$$

where n is the number of dissolution time points considered and R_t and T_t are the percentage of drug dissolved of the reference and test formulations at time point t. In general, an f_2 value in the range of 50-100 indicates that the dissolution profiles are similar.

Drug quantification

Drug quantification of the dissolution samples was performed via reversed phase (RP) high performance liquid chromatography (HPLC) for antipyrine and via UV/VIS spectroscopy for codeine phosphate.

The HPLC analysis was carried out using a Merck-Hitachi system (Tokio, Japan) at 35 °C. As the stationary phase, a C18 MOS-Hypersil column (250 x 4 mm x 5 µm; 120 Å pore size; VDS optilab, Berlin, Germany) was applied. The mobile phase consisted of MilliQ water, which was adjusted to pH 3.0 with phosphoric acid and a 50:50 (V/V) mixture of acetonitrile and methanol (isocratic mode 58:42 (V/V)). The injection volume was 20 µl and the flow rate was 1 ml/min. The drug was analyzed with a model series L-4250 UV-VIS detector at a wavelength 230 nm. For quantification, a single-point calibration with 100% standard solution of the active pharmaceutical ingredient (API) was used.

The codeine phosphate quantification was performed with a UV spectrophotometer (Spectronic Genesys 5, Spectronic Instruments Inc., Rochester, USA) at a wavelength of 248 nm. The samples were diluted, if necessary, and quantified via an external standard (i.e., calibration curve).

4.4 Results and discussion

4.4.1 Drug solubility determination

Since a drug's solubility in the dissolution medium strongly affects the dissolution rate, the solubility of antipyrine and codeine phosphate was determined in water, acidic media with and without ethanol (20%, 40%), and in 96% ethanol (Fig. 2). The results indicate that antipyrine is highly soluble in all tested media. The ethanol content did not affect the solubility until its concentration reached 40%. In 96% ethanol, the solubility decreased significantly due to the different polarity/dielectric constants of the solute and the solvent. However, antipyrin was still highly soluble in 96% ethanol [30]. In contrast, the solubility of codeine phosphate markedly decreased with the increasing ethanol concentrations [31], and was very low in 96% ethanol. It can be concluded that the addition of ethanol lowered the dielectric constant in relation to pure water, and hence, the solubility decreased [17, 32, 33].

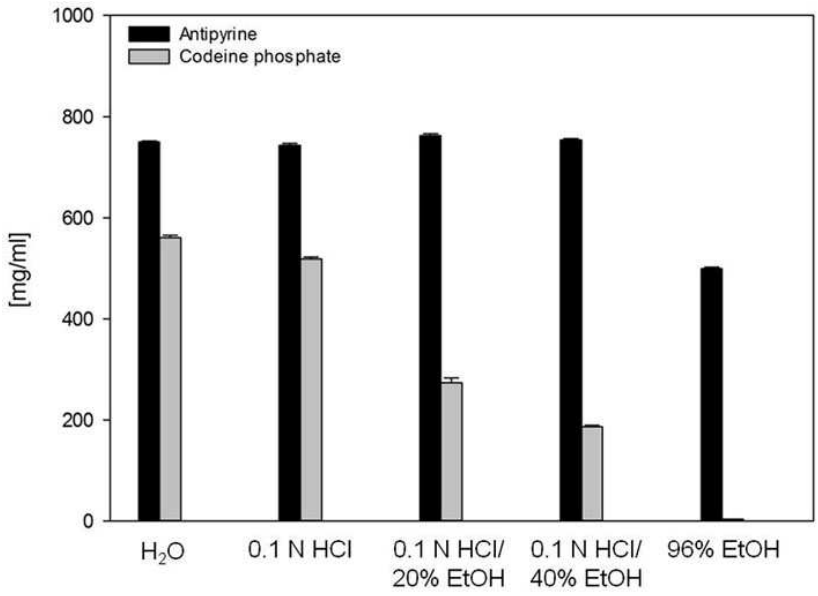

Figure 2: Solubility of model drugs in various media at 37 ± 0.5 °C. Mean values ± SD (n = 3). As the standard deviation was very low, it is not clearly visible from the graph. Solubility of codeine phosphate is based on the data of Jedinger et al. [27].

4.4.2 Preparation of pellets via HME

According to the literature, extrusion of pure native starch is not possible and adding water is required to achieve gelatinization and to transform starch into a homogenous matrix [34]. Starch is composed of α-D-glucosyl units. It comprises amorphous regions as well as crystalline domains in the short chain clusters of amylopectine. During extrusion the starch

granules are destroyed by mechanical disruption of molecular bonds due to the intense shear forces within the extruder and loss of crystallinity is caused (i.e., gelatinization of starch) [35].

When cornstarch was extruded in our experiments with water at process temperatures between 65 and 85 °C, glassy-like yellowish spherical pellets with a smooth, homogeneous surface structure were obtained. The pellets were very flexible and elastic, exhibiting mechanical properties suitable for abuse-deterrent dosage forms.

To the best of our knowledge, xanthan and gum arabic have not been used as matrix materials for HME to date. Xanthan is assigned to the polysaccharides from the chemical point of view and comprises D-glucose, D-mannose, and D-glucuronic acid. Gum arabic is a complex mixture of glycoproteins and polysaccharides. Both, xanthan and gum arabic are crystalline. During extrusion it is assumed that crystallite softening occurs.

When gum arabic and xanthan were extruded without any plasticizers (i.e., water) at process temperatures of 60-85 °C, a non-molten powdery and brittle mass was obtained. At higher process temperatures (i.e., 80-200 °C), the substances failed to melt and became charred. However, when water was added as a plasticizer, smooth pellets with a yellowish coloration were produced via HME. They were slightly sticky since the amount of water added was rather high (~ 20%), which was necessary to obtain suitable strands for further downstream processing (die-face cutting). The gum arabic and xanthan pellets had a cylindrical shape, possibly due to faster solidification (and thus less time for forming a spherical shape), compared to cornstarch [24]. Nevertheless, they were considered to be suitable for providing abuse deterrence due to their deformable character.

The next step was to incorporate drugs at various concentrations. While adding antipyrine to the starch matrix decreased the torque from 18% to 7% (Table 1) due to the plasticizing effect of the drug, incorporating codeine phosphate increased the torque values (i.e., 22%; Table 1). Adding 20% codeine phosphate resulted in highly viscous strands that were not suitable for hot die-face pelletizing. Decreasing the drug loading to 10% yielded strands that could be cut into spherical pellets via die-face pelletizing. Once again, the pellets were very flexible and elastic.

Incorporating antipyrine into the xanthan matrix decreased the extrusion temperatures from 70-85 °C to 50-83 °C due to the plasticizing effect of the drug. This is confirmed by the torque value that decreased from 16 to 2% (Table 1). Adding antipyrine to the gum arabic matrix slightly reduced the required process temperatures (i.e., from 60-75 °C to 60-65 °C). Additionally, the torque decreased from 25 to 11% (Table 1), indicating the plasticizing effect of antipyrine. Similarly to the drug-free pellets, the drug-loaded xanthan and gum arabic pellets were smooth and sticky, with a yellowish coloration. As before, the pellets were not spherical but rather cylindrical in shape. The placebo pellets exhibited approximately 20%

w/w LOD, which decreased by drug addition. Incorporating antipyrine led to approximately 17% w/w LOD for all pellet formulations. The cornstarch/codeine phosphate pellets showed 15% w/w LOD. However, the added total amount of water was kept constant for all formulations. It is assumed, that the lower weight loss during drying of antipyrine and codeine phosphate containing pellets may be due to drug-bound water.

The pellets that were extruded with the 1.0 mm die had a yield of > 50% of the sieve fraction between 1.25 and 1.40 mm.

4.4.3 Characterization of pellets

Thermal characterization

First, we evaluated the thermal behavior of the matrix materials in the presence of water (i.e., a plasticizer during extrusion) via DSC (Fig. 3A-2D). For pure cornstarch and xanthan, a broad endothermic event with an onset at 107.4 °C and 115.0 °C was recorded during the first heating cycle (data not shown) due to water loss [36]. Upon cooling and reheating, no thermal events were observed. The glass transition (Tg) of pure cornstarch, which occurs at around 58 °C [37], was not detected via conventional DSC with comparatively low heating rates [37, 38]. The thermogram of pure gum arabic showed no thermal events in the investigated temperature range (i.e., 20-200 °C). Adding water to the matrix materials resulted in a broad endotherm with an onset between 100 and 120 °C due to water evaporation (Fig. 3A-2D). No thermal events were observed during cooling and the second heating cycle for all matrix materials. Since no degradation occurred under 200 °C, the matrix materials were considered to be stable at the applied extrusion temperatures (i.e., 50-85 °C).

Additionally, DSC was used to investigate the solid state of the model drugs and hot-melt extruded pellets (Fig. 3A-2D). The thermogram of the first heating cycle of antipyrine clearly indicated one sharp endotherm at 113.6 °C (onset 107.6 °C), which corresponds to melting. No thermal events were observed during cooling, suggesting that the drug was in its amorphous state after cooling. Upon reheating, one exothermic event and one endothermic event were recorded. The exothermic signal at 31.8 °C (onset 26.5 °C) was due to recrystallization of the amorphous drug, followed by melting at 113.6 °C (onset 104.7 °C) [39]. Upon heating, codeine phosphate had three endothermic events (Fig. 3D) corresponding to water loss, structural rearrangement and melting. For detailed interpretation, please refer to Jedinger et al. [31].

The DSC scan of the cornstarch/antipyrine pellets indicated one endothermic event at 70.8 °C (onset 63.3 °C) (Fig. 3A). The endotherm was attributed to the gelatinization (melting) of the starch granules, which occurs at around 70 °C with high water contents [40]. For the gum arabic/antipyrine pellets, one endotherm was detected at 71.0 °C (onset 63.7 °C), which corresponds to crystallite melting of gum arabic (Fig. 3B) [41]. During the first heating of

xanthan/antipyrine pellets, a broad endothermic event occurred at 129.4 °C (onset 88.7°C) due to moisture evaporation (Fig. 3C). Since the melting peak of antipyrine did not show in the heating thermograms of starch/antipyrine and gum arabic/antipyrine pellets, it was assumed that the drug molecularly dissolved in the matrix, which agrees with previous studies [24, 42]. For the xanthan/antipyrine pellets, the solid state of antipyrine could not be determined since the melting endotherm of antipyrine appears in the same temperature range as the moisture evaporation does.

The thermogram of the cornstarch/codeine phosphate pellets suggest an endothermic event at 181.2 °C (onset 176.4°C), which corresponds to the structural rearrangement [43] of codeine phosphate (Fig. 3D). The presence of crystalline codeine phosphate indicates that the drug did not molecularly dissolve in the cornstarch matrix. However, the characteristic endotherm of the drug broadened and shifted slightly towards lower temperature.

No thermal events were observed during cooling and the second heating cycle for all pellet formulations (data not shown).

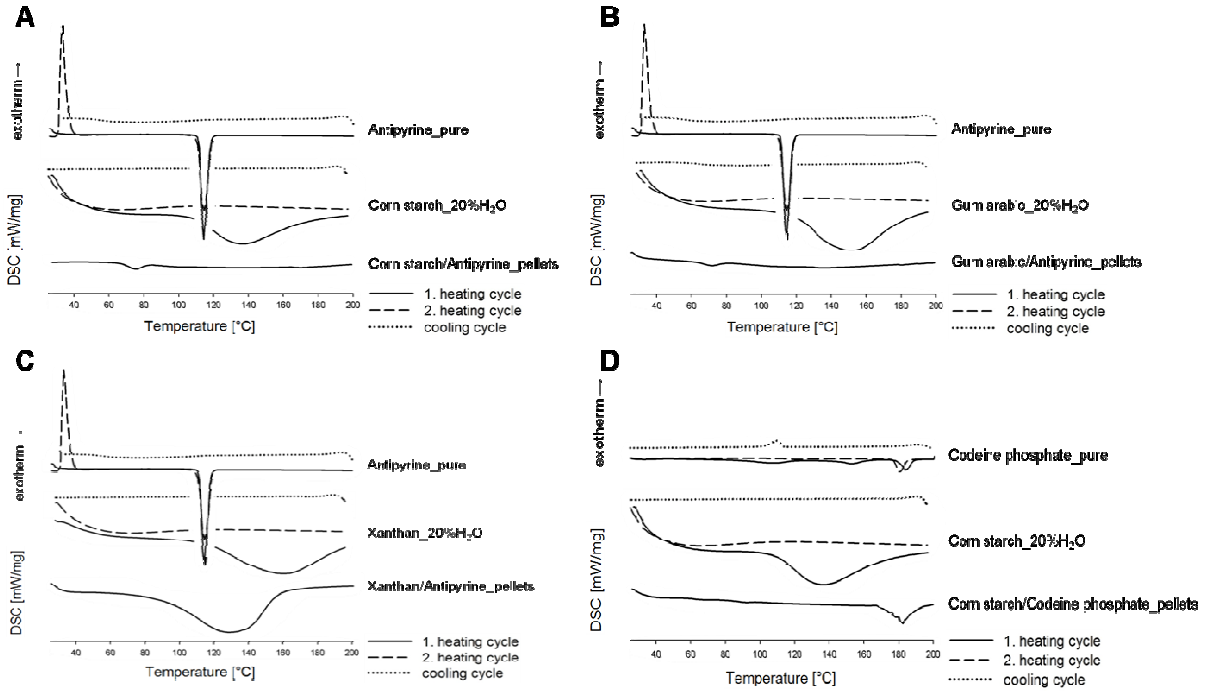

Figure 3: DSC scans of the model drugs (i.e., antipyrine, codeine phosphate), matrix materials (i.e., cornstarch, gum arabic, xanthan) with the addition of 20% purified water (2 heating cycles shown) and hot-melt extruded pellets (one heating cycle shown).

Pellet compression strength and physical manipulation

The compression force of the drug-loaded pellet formulations exceeded the maximum force that can be applied by the rheometer (i.e., 50 N). All tested pellets deformed but, yet did not break, suggesting that the force required for compression was higher than 50 N. Consequently, the compression force could not be determined and the compression strength could not be calculated from Equation 1.

Additionally, the compression force was determined via a conventional tablet hardness tester with a maximum applicable force of 500 N. Again, the pellets deformed, but did not recover (i.e., plastic deformation) implying that the force necessary to crush the pellets exceeds even 500 N. That means that a single pellet can be loaded with a mass of 50 kg without being crushed.

Physical (mechanical) manipulation was tested according to the FDA's draft guidance on abuse-deterrent opioids [8]: the pellet formulations were grinded first with a spoon (i.e., a common household device) and then, more sophisticated, with a mortar and a pestle. Both manipulation methods resulted in large sticky fragments and no fine powders were obtained (Fig. 4). This shows that physical manipulation is impeded for all tested pellet formulations due to their high compression strengths independent upon the formulation composition.

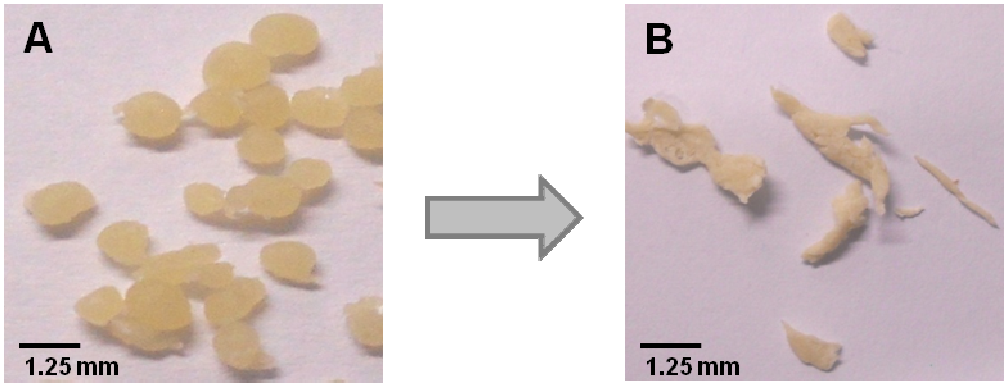

Figure 4: Hot-melt extruded xanthan/antipyrine(20%) pellets (A) before and (B) after grinding with a mortar and a pestle.

In-vitro drug release of hot-melt extruded pellets

Figure 5A illustrates the API release from the antipyrine pellets in non-alcoholic media. Due to the physicochemical properties of both, the pellet matrix and the drug, all pellets had an immediate drug release. High solubility of antipyrine in the dissolution media (i.e., 743.3 mg/ml) led to a fast drug release. Dissolution was fast also because the tested matrix materials (gum arabic, xanthan and cornstarch) did not contain their shape during dissolution testing and did not retard release. Hence, diffusion of dissolved antipyrine through the matrix was not a rate-limiting step. While the gum arabic-based pellets dissolved completely within 30 min due to physical erosion and subsequent degradation [44], the xanthan pellets swelled without dissolving, forming a highly viscous gel due to uncoiling of the structure and the formation of hydrogen bonds with the water molecules [45]. Typically, a gel layer forming on the outer surface of a dosage form is considered to control drug release [46]. However, the pellets produced in the process had a high specific surface area, resulting in complete hydration and dissolution of the pellets. After 30 minutes individual pellets were not visible anymore and the rate-controlling effect was not observed. Also, the cornstarch pellets

swelled to a great extent. Here, individual pellets were still present throughout dissolution testing (see also Bialleck et al. [24]). Again, the hydrophilic gel layer that formed upon contact with the aqueous media did not control the drug release due to the high specific surface area of the pellets.

Since starch was the most promising matrix for achieving a prolonged drug release, a different model drug, codeine phosphate, was incorporated. As illustrated in Fig. 5B, the amount of codeine phosphate released was lower compared to the starch/anitpyrine pellets. Around 33% of codeine phosphate was detected in the dissolution media after 10 min. The pellets continued the drug release for 2 h, followed by an entire release of the API after 3 h. This can be explained by a lower solubility of codeine phosphate in 0.1 N HCl compared to antipyrine.

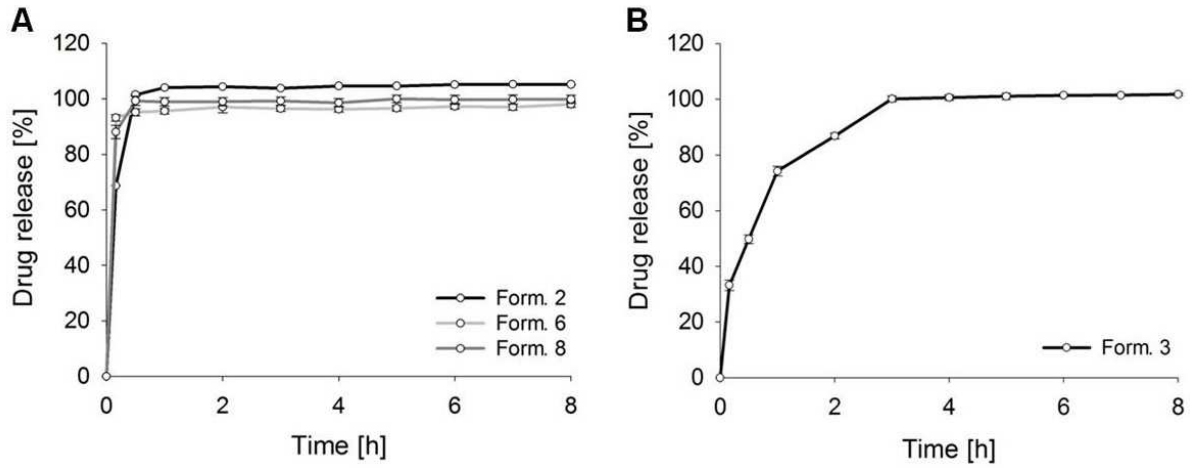

Figure 5: In-vitro drug release profiles of: (A) Formulation 2 (cornstarch/antipyrine(20%) pellets), Formulation 6 (xanthan/antipyrine(20%) pellets) and Formulation 8 (gum arabic/antipyrine(20%) pellets), (B) Formulation 3 (cornstarch/codeine phosphate(10%) pellets) in non-alcoholic media over 8 h; Mean values ± SD (n = 3). As SDs were very low, they are not clearly visible in the graph.

Although none of the cornstarch-based formulations had a prolonged release profile, they stayed intact throughout the dissolution testing. Together with their elastic behavior and high mechanical resistance to tampering with common household devices, this makes cornstarch-based codeine phosphate loaded pellets perfect candidates for further development. Thus, Aquacoat® ARC, a coating material known to retard drug release and to prevent ADD, was applied [25, 27, 47]. Aquacoat® ARC consists of ethanol soluble Aquacoat® ECD 30 and ethanol insoluble guar gum. Aquacoat® ECD 30 remains intact in water and thus, retards the release in aqueous media. The rate controlling effect of the coating in the presence of ethanol is due to guar gum, which is insoluble in ethanol [47]. Thereby, guar gum acts as a protective layer for the ethanol soluble ethylcellulose, leaving the release-controlling film intact in the presence of ethanol [47]. Moreover, guar gum increases the mechanical strength of the film [27], which is further enhanced by adding TEC (plasticizer), resulting in high elongation at breaking. The cornstarch pellets also showed high compression strengths and

did not break but rather deformed, which means that grinding was impossible. Thus, if two highly flexible systems are combined, the possibility for abuse by mechanical destruction is decreased.

The dissolution studies of the coated pellets demonstrated that a coating level of 20% led to a significantly ($p < 0.05$) decreased drug release rate, compared to the non-coated pellets (Fig. 6). After 1 h, 20% of the drug was released and after 2 h only 40% were detected in the dissolution media. This indicates that adding Aquacoat® ARC was suitable for achieving a prolonged release from cornstarch pellets. To verify if this coating material can be alcohol-resistant for 2 h, the pellets were tested in 20% and 40% ethanolic media and compared with the uncoated pellet formulation.

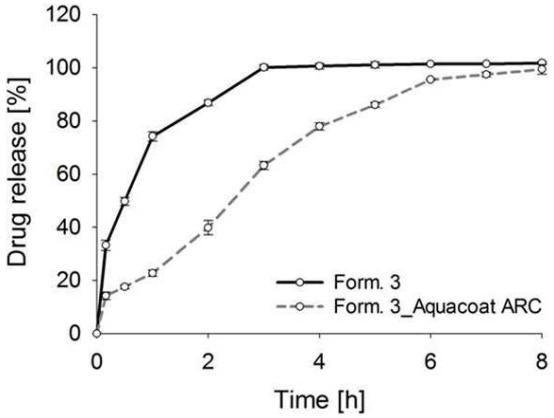

Figure 6: In-vitro drug release profiles of Formulation 3 (cornstarch/codeine phosphate(10%) pellets) and Formulation 3 coated with 20% Aquacoat® ARC in non-alcoholic media over 8 h; Mean values ± SD (n = 3).

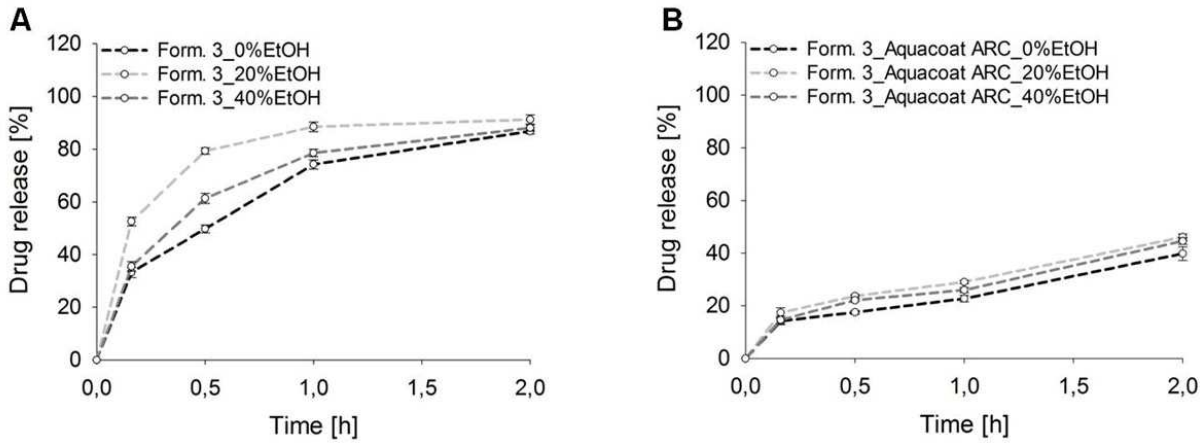

Figure 7: In-vitro drug release profiles of: (A) Formulation 3 (cornstarch/codeine phosphate(10%) pellets) and (B) Formulation 3 coated with 20% Aquacoat® ARC in alcoholic media over 2 h; Mean values ± SD (n = 3).

Fig. 7A clearly shows that the drug release of uncoated pellets depends on the ethanol concentration. Interestingly, the pellets were robust in 40% alcoholic media (f_2 = 59.77). However, adding 20% ethanol to acidic media markedly increased the drug release rate (f_2 =

35.86) and led to dose dumping. This can be attributed to the effect of ethanol on the starch gel layer formation and the solubility of codeine phosphate [17, 48]. In general, the swelling behavior and the API release depend on the penetration of dissolution media into the pellet. Thereby, the free volume between the polymer chains increases and a gel layer that controls the drug release is formed [48]. Upon contact with acidic media (without any ethanol) the cornstarch/codeine phosphate pellets immediately begin to swell. The formed gel layer acts as protective barrier, which controls diffusion of the drug from the pellets and the drug release rate. Adding ethanol to the dissolution media inhibits the initial interaction between the ethanol-insoluble cornstarch-matrix and the surrounding media and hinders the formation of a uniform and stable gel layer, leading to an uncontrolled release of the drug from the pellets. As such, the drug release rate is not controlled by the gel layer but is rather a function of the drug´s solubility in ethanol, which is lower in 40% ethanol than in 20% ethanol (i.e., 186.09 mg/ml and 273.33 mg/ml, respectively). Fig. 8B and 8C clearly indicate that swelling is impeded with increasing alcohol content.

Figure 7B shows that drug release from the coated cornstarch/codeine phosphate pellets was not significantly affected by adding 20% and 40% ethanol (p = 0.54 and 0.72; (Fig. 7B). The estimated f_2-values of 62.13 and 70.96 confirmed that no dose dumping occurred. Again, the drug release was higher in 20% than in 40% alcoholic media, which was also observed in a previous study [31].

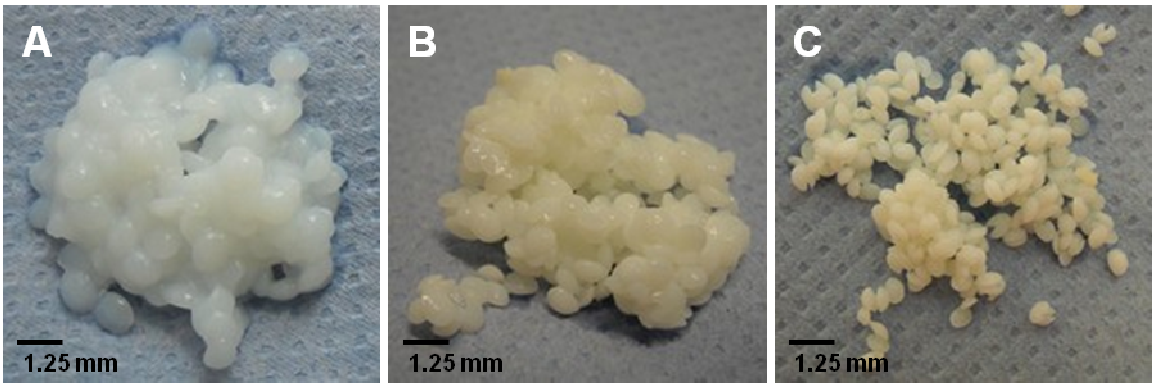

Figure 8: Swelling behavior of cornstarch/codeine phosphate pellets after 2 h of exposure to (A) 0.1 N HCl, (B) 0.1 N HCl/20% EtOH and (C) 0.1 N HCl/40% EtOH.

4.5 Conclusions

This paper reports the development of drug abuse alcohol deterrent multi-unit dosage forms (i.e., pellets) based on matrix systems (i.e., cornstarch, gum arabic, xanthan). The pellets were manufactured via an advanced, continuous one-step HME process, during which a defined amount of water was directly fed into the matrix melt yielding deformable pellets that are tamper resistant. Formulations based on xanthan and gum arabic showed immediate drug release (i.e., complete release within less than 30 min). In contrast, cornstarch based pellets retarded the drug release up to 3 h. To prolong the drug release and to provide

resistance against ADD, cornstarch pellets were coated with Aquacoat® ARC. Overall, it was shown that processing cornstarch via advanced HME increased its resistance to common tampering practices. In combination with a coating process, this matrix system has the potential not only to diminish the abuse but also to prevent ADD.

4.6 Acknowledgements

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4.7 Declaration of conflicts of interest

The authors report no conflicts of interest.

4.8 References

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5 Summary of major findings

The main goal of this thesis was the rational design of robust and alcohol-resistant controlled-release dosage forms using HME as innovative manufacturing technology. For this, it was vital to systematically review the literature taking into account regulations, serious safety concerns and physico-chemical key factors of the drug, the excipients as well as the final dosage form under alcoholic conditions.

According to chapter two it is preferred to use formulation compounds with appropriate physico-chemical properties, such as low solubility and an appropriate wettability and swellability behavior in alcoholic media to minimize the risk of alcohol-induced dose dumping. Suitable technologies to prevent dose dumping include HME, which is a promising manufacturing process to design robust and dense matrix systems with low porosities.
Chapter three focused on the investigation of the interactions between alcohol and the dosage form. Taking the aforementioned findings into account, pellets were prepared via HME and hydrophobic vegetable calcium stearate (CaSt) acted as matrix carrier. To improve the robustness/compactness of the pellets, two ethanol- and water-insoluble solid lipids (Compritol® and Precirol®) were incorporated into the formulation, since they are expected i) to protect the drug against the influence of ethanol and ii) to tailor the release profile. Paracetamol, which is highly ethanol-soluble and codeine phosphate, showing a lower solubility in alcoholic media than in acidic media, were used as model drugs. The major findings of this study include:

- Pellets containing paracetamol showed accelerated drug liberation with increasing alcohol concentrations (regardless of the matrix composition), which was attributed to the high solubility of the drug in alcohol and correspondingly, increased wettability in alcoholic media.
- Pellets containing codeine phosphate and CaSt as single matrix material showed robustness in alcoholic media due to the low solubility of the drug in alcoholic media and wettabilities that were not affected by the addition of alcohol. However, the incorporation of Compritol® and Precirol® led to increased wettabilites with increasing alcohol levels and dose dumping occurred.

Accordingly, the drug release behavior of the pellet formulations was dependent on the drug solubility, the addition of Compritol® and Precirol®, the alcohol level in the dissolution media and hence, the pellets wettability. Although the solid lipids are ethanol/water-insoluble the media uptake of pure Compritol® and Precirol® in alcoholic media increased leading to enhanced wettabilities. In contrast, neither the wetting nor the media uptake of hydrophobic CaSt was altered by alcoholic media.

To develop pellets with abuse-deterrent properties chapter four focused on the design of flexible/deformable pellets that impede tampering with the most common household devices. To that end, an innovative continuous one-step HME technique was applied, where the (visco)elastic properties of the matrix materials (i.e., cornstarch, gum arabic and xanthan) can be achieved by introducing the drug (i.e., antipyrine and codeine phosphate) as aqueous solution directly into the matrix melt. The mechanical properties (i.e., high compression strength) of the pellets and their in vitro drug release behavior were studied and pellet formulations identified as suitable were coated with a flexible Aquacoat® ARC film, to provide controlled drug release rates, while withstanding the impact of alcohol. The major findings include:

- All pellet formulations showed high compression strengths and grinding into powder was impossible.
- Pellets composed of gum arabic and xanthan as matrix materials did not remain intact during dissolution testing and showed immediate drug release.
- Pellets composed of cornstarch swelled but remained intact in the dissolution media and retarded the drug liberation up to 3 h.
- Coated cornstarch-based pellets had a prolonged release over eight hours. Moreover, the formulation revealed resistance to dose dumping even at high alcohol concentrations.

In conclusion, to develop dosage forms robust to alcohol-induced dose dumping, it is beneficial to use formulation compounds with appropriate physico-chemical key factors. Due to wettabilities that were not affected in alcoholic media, hydrophobic CaSt can be considered a suitable matrix system that minimizes the risk of alcohol-induced dose dumping for certain drugs. Furthermore, the combination of two highly flexible systems (i.e., deformable pellets that do not break but rather deform and an alcohol-resistant coating with high elongation at break) has the potential to diminish drug abuse by mechanical destruction and additionally prevent alcohol-induced dose dumping.

6 Outlook

Although in recent years considerable attention has been given to the development of ADFs and the alcohol-induced dose dumping phenomenon, there is still necessity for further investigations in these fields.

Regarding the issue of alcohol-induced dose dumping a mechanistic fundamental understanding of how alcohol interacts with drug formulations and how this impacts drug dissolution and absorption is needed. The authorities recommend the application of in-vitro dissolution studies to test for alcohol sensitivity of controlled-release oral dosage forms in acidic media with different alcohol concentrations. However, prediction of the in-vivo performance of a drug from conventional in-vitro dissolution tests is challenging. Thus, in order to perform rational in-vitro in-vivo correlations the in-vitro dissolution test methods have to be optimized (i.e., usage of biorelevant dissolution media) to reflect the actual physiological conditions. Moreover, conventional in-vitro dissolution tests do not cover the effect of different types of alcoholic beverages (e.g., sparkling wine and beer include carbonic acids; Alcopops contain a great amount of sugar) on the absorption characteristics in the small intestine. Apart from that, differences between men and women including the amount of consumed alcohol and different drinking habits should also be considered. Due to ethical issues associated with in vivo-testing in human volunteers, innovative in-vitro and ex-vivo methods, which take into account the aforementioned facts, have to be developed to gain insight in how alcohol affects the in-vivo behavior and bioavailability of drugs as accurately as possible.

Concerning ADFs no product is available, which is capable of addressing all types of drug tampering. Thus, numerous concerns with the implementation of ADFs into the market remain. Although the FDA recently issued a document regarding the evaluation and labeling of ADFs, it seems unlikely that boxed warnings and added risk information dam inappropriate medication prescribing or hinder patients/abusers from drug tampering. Actually, it is unrealistic to design ADFs such that they are completely abuse-resistant, since the medication needs to be therapeutically effective and thus, the drug needs to be bioavailable to patients. Consequently, the overall goals of ADFs have to be the followings:

- Making drug abuse more costly to abusers in terms of money, time and risk.
- Being resilient to as many forms of tampering as possible in order to be most effective at discourage drug abuse.
- Shifting the risk-benefit balance of clinically important opioid analgesics and other drugs with high abuse potential.

To reach these goals a comprehensive and individual characterization of an ADF to help identifying its strengths and weaknesses regarding the most common tampering methods suspected for the specific drug and dosage form should be conducted. Furthermore, after a new ADF enters the market one should keep the product in sight and continuously study its robustness to potential new tampering methods since abusers often discover new ways to administer the drug.

However, it has to be noted that the efforts in developing ADFs can also lead to a shift to an easily tampered product or, in the worst case, to an illegal drug such as heroin, which is often easier to get and cheaper than prescription opioid drugs.

In summary, the research field of ADFs and alcohol-induced dose dumping is only just in its beginning era and there is still significant demand for innovative technologies and ideas to overcome the growing public health concern of prescription drug abuse.

7 List of Publications

Articles in peer-reviewed journals

N. Jedinger, J. Khinast, E. Roblegg, *The design of controlled-release formulations resistant to alcohol-induced dose dumping – A review*, Eur. J. Pharm. Biopharm. 87 (2014) 217-226.

N. Jedinger, S. Schrank, S. Mohr, A. Feichtinger, J. Khinast, E. Roblegg, *Alcohol dose dumping: The influence of ethanol on hot-melt extruded pellets comprising solid lipids*, Eur. J. Pharm. Biopharm. 92 (2015) 83-95.

N. Jedinger, S. Schrank, J. M. Fischer, K. Breinhälter, J. Khinast, E. Roblegg, *Development of an abuse and alcohol-resistant formulation based on hot-melt extrusion and film coating*, accepted in AAPS PharmSciTech (15.07.2015)

Presentation

N. Jedinger, E. Jäger, A. Hodzic, G. Koscher, S. Mohr, A. Zimmer, J. Khinast, E. Roblegg, *Effect of plasticizers on the development of sustained-release lipophilic calciumstearate pellets produced via hot-melt extrusion*, 5th International Congress on Pharmaceutical Engineering (ICPE), September 2011, Graz, Austria.

A. Eitzlmayr, D.F. Treffer, N. Jedinger, G. Koscher, E. Roblegg, J. Khinast, *Hot melt extrusion: Product and process development,* 6th Annual PSSRC Symposium, August 2012, Lisbon, Portugal.

Poster used within an academic meeting

N. Jedinger, K. Fuchs, G. Koscher, J. Khinast, E. Roblegg, *Rational design of lipophilic calcium stearate pellets produced via HME,* 8th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, March 2012, Istanbul, Turkey.

N. Jedinger, G. Koscher, J. Khinast, E. Roblegg, *Lipophilic calcium stearate pellets produced via HME: Impact of plasticizers on the in-vitro release,* 8. Minisymposium der Verfahrenstechnik, May 2012, JKU Linz, Austria.

N. Jedinger, G. Koscher, J. Khinast, E. Roblegg, *The influence of ethanol on hot melt extruded micropellets containing Compritol® and Precirol® as additives,* 9. Minisymposium der Verfahrenstechnik, April 2013, Montanuniversität Leoben, Austria.

N. Jedinger, G. Koscher, J. Khinast, E. Roblegg, *Impact of ethanol on hot-melt extruded micropellets comprising solid lipids as functional additives,* AAPS Annual Meeting and Exposition, November 2013, San Antonio, Texas, USA.

N. Jedinger, J. Khinast, E. Roblegg, *Untersuchung des Einflusses von Alkohol auf lipophile schmelzextrudierte Pellets,* 47. Wissenschaftliche Fortbildungswoche der Österreichischen Apothekerkammer, Februar 2014, Schladming, Austria.

N. Jedinger, J. Khinast, E. Roblegg, *The influence of ethanol on hot-melt extruded pellets containing solid lipids as functional excipients,* 9th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, March 2014, Lisbon, Portugal.

N. Jedinger, J. Khinast, E. Roblegg, *How does alcohol impact hot-melt extruded pellets comprising solid lipids as functional additives?,* 23rd Scientific Congress of the Austrian Pharmaceutical Society (ÖPhG), April 2014, Graz, Austria.

N. Jedinger, J. Khinast, E. Roblegg, *Development of a drug abuse-alcohol-resistant formulation produced via hot-melt extrusion,* 6th International Congress on Pharmaceutical Engineering (ICPE), June 2014, Graz, Austria.

N. Jedinger, S. Mohr, J. Khinast, E. Roblegg, *Development of lipophilic hot-melt extruded alcohol-resistant pellets containing nicomorphine,* 6th International Congress on Pharmaceutical Engineering (ICPE), June 2014, Graz, Austria.