



Development of alcohol-resistant single- and multiple-unit matrix formulations

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*Alla mia famiglia,
per l'amore e la forza che mi ha sempre trasmesso*

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ABBREVIATIONS

ADD	Alcohol-induced dose dumping
API	Active pharmaceutical ingredient
AS	Absolute swelling
AUC	Area under the curve
BCS	Biopharmaceutical Classification System
d	Tablet diameter
DCPA	Dicalcium phosphate anhydrous
D_{eff}	Effective matrix drug diffusion coefficient
DMU	Dissolution media uptake [%]
DoE	Design of experiments
DSC	Differential Scanning Calorimetry
EMA	European Medicines Agency
EtOH	Ethanol
F	Crushing force
f_2	Similarity factor
FDA	United States Food and Drug Administration
h	Thickness
HME	Hot-melt extrusion
HPMC	Hydroxypropyl methylcellulose, hypromellose
IVIVC	In-vitro in-vivo correlation
JPE	Japanese Pharmaceutical Excipients
K_H	Slope Higuchi plot
L/S	Liquid to solid ratio
m	mass
M_0	Drug dose
MCC	Microcrystalline cellulose
ML	Mass loss [%]
MR	Modified-release
M_t	Amount of drug released at time t

MTR	Mixer torque rheometer
M_w	Mean molecular weight [g/mol]
n_{KP}	Exponent of Korsmeyer-Peppas plot
P	Compression pressure
PEO	Polyethylene oxide, high molecular macrogol
PGS	Pregelatinized starch
Ph. Eur.	European Pharmacopeia
PS	Particle size
PTFE	Polytetrafluoroethylene, Teflon [®]
PVAc	Polyvinyl acetate
PVP	Polyvinyl pyrrolidone, povidone
Q	Drug release per tablet surface unit
Q^2	Coefficient of prediction
R^2	Coefficient of determination
RH	Relative humidity [%]
RS	Relative swelling
SA	Surface area
SD	Standard deviation
SEM	Scanning electron microscopy
SR	Sustained release
SSA	Specific surface area
t	Tablet thickness
TA	Texture analyzer
T_g	Glass transition temperature
TiO ₂	Titanium dioxide
USP	United States Pharmacopeia
UV	Ultraviolet
V	Volume
W_d	Dried weight
W_i	Initial weight
W_w	Wet weight

Abbreviations

XG	Xanthan gum
XGc	Xanthan gum concentration
ε	Porosity
σ	Tensile strength

1 INTRODUCTION

1.1 Alcohol-induced dose dumping (ADD)

Dose dumping is often referred to an “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 (MR) dosage form” [1].

Food-induced dose dumping of once-a-day MR products has been already recognized for about 20 years and regulatory guidelines have been established to address it [1, 2]. For instance, symptoms of drug toxicity appeared on an 11-year-old girl after concomitant ingestion of the once-a-day product “Theo-24” with food [3]. Dose dumping has most likely occurred due to the pH change in the duodenum which took place in response of food. As a matter of fact, the coating of the beads was soluble at pH 7.4, released significant fraction of the drug, which resulted in a drastic increase of the drug concentration in serum [3].

Some MR oral dosage forms embed drugs and/or excipients whose solubility is enhanced in hydro-alcoholic solutions compared to water [1]. A more rapid drug release is therefore expected for such products after accidental misuse or intentional abuse of alcohol [4]. Dose dumping which results from the consumption of alcohol in concomitance with the administration of a medication is referred to as alcohol-induced dose dumping, or ADD [5]. Depending upon therapeutic index, pharmacokinetics and therapeutic indication of the drug, critical toxicological effects or even fatality can occur, due to the high doses embedded in MR dosage forms [5]. Furthermore, ADD can represent a major risk for patients because the therapeutic efficiency might not be assured for the intended period of time [6].

Moreover, alcohol can further complicate the scenario, since it can influence absorption, metabolism and excretion of drugs [4, 7, 8].

In the past, the potential risk of dose dumping has been rarely highlighted by clinicians, formulation developers, as well as regulatory officers [9]. One of the reasons for this might be a scarcity of clinical data confirming a significant change in drug release rate *in-vivo* upon concomitant administration of MR products with alcohol [1]. The clinical study, performed on healthy volunteers by Wills et al. in 1982 [10] focused on the influence of alcohol on the pharmacokinetics of diazepam controlled-release formulation. The study showed the absence of alcohol effect on both drug release properties of the capsules and the overall drug absorption, since the “onset magnitude and duration of plateau concentrations” were “nearly identical” to the control [10]. Differently, Frömme and Topaloglu observed that the release of acetylsalicylic acid from prolonged release tablets based on Eudragit ret-l (PM) was faster upon concomitant intake of 120 mL commercial brandy, both *in-vitro* and *in-vivo* [9].

However, a breakthrough happened in July 2005, when the FDA withdrew an extended-release capsule based on hydromorphone, Palladone™ (Purdue Pharma, US), from the US market. As a matter of fact, drastically increased and potentially lethal peak plasma concentrations of the drug were reported after ingestion of Palladone™ with alcohol, thus giving evidences of ADD [11]. A pharmacokinetic study was performed on healthy subjects and it was demonstrated that the concomitant ingestion of Palladone™ with 240 mL of 40 % alcohol led to a 6-fold higher average

peak concentration of hydromorphone compared to water [1]. In this study, one subject experienced a 16-fold increase in the peak concentration when the drug was ingested with 40 % ethanol compared with water [11]. In certain subjects who consumed 8 ounces of 4 % ethanol (equivalent to 237 mL beer) the peak plasma hydromorphone concentration resulted 2-times higher than when the drug was administered with water [11].

These findings resulted in new perspectives about the influence of concomitant intake of alcohol with drug delivery systems on drug release mechanism. Namely, new guidelines have been initiated, which highlight the ADD risk assessment in the formulation development of MR dosage forms [12]. The aim of this approach has been to encourage the design of alcohol-robust MR formulations with the purpose of minimising the risk of ADD, even when proper warnings on the adverse consequences of concomitant alcohol consumption have been included in the product labels [12].

For instance, MR opioid dosage forms have been prescribed as first choice medication in the treatment of chronic pain [13-15]. It was reported that, despite appropriate warnings on the product labelling, patients who suffer from chronic pain often turn to alcohol to cope with the pain-related stress and to reduce pain perception [16]. As a matter of fact, physiological effects of alcohol are considered similar to those of anaesthetics [17]. Brennan et al. [16] conducted a study on an elderly population (n= 401) suffering from chronic pain and classified the older adults as problem and non-problem drinkers. The findings of this study highlighted that both problem and non-problem drinkers consume alcohol to cope with pain.

Besides, accidental ADD may occur to any patient, since alcoholic beverages are commonly consumed in most cultures [12]. As a matter of fact, WHO database has shown that more than 50 % of the population consumes alcohol in America, Europe and Western Pacific, and, worldwide, 44.8 % of totally recorded alcohol is consumed in form of spirits, 34.3 % in form of beer and 11.7 % in form of wine [18]. Moreover, it has been reported that accidental ADD might also occur due to residual alcohol in the stomach upon earlier intake [5].

1.2 Regulatory considerations

Regulatory agencies have provided guidance for ADD in various documents in the European Union [19, 20], US [1, 21] and other countries [22]. General recommendations state that appropriate *in-vitro* dissolution tests should be assessed in the presence of ethanol in order to identify the risk of ADD. However, the International Conference on Harmonization has not provided any guidance yet and, to date, no major regulatory agency has summarized all regarding information in one single document [5]. For instance, EMA recommends ADD testing in regard to all MR dosage forms, whereas FDA limited the ADD risk assessment solely to API with a narrow therapeutic window [12, 23, 24].

The requirements of the two regulatory agencies FDA and EMA are summarized in Table 1. As listed below, the ADD requirements are different regarding three major topics, i.e. methodological requirements, products to be tested and acceptance criterion. To be highlighted is the requirement of FDA for testing in dissolution media containing up to 40 % (v/v) ethanol, whereas EMA requires a maximum ethanol concentration of 20 % (v/v). According to the literature, an ethanol concentration of 40 % in the stomach would require an intake of 240 ml of a beverage containing 56 % alcohol into an

empty stomach which contains 100 mL gastric liquid [25, 26]. However, such an extreme intake of alcohol seems to be a consequence of so-called “binge drinking” (i.e. consumption of 4 or 5 drinks in a short time interval) [6, 27] and the requirement for robustness *in-vitro* at 40 % ethanol concentration seems to be more relevant in the case of abuse-deterrence [28]. Differently, an ethanol concentration of 20 % (v/v) is more likely to be realistic in case of accidental ADD [5]. Moreover, testing time has been defined only by FDA, which indicates 2 h testing, whereas EMA does not define it (Table 1).

Table 1: Requirements of FDA and EMA regarding the in-vitro dissolution testing of formulations at risk for ADD (according to Friebe et al. [5])

Topic	FDA	EMA
Products to be tested	At least each (generic) version for MR opioid drug products; more preferably for (all) MR drug products with risk of ADD	All oral MR applications
Methodological requirements	Dissolution medium: 0.1 N HCl Alcohol concentrations: 0%, 5%, 20% and 40% (v/v) Time: every 15 min until 2 h	Dissolution medium: equivalent to that suggested for routine testing Alcohol concentrations: 5%, 10%, and 20% (v/v) Time: not specified
Acceptance criterion	Generic drug formulation should be robust in alcohol. In the case that a generic formulation releases the API more rapidly in alcoholic media, the dissolution rate should be similar to that of the reference product.	If ADD occurs, the drug product should be reformulated. In the case that ADD risk cannot be avoided and is present also with the reference drug product, applicant should justify absence of clinical relevance.

On the one side, FDA recommends 0.1 N HCl as a baseline medium in order to approximate the gastric conditions [29], while, on the other side, EMA recommends to use the same dissolution medium and apparatus as that utilized in the routine testing. The percentages of alcohol (v/v) considered by the FDA for the in-vitro dissolution testing are “representative for the consumption of beer (5 % ethanol), mixed drinks (20 % ethanol), and neat liquor (40 % ethanol)” [29], whereas EMA considers ethanol concentrations of 0, 5, 10 and 20 % [4, 19, 20].

The discrepancy between EMA and FDA requirements can lead to misunderstandings and confusion about which guideline to follow. In order to be able to market products globally, pharmaceutical companies are forced to rely on the more strict FDA requirements upon submission of the drug product documentation to the regulatory agencies [5]. For this reason, formulations which may be robust in 20 % ethanol but vulnerable in 40 % ethanol would be dismissed and the launch of potentially valuable medications may even be compromised [5].

The above reported regulatory guidances concern exclusively the *in-vitro* dissolution testing. As a matter of fact, the performance of clinical trials to determine the risk of ADD *in-vivo* would represent an unnecessary risk for the volunteers and may be considered, therefore, unethical. However, it has been shown that *in-vitro* testing in 40 % ethanol do not necessarily predict *in-vivo* behavior [25]. A

lack of *in-vitro in-vivo* correlation (IVIVC) is due to the complex environment *in-vivo*. In the literature, two examples were reported in order to highlight this issue:

- Extended-release matrix tablets have often been reported as robust against ADD. Opana[®] ER is an oxycodone extended-release matrix, with the alcohol-insoluble xanthan gum and locust bean gum used as rate-controlling polymers (TIMERx drug-delivery technology). Although Opana[®] ER resulted in a robust product in alcohol *in-vitro*, it failed *in-vivo* experiments and led to significant rise in maximum drug concentration taken with 40 % ethanol [30].
- MR multiparticulates coated with methacrylic copolymers are usually expected to be more vulnerable against ADD due to generally high solubility in alcohol of the polymers and the high specific surface area in contact with the media. The multiparticulate system Micropump[®], with carvedilol as API, contains methacrylic copolymers in the MR coating. It failed the ADD requirements of robustness *in vitro* in 40 % ethanol. However, the *in-vivo* performance was not affected by the presence of alcohol in the stomach [31].

These two examples have shown that there is a need for specifically designed methods for ADD risk assessment [5]. However, it should be noted that apart from API and excipients properties, as well as formulation design, fasted/ fed state may have a relevant impact on the formulation performance. For instance, Lennernäs et al. [25] reported that the lack of IVIVC of the above mentioned Micropump[®] might be due to the presence of food in the gastro-intestinal tract, upon testing.

Under which circumstances and in which patient a clinically relevant ADD will occur is nearly impossible to predict. Therefore, it is suggested that products which show vulnerability in media with up to 40 % ethanol concentrations *in vitro* during 2 hours should be withdrawn from the market unless clinical evidences about their safety have been reported upon *in-vivo* testing [25]. In alternative, a reformulation of the product should be performed according to quality-by-design principles [24].

1.3 Alcohol affecting physiological conditions

The variations in physiological conditions which follow the intake of alcoholic beverages have been investigated by several authors [15, 25, 31-35].

Walden et al. reported that ingestion of alcohol may influence the plasma pharmacokinetics of some oral prolonged release dosage forms containing opioids, leading to higher *in-vivo* absorption rate and a completely changed profile of the plasma concentration versus time curve [15].

As a matter of fact, the pharmacological effect(s) of most orally administered drugs depends on (i) absorption rate, (ii) absorption extent and (iii) bioavailability of the drug in the active form(s) [25]. When alcohol is ingested, the dissolution rate of the prolonged release dosage forms may be increased, resulting in higher luminal concentration of the drug and therefore to proportionally higher absorption rate in the intestine, and consequently higher bioavailability [25].

A crucial role for the drug absorption onset is the gastric emptying time. Several factors, such as certain drugs, food, gastric dysmotility, age but also alcohol, can delay the gastric emptying [36]. This means that upon intake of high concentration of ethanol and due to the prolonged gastric emptying

time, the dosage form can stay in contact with the hydro-alcoholic media for a time sufficient enough to enable an unintended and fast drug dissolution [25].

The exposure of significant fractions of the drug to high ethanol concentrations will also depend on the profile concentration-time of ethanol in the gastric compartment, as defined by oral intake, dilution in the stomach, metabolism, as well as absorption and emptying [25]. This ethanol profile combined with the properties of the administered dosage form (for instance, solubility of drug and pharmaceutical excipients in ethanol as well as surface area) will indicate the risk of a potential dose dumping [25].

Levitt et al. conducted a study to quantify the ethanol absorption rate in humans, by measuring both gastric emptying rate and gastric absorption rate, with and without food [34]. The authors stated that the ethanol removal from the stomach was extremely rapid in fasting state with approximately 47 %, 85 % and 96 % of the total alcohol dose leaving the stomach after 3 min, 13 min and 23 min, respectively. However, the presence of food delayed ethanol disappearance from the stomach, where 23% of the ethanol ingested with a meal was emptied in the duodenum after 6 min and the ethanol removal from the gastric compartment was nearly concluded after 126 min. By observing the blood plasma level of ethanol, the peak blood levels and AUC were respectively 2.5- and 2.8-times higher when the stomach was in fasting state than in fed-state. As a matter of fact, gastric emptying is a major factor which affects the onset of drug absorption in the small intestine.

Higaki et al. [36] reported that the gastric retention time may be even longer than 2 h in healthy subjects in light fed state. These data therefore validate the physiological relevance of the FDA requirements, which recommends a dissolution testing time of 2 h in 40 % ethanolic media, to assess the sensitivity of a MR dosage forms against ethanol.

Furthermore, it has been shown that the energy load of many alcoholic beverages may lead to significant lag-time in the gastric emptying, therefore it is physiologically possible that an alcoholic beverage might have a sufficient gastric residence time to dissolve significant fraction of the controlled release dose, leading to ADD [25, 36, 37]. Franke et al. has shown that beer and red wine inhibit the gastric emptying more strongly than their comparable concentrations of pure alcohol (4% and 10 %, v/v). On the contrary, whisky did not. This is due, firstly, to the caloric content and, secondly, to the presence of non-alcoholic ingredients in alcoholic drinks which are produced by fermentation and not by distillation, as e.g. whisky [37].

Furthermore, the secretion of the stomach which follows the oral intake of ethanol has been studied. The results have shown that beer, red and white wine, however not whisky and cognac, were highly stimulating the secretion of gastric acids [38-40]. Therefore, it is assumed that strong alcoholic beverages, such as vodka, gin, whisky and cognac, in the fasted state may lead to a low dilution, due to the negligible gastric secretion and the rather low gastric fluid volume [41]. This certainly increase the ADD risk, since high ethanol concentrations can be reached in the stomach, able to compromise the controlled release mechanism(s) of vulnerable dosage forms. To be highlighted is also the low gastric absorption of the ingested ethanol (10-20 %) in comparison to the absorption in the small intestine (80-90 %), which allow a prolonged residence time of alcohol in the stomach.

1.4 Alcohol affecting the formulation

In conjunction with the affected physiological conditions, the dosage form properties may be influenced by the presence of alcohol. In accordance to Jedinger et al. [24], key physico-chemical factors of the formulation components have to be taken into account to develop an ADD-resistant modified release dosage form. Among these factors, solubility, wettability, as well as swellability of API and excipient(s) are of high importance. Furthermore, also the mechanical properties of the final dosage form must be considered.

Generally, the solubility of a compound is influenced by the ratio of hydrophilic and hydrophobic groups within the molecule, and it is recognized that polar molecules are most soluble in polar solvents and non-polar molecules in non-polar solvents. Ethanol has a lower capacity of building hydrogen bonding than pure water, therefore the solubility of very hydrophilic molecules decreases in presence of ethanol, whereas it increases in case of hydrophobic or poorly soluble compounds [42, 43].

When taking into consideration, for instance, matrix systems, drug release from such drug delivery systems is controlled by medium penetration into the matrix, hydration of the rate-controlling polymer, swelling and finally diffusion of the solubilized drug and/or matrix erosion [44]. Based on this, it is clear that the media in contact with the matrix system can significantly affect the drug release rate. Thus, if the matrix formulation is highly soluble in hydro-alcoholic media, a fast disintegration/dissolution of the dosage form will occur, resulting in ADD [24]. For this reason, the development of matrix systems able to withstand the influence of alcohol and which stay intact during dissolution is required. In addition, besides matrix systems, controlled release coated systems, which are surrounded by thin release rate-controlling polymeric films, can be highly vulnerable against alcohol, in case of coating dissolution in alcoholic media [6, 9].

Wettability is another crucial parameter which can affect dose dumping [24]. If the wettability of e.g. matrix system is improved by the presence of alcohol in the dissolution media, accelerated dissolution media uptake and therefore faster drug release will occur [24]. For this reason, excipients which are less prone to significant wettability variation in presence of ethanol should be selected in the development of ADD-resistant dosage forms.

Especially in regard to hydrophilic polymers, swellability is an additional parameter which has to be considered in order to control the drug release. Thus, the ability of the polymer to swell depends on the composition of the dissolution media. Indeed, the thermodynamic compatibility between polymer chains and molecules of the surrounding dissolution media is responsible for the swelling process [45]. According to Missaghi et al. [46], ethanol can affect the formation of the gel layer, which results from the polymer swelling, and may therefore lead to the disruption of the matrix system. For this reason, a fast formation of a strong gel layer around the matrix has to be achieved also in presence of ethanol. In other words, a thermodynamic equilibrium between the hydrophilic polymer and the alcoholic media has to be reached fast enough in order to avoid a rapid penetration of the dissolution media into the matrix and an increase in drug release [24].

At last, the mechanical properties of the oral dosage form have to be evaluated. From the literature it is well known that the compression pressure as well as compression speed can strongly impact the

tensile strength of matrix systems [47, 48] and therefore the drug release. In particular, matrices of decreased porosity and higher compactness can be manufactured by using higher compression pressures during tableting or by increasing the process temperatures during HME [49]. Decreased porosity might lead to decreased media uptake, thus hindering an eventual fast media penetration due to the presence of alcohol.

1.5 Technological strategies to reduce ADD risk

Technological approaches for the development of controlled-release dosage forms include (i) controlled-release coated systems, (ii) controlled-release matrix systems and (iii) osmotic drug delivery devices.

In regard to controlled-release coated systems, one coating material is available on the market, which shows alcohol-resistant properties, developed by FMC BioPolymer under the trade name Aquacoat[®] ARC (Alcohol Resistance Coating). This coating polymer consists of guar gum blended together with Aquacoat[®] ECD, an aqueous dispersion of ethylcellulose [50]. Due to the insolubility of guar gum in ethanolic media, a gel layer able to hinder the solubilisation of the alcohol-soluble ethylcellulose can be formed, thus leading to an intact controlled release coating. Pellets coated with Aquacoat[®] ARC have been tested in media containing 10, 20 and 40 % ethanol. Similar dissolution profiles were achieved in all media, showing therefore robustness of the coating polymer against alcohol [24].

However, polymers commonly used in coatings of controlled-release systems generally failed in ethanol concentration up to 40 %. For instance, Traynor et al. reported immediate drug release in presence of ethanol from capsules containing controlled-release tramadol pellets coated with Eudragit NE30D [51]. Furthermore, Walden et al. [15] and Sundari et al. [52] indicated risk of ADD from pellets coated with excipients, such as ethylcellulose, dibutyl sebacate, as well as Eudragit RSPO/RLPO and cellulose acetate butyrate.

Furthermore, hydrophilic matrix systems are a widely used technology for tailoring controlled-drug release. Levina et al. [53] assessed the influence of alcohol on hydration, gel formation and dissolution of three differently soluble APIs from hydroxypropylmethylcellulose (HPMC)-based matrix tablets. The formulations did not show vulnerability against alcohol or ADD. Differently, Roberts et al. [54] observed a significantly increased initial dissolution rate of the drug acetylsalicylic acid from HPMC matrix tablets in 40 % alcohol. However, the authors hypothesized that after the initial period a stronger and less porous gel layer was formed, which decreased the dissolution rate and therefore prevented ADD. Traynor et al. [51], moreover, reported the robustness against 40 % ethanol of the extended-release tablet Tridural[™], which contains tramadol as API and rate-controlling polymers, such as cross-linked high-amylose starch (Contramid[®]) and xanthan gum (see also section 3.2.2). Moreover, Cvijić et al. reported that hydrophilic matrix tablets showed to be less vulnerable against ADD in comparison to lipophilic matrices (containing, for instance, stearic acid and cetyl alcohol) [12]. However, the results were affected by the type of dissolution setup which was used.

In addition, Grünenthal GmbH has developed the INTAC[®] drug delivery platform, with the aim of preparing matrices able to resist crushing (thus deterring tampering of the dosage form) and to withstand (i) dissolution and (ii) chemical extraction in diverse solvents [55, 56]. The manufacturing

steps comprised hot-melt extrusion (HME) of mixtures containing the opioid drug such as tramadol hydrochloride and high-molecular-weight polyethylenoxide (PEO) as matrix former. Subsequently, the obtained extrudates were cooled, sliced and shaped into tablet form by using an eccentric tablet press. The produced tablets were able to withstand both crushing and chemical extraction in presence of simulated alcoholic beverages. In particular, in 40 % ethanolic media, the tablets have shown to release the embedded drug slower than in 0.1 N HCl, thus demonstrating that the PEO matrices produced via HME were less prone to abuse than the directly compressed tablets [55, 56].

Sathyan et al. studied the effect of alcohol on the pharmacokinetic properties of the novel oral osmotic (OROS®) Push-Pull delivery system based on hydromorphone as API [57]. The results indicated that the pharmacokinetics of OROS hydromorphone was minimally affected by alcohol and no ADD occurred [57]. These findings were in accordance with the study of Koziara et al. [58], who assessed the risk of ADD with membranes based on semipermeable cellulose acetate, used as osmotic drug delivery system. Although ethanol led to increased permeability, elasticity, as well as increased swellability of the cellulose acetate-based membranes, only a slightly increased drug release was seen in ethanol concentrations up to 60 % and no dose dumping occurred [58].

CIMA Labs developed the extended-release technology OraGuard™, able to provide resistance against ADD [59]. These properties were achieved through a multistep process, where the drug is firstly granulated with polymers of suitable solubility in hydrous and hydro-alcoholic media. Secondly, the resulting granules are coated by a robust film-forming polymer, and then compressed into tablets together with swellable polymers [24].

Due to cost-effectiveness, simple manufacturing and the above reported lower susceptibility of hydrophilic matrix tablets in ethanolic media, the present work will particularly focus on the development of such dosage forms as promising platform technology to hinder the risk of ADD.

1.6 Modified-release hydrophilic matrices

Over the past decades, drug delivery has been revolutionized by the development of modified-release matrix systems [47].

By definition, a hydrophilic matrix is a homogeneous dispersion of drug molecules or drug particles within a skeleton in which one or several of the excipients incorporated are hydrophilic polymers [47]. Hydrophilic polymers are able to swell upon contact with the dissolution media, due to the relaxation of the polymer chains as a consequence of media penetration, and this hydration leads to the formation of a zone in which the polymer transit from the crystalline “glassy” state to a “rubbery” state, also known as gel layer [47, 60]. Different transport phenomena take place through the formed gel layer and thus, the penetration of the medium within the matrix, the exit of the solubilized drug outside of the swollen system, and the matrix erosion. As more and more medium enters the matrix, the thickness of the gel layer increases, thus leading to an increase of the path length through which the drug has to diffuse, resulting in a decreased drug release [61]. Simultaneously, the polymer chains which are most proximal to the surface of the matrix and which become hydrated earlier than the others, lose gradually consistency and lead to the matrix erosion.

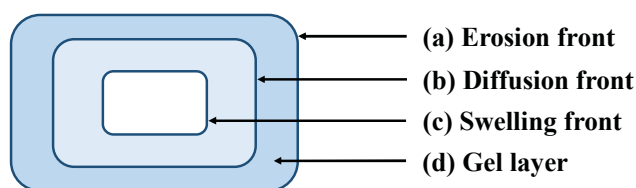


Figure 1: Series of fronts formed in the hydrophilic matrix after the penetration of the dissolution medium, according to Maderuelo et al. [47]

Series of fronts (i.e. the location in the matrix where the physical properties sharply change [45]) are formed within the matrix upon contact with the dissolution medium (Figure 1), which afterwards disappear along the dissolution of the matrix [45, 62].

On the one side, the “swelling front” (Figure 1, c) separates the rubbery region (containing enough water to lower the glass transition temperature T_g below the experimental temperature) from the glassy region (where the T_g of the polymer is above the experimental temperature) [45]. On the other side, the “erosion or dissolution front” (Figure 1, a) separates the matrix system from the dissolution media. The gel layer thickness, as already mentioned, is a function of time and is determined by the relative position of the swelling and erosion moving fronts (Figure 1, d). Furthermore, a “diffusion front”, which is positioned between the swelling and the erosion front, represents the boundary that separates the region of the swollen matrix containing the undissolved drug from the matrix region containing the dissolved drug [47]. Colombo et al. [62] reported that the location of the diffusion front within the gel layer depends on the drug solubility and the drug loading [63]. It has to be highlighted that the thickness of the gel layer is a critical factor in drug release and depends on both drug load and viscosity of the polymer.

Most commercial hydrophilic matrices are produced by compression, which is fast, simple and easy to implement industrially. However, other technological approaches can be also used with rate-controlling polymers, such as wet extrusion and hot-melt extrusion [55, 56, 64].

In particular, wet extrusion involves the following phases: a uniform powder blend of drug and excipient(s) is wet massed within the extruder by the addition of a liquid binder and intense shear forces through co- or contra-rotating twin screws, succeeded by the pressing of the wet mass through a die plate (extrusion) to shape cylindrical extrudates [65]. The extrudates can be either further spheronized into pellets [65] or cut directly at the die face using a pelletizer with rotating knives [66]. The resulting multiple units have then to be dried. This process is efficient and allows a high throughput through the continuity of the extrusion process, where different steps are carried out on a single machine [67].

In this work, both direct compression and wet extrusion will be the manufacturing processes of choice.

1.7 Single- and multiple-unit oral dosage forms

Although a variety of dosage forms have been developed to produce oral controlled release formulation, they can be generally divided into two categories: single-unit dosage forms and multiple-units (or multiparticulate) dosage forms [64].

A single-unit dosage form, for instance a matrix tablet, is a depot which releases the drug dose throughout the all gastro-intestinal tract without disintegrating [68]. Before administrating a single-unit dosage form, it is therefore imperative that the dosage form is not manipulated, but swallowed intact, in order to maintain the depot effect and to hinder potential unintended dose dumping [69]. Advantages associated with the administration of single-unit dosage forms include the simple and cost-effective manufacturing process, the high drug loading, the wide availability of polymers and excipients and the possibility of using several mechanism for the drug release control, such as diffusion or swelling or erosion control [64].

However, single-unit dosage forms have faced several disadvantages. The literature reported that the transport of single-unit dosage forms is highly dependent on the gastric emptying time, due to the considerable dimensions of these oral dosage forms. The emptying of undisintegrated tablets from the gastric compartment has shown variations which ranged from less than half an hour to more than 7 hours [68]. As a matter of fact, both intra- and inter-individual variations in gastric emptying time are high due to multiple factors. In many cases, this can affect both rate and extent of bioavailability of a drug [68]. Another particular disadvantage of the single-unit dosage forms is the risk of local irritation, which follows the entrapment of the dose in a narrow passage and the consequent high drug concentrations at the site of the trap.

A multiple-unit dosage form, such as pellets, granules, mini-tablets, can offer different advantages over the single-unit systems [70, 71]. It is defined as an oral pharmaceutical formulation consisting of a unit which disintegrates in the stomach, upon contact with the gastric fluids, into a variety of small mini-depots (e.g. tablets compressed from pellets, hard gelatine capsule filled with mini-tablets or pellets) [68]. Therefore, differently from the single-unit dosage forms, multiple-unit formulations can be divided without compromising the depot effect.

The major advantages of this dosage forms derived by the reduced dimensions of the mini-depots (diameter < 1 , in some application up to 3 mm [64]), which enable their passage through the pylorus even between its actual openings [72, 73]. Consequently, the drug reaches the site of absorption in a more reproducible manner, thus leading to a more reproducible bioavailability [68]. A uniform drug absorption results subsequently in a higher reproducibility of plasma concentration. In addition, since the mini-depots are distributed through the gastro-intestinal tract [72], the risk of mucus irritation is reduced. Minor risk of dose dumping and the possibility of an individual dosing represents further advantages. However, the preparation of multiple-unit dosage forms is generally more complicated and expensive.



Figure 2: 8 mm tablets in comparison to 2 mm mini-tablets (used by courtesy of the International Journal of Pharmaceutics, Elsevier [74])

In this work, mini-tablets will be considered as the multiple-unit dosage form of choice. Mini-tablets are defined as tablets with the diameter between 1 mm and 3 mm [75, 76]. Due to their reduced dimensions (Figure 2), the administration of mini-tablets can help to overcome the issues connected to dysphagia [77].

This dosage form is competing with pellets, due to more reproducible and continuous production, their uniform size, smooth surface, low porosity and high strength, which eventually allow a more reproducible coating process in comparison to granules or pellets [75]. Mini-tablets can be produced by direct compression or after granulation, using a multiple tooling [76]. However, the preparation of mini-tablets requires extra care and fine adjustment of tableting machines and problems derived by the durability of small-sized punches have been described in a patent by Hershberg et al. [78]. In addition, the mixtures should have sufficient flow properties and the requirements regarding flowability have been investigated by Flemming and Mielck [79].

As mentioned above, mini-tablets are particularly suitable for coating in order to control the drug release. However, the coating process is time consuming, expensive and sometimes connected to irreproducible release performances during storage [80]. Therefore, the development of matrix mini-tablets has arisen great interest.

Several authors have studied matrix mini-tablets based on hydrophilic and hydrophobic polymers [67, 77, 80-84]. Furthermore, Jedinger et al. [66] developed multiparticulate pellets able to prolong the drug release, minimize the risk of ADD and provide drug abuse deterrence. The authors prepared pellets *via* a HME technique and pelletization, based on codeine phosphate as API and cornstarch as matrix polymer. However, in order to prevent ADD, the pellets needed to be coated with Aquacoat[®] ARC [66]. Furthermore, pellets based on pure calcium stearate or calcium stearate in association with the solid lipids Compritol[®] and Precirol[®] were used to develop an alcohol resistant formulation for the model drugs paracetamol and codeine phosphate [85]. The drug release characteristics were a strong function of the drug solubility, composition of the dissolution media, presence of solid lipids in the formulation and pellets wettability. In particular, formulations containing solid lipids exhibited accelerated drug release in alcohol for both APIs, due to the increased matrix wettability and media uptake in hydro-alcoholic media. In contrast, pellets consisting solely of hydrophobic calcium stearate and the less alcohol soluble codeine phosphate showed ADD robustness. Furthermore, ethanol-robust coated pellets were developed by Rosiaux et al. [6] by adding small amounts of the hydrophilic guar gum to the hydrophobic ethylcellulose-based film coating.

However, to our knowledge no data are available regarding the development of matrix mini-tablets based on hydrophilic polymers which are able to feature both prolonged drug release and robustness against ADD. As a matter of fact, hydrophilic polymers are often insoluble in ethanol and are expected to be unaffected when administered together with alcohol [24].

2 AIMS AND OUTLINE

This work focuses on development, manufacturing, and characterization of oral matrix formulations intended to achieve robustness against alcohol-induced dose dumping (ADD).

For this purpose, theophylline has been chosen as a model drug, due to its narrow therapeutic index and increased solubility in dissolution media containing ethanol.

More specifically, the aims of this thesis were:

- to produce directly compressed matrix tablets based on HPMC as a rate-controlling polymer (RetaLac[®]), by using an uniaxial compaction simulator, and to analyse the influence of (i) tableting process (compression pressure and compression velocity) and (ii) alcohol in the dissolution media on *in-vitro* drug release, swelling, erosion and textural properties of the resulting matrices (Chapter 3.1)
- to study the suitability of xanthan gum (XG) as a rate-controlling polymer and alcohol-robust polymer in 8 mm tablets and 2 mm mini-tablets, where both polymer concentration and polymer particle size were varied in order to assess their influence on drug release and swelling behaviour in non-alcoholic and alcoholic media (Chapter 3.2)
- to produce a XG-based multiple-unit dosage form, by using wet extrusion as a manufacturing process, and investigate the suitability of different fillers as pore-blockers in the formulations, in order to slow the drug release and achieve alcohol-resistance (Chapter 3.3)
- to screen polymer candidates for the development of alcohol-resistant matrix mini-tablets and develop a test based on mixer torque rheometry for the characterisation of the polymer swelling in media with different concentrations of ethanol (Chapter 3.3)
- to study the influence of the matrix tablets dimensions on the drug release kinetics and drug release mechanism, either in dissolution media containing different volumes of ethanol (Chapter 3.4)

3 RESULTS AND DISCUSSION

3.1 Development of single-unit matrix tablets by using RetaLac[®] as swellable co-processed excipient

3.1.1 Introduction and Objectives

Cellulose ethers have been widely used in the preparation of hydrophilic matrix systems. In particular, hydroxypropyl methylcellulose (HPMC) is considered the polymer of choice in the development of oral controlled drug delivery systems [45-48, 53]. Since HPMC is soluble in water but practically insoluble in ethanol, it was chosen in this study for the production of directly compressed tablets, with the aim of tailoring alcohol-robust formulations.

The first aim of this work was to investigate the influence of (i) the tableting process, considering the following variables: tableting pressure and tableting speed; (ii) the presence of ethanol in the dissolution media on swelling, erosion and *in-vitro* drug release behaviour of HPMC- containing matrix tablets. For this purpose, a 2³ full factorial design of experiments (DoE) was performed and the resulting coefficient plots have been analysed. The formulations were directly compressed.

As model API, theophylline anhydrous was chosen. Commonly used as bronchodilator in the treatment of asthma and several respiratory diseases, this API is characterized by a narrow therapeutic index, which, in the case of formulation vulnerability against alcohol, can lead to critical side effects or even fatality [5].

As already mentioned above, HPMC was selected as a rate-controlling polymer, also due to the high drug loading which can be accommodated and the compatibility with most APIs [86-88]. However, because of the small particle size and the irregular particle shape, HPMC tends to be poorly flowable [89] and therefore not suitable for direct compression. Consequently, in this study a co-processed excipient consisting of HPMC 2208 and α -lactose monohydrate (50:50), known on the market as RetaLac[®] [90], was used in order to overcome this issue. To the best of our knowledge, RetaLac[®] has not been used yet with the aim of tailoring alcohol resistance.

Furthermore, this chapter will focus on the development of analytical methods suitable for the determination of the gel strength and the gel visualisation, after the hydration of the tablets in hydrous and hydro-alcoholic media. Several methods have been described in the literature, based on texture analysis [91-93], optical image analysis [94, 95] and nuclear magnetic resonance (NMR) microimaging [96, 97]. In this study, image and texture analysis were the methods of interest.

3.1.2 Formulation and Design of Experiments (DoE)

As can be seen in the scanning electron microscope (SEM) images (Figure 3), theophylline anhydrous (Figure 3A) showed tetrahedra-shaped crystals, where large particles could be found covered with smaller particles. This agglomeration phenomenon leads to reduced flow properties of the drug, thus causing tableting issues in particular when the powder is processed by direct compression [88]. The

co-processed excipient RetaLac[®] was therefore added to the formulation. RetaLac[®] consists of equal parts of HPMC (2208 type, nominal viscosity of 4000 mPa·s) and milled α -lactose monohydrate. It is produced by a specialized spray-agglomeration process [98], which generates spheroidal (Figure 3B) and porous (Figure 3C) particles, thus improving the flow properties of the blends.

The composition of the considered formulation is depicted in Table 28 (see section 5.2.1.1.2). Matrix tablets of 8 mm diameter were produced with a theophylline: RetaLac[®] ratio of 1:1, in order to achieve a high drug load in the formulations.

The influence of manufacturing variables and ethanol concentration in the medium on the dissolution performances of the HPMC-containing tablets was statistically analysed by design of experiments (DoE) (see Table 33 in section 5.2.2).

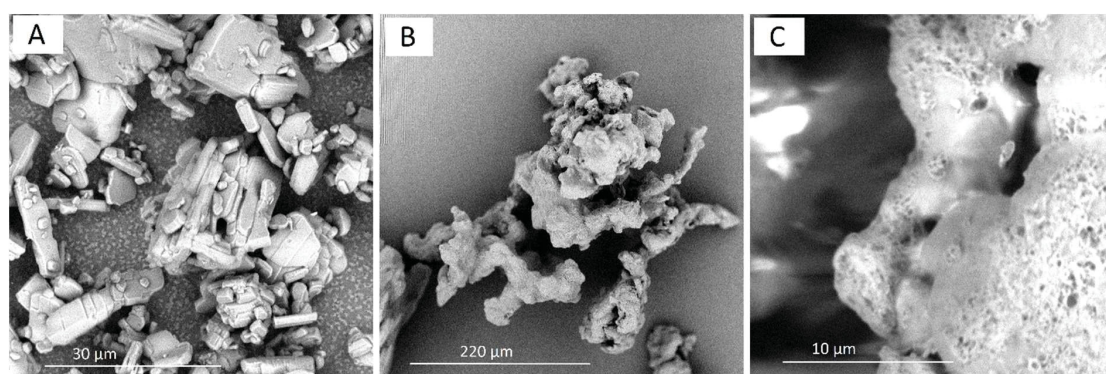


Figure 3: SEM images of (A) theophylline anhydrous and (B and C) RetaLac[®]

3.1.3 Mass variation, tensile strength and porosity

The produced tablets of 8 mm diameter were characterized in terms of mass, thickness, tensile strength and porosity. The results are depicted in Table 2. As can be seen, by increasing the compression pressure, the tensile strength increased 1.7 times for the tablets compressed at 10 rpm and 1.8 times for the tablets compressed at 50 rpm. Furthermore, when considering the formulations produced at the same compression pressure, the tensile strength decreased by increasing the compression speed. As a matter of fact, the tableability (tensile strength vs. compaction pressure) has already been shown to be speed dependent for many materials [99]. Indeed, the time dependency is related to a mechanism of consolidation and the higher the compaction speed, the lower the tensile strength [99]. The porosity was also affected by both compression pressure and speed: a porosity decrease of approximately 3 % was seen by tableting at higher compression pressure, while a slight porosity increase of less than 1 % was seen by increasing the compression speed.

Generally, it is believed that tablet porosity, as a result of the applied compression pressure, does not have a relevant impact on the release behavior of swellable matrices [60, 100]. As a matter of fact, the porosity of the hydrated matrices has been shown to be independent of the initial tablet porosity and consequently the compression pressure seems to have only a slight influence on the drug dissolution [60]. However, in formulations which contain low amounts of polymer and high amount of highly soluble additives, capillary forces may partially contribute to a faster water transport into the matrix, especially in the early phases of the dissolution testing [101].

Table 2: Mechanical properties of the produced tablets (8 mm diameter) depending on varied compression pressure and compression speed; mean \pm SD

Compression parameters		Weight [mg]	Thickness [mm]	Tensile strength	Porosity
Pressure [MPa]	Speed [rpm]	n = 20	n = 10	[MPa] n = 10	[%] n = 10
199	10	246.5 \pm 6.8	3.8 \pm 0.1	2.0 \pm 0.1	12.5 \pm 0.2
	50	261.1 \pm 9.1	4.0 \pm 0.1	1.6 \pm 0.0	13.2 \pm 0.3
398	10	254.3 \pm 9.4	3.7 \pm 0.1	3.4 \pm 0.1	8.9 \pm 0.2
	50	262.0 \pm 6.3	3.9 \pm 0.1	2.9 \pm 0.1	9.7 \pm 0.2

3.1.4 Dissolution

The *in-vitro* drug dissolution was performed on a modified version of the USP App. II. The phenomenon of tablet sticking on the vessel bottom, which lead to partial surface occlusion and therefore variability in dissolution kinetics, is already reported in the literature [102]. For instance, the occlusion of one face of a flat-faced tablet with an 8 mm diameter might lead to a surface area loss of approximately 29 %. To avoid this phenomenon, the tablets were incorporated inside home-manufactured stainless steel sinkers and then placed inside the vessel (see section 5.2.3.9). Preliminary studies (data not shown) showed that a higher reproducibility could be achieved by applying this dissolution setup.

The dissolution profiles of the RetaLac[®] tablets are depicted in Figure 4. The matrices maintained integrity over the entire dissolution time and did not show alcohol-induced dose dumping (ADD).

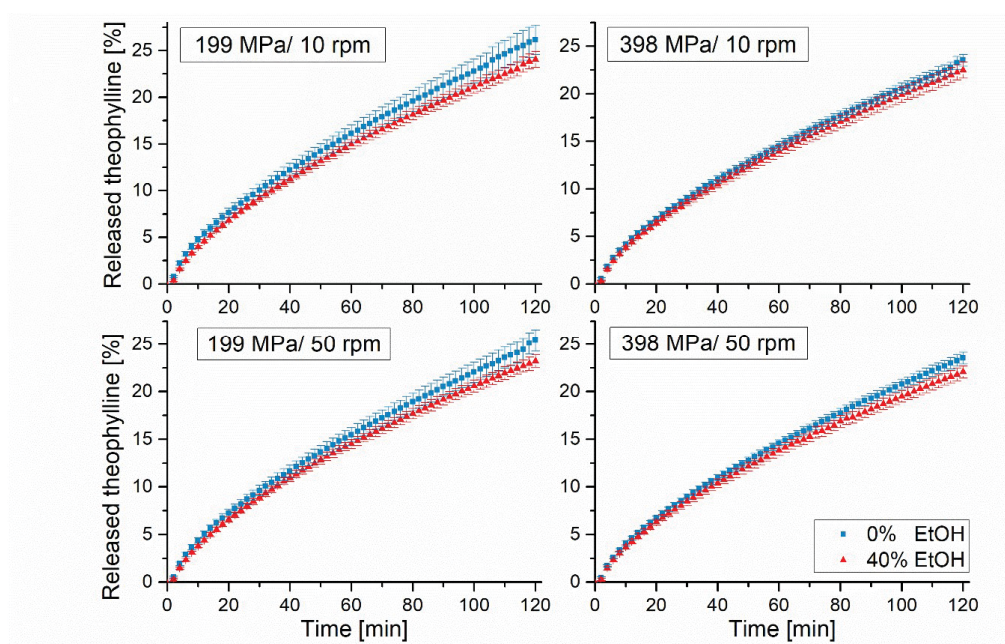


Figure 4: Dissolution profiles of the tablets produced at different compression pressure and speed, in hydrous (blue squares) and in hydro-alcoholic (red triangles) media; mean \pm SD, n = 6

As can be seen, the drug release was only slightly affected by the presence of alcohol and in particular, the dissolution of the API in alcohol was slightly slower than in the aqueous one. This effect was shown by the slightly lower values of the determined area under the curve (AUC) (Table 3). However, the calculated similarity factor f_2 resulted higher than 50 for all formulations, demonstrating that the RetaLac[®] matrices were robust to alcohol.

There are several authors who studied the impact of alcohol on HPMC matrices. Asare-Addo et al. [103], for instance, studied the dissolution behavior of directly compressed HPMC matrix tablets, which contained theophylline as API and the polyol maltitol as diluent. The authors reported that there was no failure of the matrices in 5-40 % ethanolic media (pH 1.2), despite the higher solubility of theophylline in alcohol. In the mentioned case, the robustness of the matrices against alcohol was attributed to the insolubility of maltitol in alcohol. Roberts et al. [54] reported that, due to the practically insolubility of HPMC in alcohol, a slower interaction of the polymer with the hydro-alcoholic media might occur, thus leading to the formation of a not uniform gel layer around the tablets and generating faster release of the model API acetylsalicylic acid in alcohol. According to the authors, the solubility of acetylsalicylic acid in hydrous and ethanolic media is intended to account for the different dissolution behavior. However, in the present studied the matrices did not show this phenomenon.

The solubility of theophylline monohydrate was determined at 37 °C in acidic media (0.1 N HCl, pH 1.2), which contained 0 % and 40 % ethanol (Figure 5). The solubility amounted respectively 13.46 mg/mL and 37.60 mg/mL, thus showing a 2.8-fold increase in 40 % ethanol. As a matter of fact, the presence of alcohol in the media lowers the dielectric constant and increases therefore the solubility of theophylline, which is predominantly neutral at pH 1.2 (pKa 8.8) [104]. However, in this case, since the drug release was slightly decreased in alcohol, other factors might have had a crucial role apart from the API solubility.

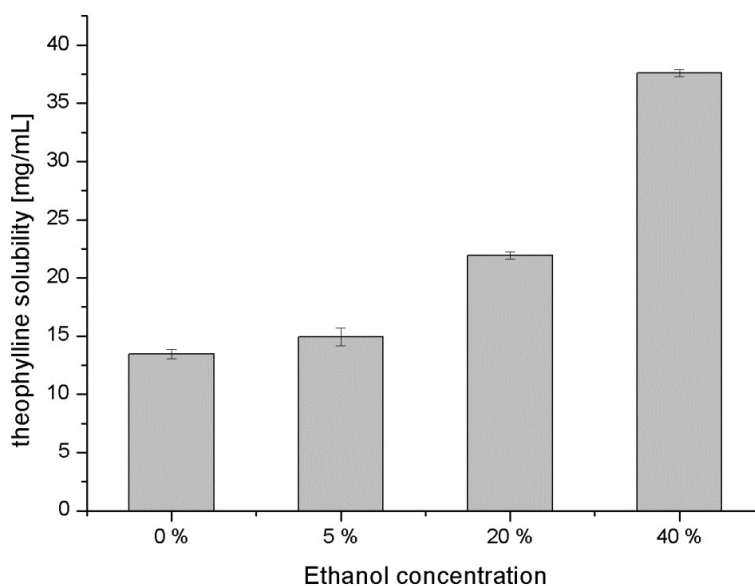


Figure 5: Theophylline solubility in 0.1 N HCl with 0, 5, 20 and 40 % (v/v) ethanol at 37 °C; the solubility values in 5 and 20 % ethanol will be of interest in chapters 3.2 and 3.3.

The α -lactose monohydrate itself, for instance, might have affected the drug release: as a matter of fact, the solubility of lactose decreases by increasing the amount of alcohol in the media, as reported by Bouchard et al. [105]. The authors determined solubility for lactose anhydrate in water and different alcoholic mixtures and the values amounted 0.29 ± 0.02 g/g in water and 0.064 ± 0.002 g/g in 37.5 % (w/w) alcohol (which corresponds to 44.7 % (v/v) alcohol). This drastic decrease of solubility in alcohol is assumed to decrease the formation of pores within the matrix gel layer and therefore to hinder, first, a fast medium penetration and drug solubilization, and second, a fast drug release.

Table 3: Calculated similarity factors f_2 (reference: dissolution data in 0 % ethanol, test: dissolution data in 40 % ethanol) and area under the curves (AUC) (mean \pm SD, n = 6)

Formulation	Similarity factor f_2	Area under the curve AUC [%·min]	
		0 % EtOH	40 % EtOH
199 MPa/10 rpm	88.9	1843.0 \pm 109.8	1693.2 \pm 56.5
398 MPa/10 rpm	96.9	1656.9 \pm 50.3	1591.3 \pm 61.9
199 MPa/50 rpm	91.1	1770.0 \pm 88.7	1646.1 \pm 52.6
398 MPa/50 rpm	93.8	1659.1 \pm 45.4	1563.9 \pm 56.3

In regard to the influence of the manufacturing process on the drug release, the matrices did not show to be significantly affected. By increasing the compression pressure and keeping the compression speed constant, the AUC decreased of only 10 % approximately, and this effect was shown in both media (Table 3). Minimal influence was seen by varying the compression speed and maintaining the compression pressure constant (Table 3). These results would support the theory of Velasco et al. [60], demonstrating how changes in the initial porosities may lead to minimal effect on dissolution behavior from HPMC tablets.

3.1.5 Swelling analysis

Image analysis was used as tool to investigate the swelling of the tablets, in particular to evaluate the formation of the gel layer in the two media and the increase of the tablet dimensions in both axial and radial directions. Since all formulations showed similar drug release profiles, the tablets compressed at 199 MPa and 10 rpm were evaluated as representative formulation.

The normalized tablet dimensions are depicted in Figure 6, after 1 h and 2 h dissolution testing in 0.1 N HCl with 40 % and without ethanol. The normalized axial and radial dimensions were calculated as the ratio of the axial (A_t/A_0) or radial (R_t/R_0) length after 1 h and 2 h swelling and the initial axial and radial length at $t=0$.

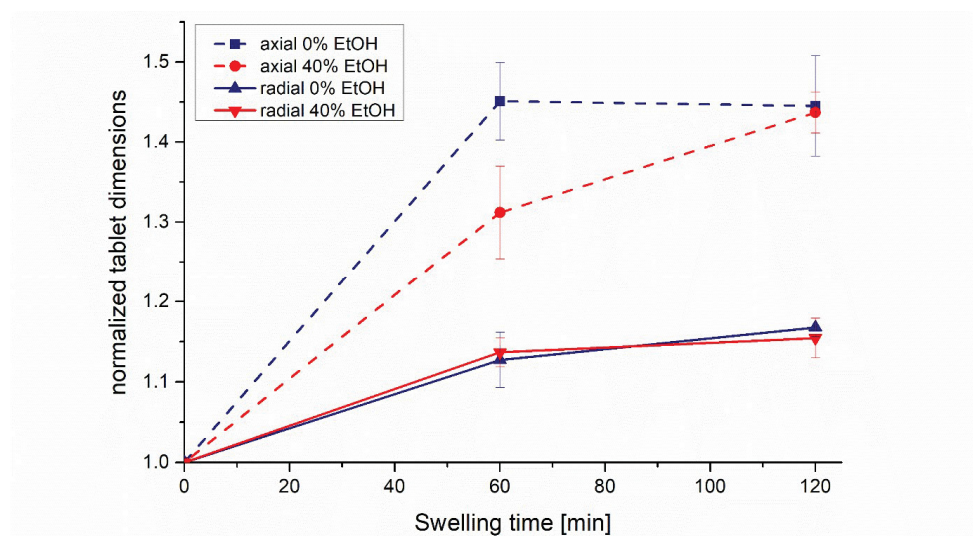


Figure 6: Normalized tablet dimensions after 1 h and 2 h dissolution in 0 % and 40 % alcohol; the continuous lines represent the radial swelling and the dash lines the axial swelling; mean \pm SD (n= 3)

It can be noticed that the RetaLac[®] tablets underwent swelling in both media, increasing the tablet dimensions in both axial and radial directions. As in accordance to other studies [54, 94, 106-108], the matrix swelling was anisotropic, where the axial swelling resulted greater than the radial one. One possible hypothesis for the higher expansion in the axial plane than in the radial one is the release of the tablet compression forces during dissolution [94].

Interestingly, the normalized radial swelling was similar in the two media and amounted 1.17 ± 0.01 in 0 % EtOH and 1.15 ± 0.02 in 40 % EtOH after 2 h. The normalized axial swelling was slightly higher without alcohol after 1 h dissolution (1.45 ± 0.05 in 0 % ethanol vs 1.31 ± 0.06 in 40 % ethanol) and then, after 2 h, showed similar values of 1.45 ± 0.06 and 1.44 ± 0.03 respectively. The slightly lower axial swelling in alcohol might be due to a slow initial interaction between HPMC and ethanol. However, in this study, a slower interaction polymer-alcohol did not cause faster drug release in alcohol in the initial phase (Figure 4).

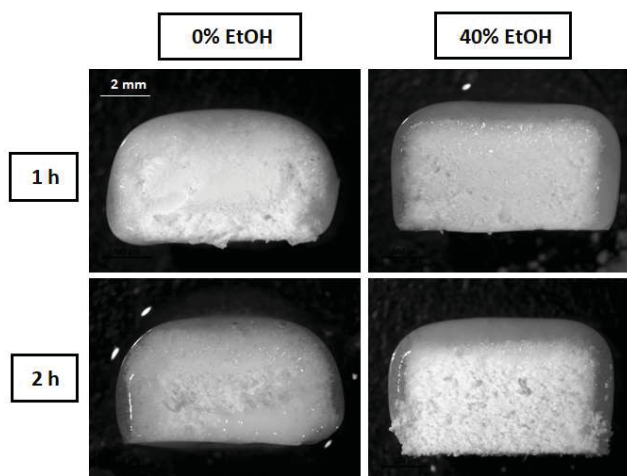


Figure 7: Images of the dynamic swelling of RetaLac[®]-based tablets (compressed at 199 MPa and 10 rpm) after 1 h and 2 h dissolution in 0 % and 40 % ethanol

As can be seen in Figure 7, the tablets in media without ethanol underwent erosion to a higher extent and no defined gel layer could be visualized. Differently, the tablets swollen in hydro-alcoholic media were more intact and showed a well-defined boundary between the dry core of the matrix and the gel layer. Interestingly, the gel layer thickness in the radial directions was comparable to that developed in the axial one, as already reported in the literature for HPMC- containing tablets [106]. In addition, Roberts et al. [54] reported how, at low shear rates, the viscosity of HPMC (4000 mPa·s type) dispersions increased by increasing the percentage of ethanol up to 40 % (v/v) in the dispersing liquid, suggesting therefore the formation of a much stronger gel layer. The authors considered that the interaction between HPMC and alcoholic solutions is greater than with water, due to the formation of hydrogen bonding and van der Waals forces.

The evaluation of the gel strength was performed by using a texture analyser (TA). The tablets were first allowed to hydrate for 2 h in the different media and then force-displacement curves associated with the TA probe penetration inside the swollen tablets were recorded. The results are depicted in Figure 8. Three regions of interest could be recognized: the first region is characterized by a gradual increase in the penetration force, the second region by a slight force drop and the third one by a sudden force increase characterized by higher curve slopes. Figure 9, which is based on the work of Gao et al. [94] and Melia et al. [109], represents the development of a gel structure during swelling and could help clarifying the findings reported above. According to the authors, as the medium diffuses into the matrices, a water concentration profile is generated, where C_{w1} represents the lowest water concentration (3-5 % w/w) and, therefore, defines the true water penetration front. Moreover, the presence of two additional fronts is hypothesised: the phase transition front, which corresponds to the region where the polymer in a glassy state is converted in a rubbery state (C_{w2}), and the apparent gel front (C_{w3}).

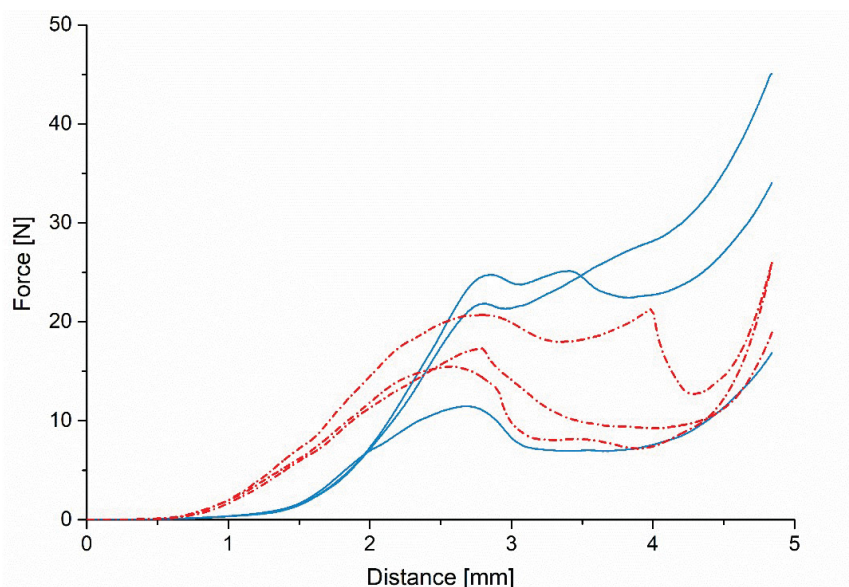


Figure 8: Gel strength by texture analysis in 0 % EtOH (continuous line in blue) and 40 % EtOH (dashed line in red); the single curves are here depicted, $n = 3$. In the box, the magnification of the first points of the curves (from 0 mm to 2 mm probe distance) are represented (samples: tablets compressed at 199 MPa and 10 rpm).

It can be assumed that force changes, which were detected by the TA probe, might have corresponded to the encountering of the reported fronts during the probe penetration within the matrix. Interesting for this study was, however, the first region. The “work of penetration”, i.e. the work done by the probe on the tablet, was calculated and was determined by the area under the force-displacement curve between 0.0 and 2.0 mm of probe penetration in the tablet. 0 mm and 2 mm were selected as a standardized distance for a meaningful comparison of the textural profiles.

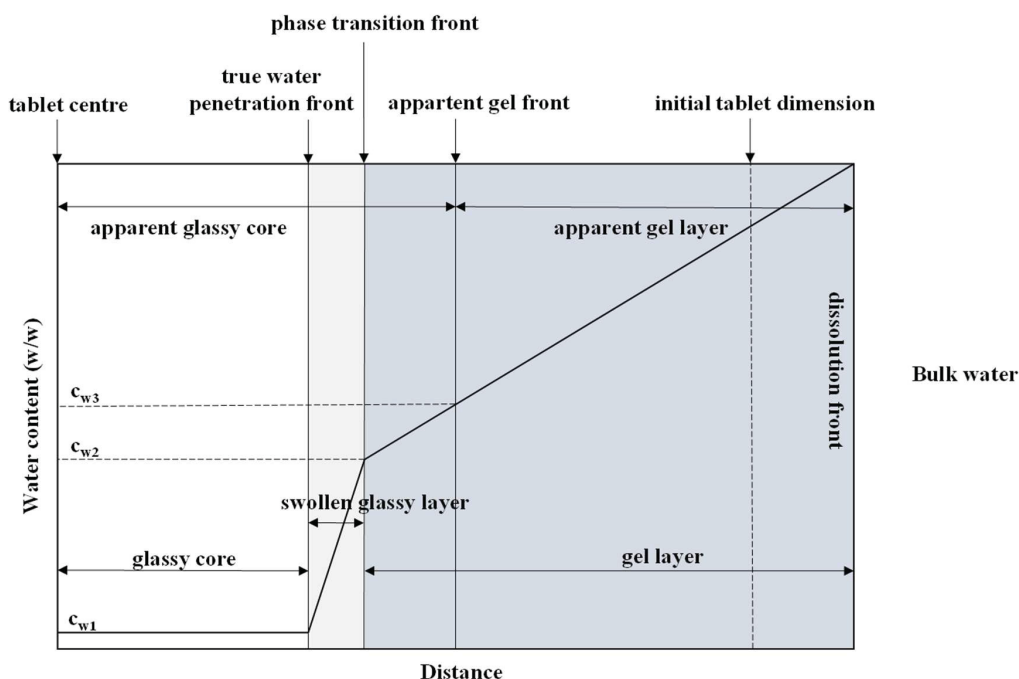


Figure 9: Schema of the structure of a HPMC swollen tablet in one direction (adapted from Gao et al. [94])

The work of penetration values resulted very different in the two media: if the work of penetration amounted 2.47 ± 0.12 N·mm in media without alcohol, by adding 40 % ethanol this value was increased up to 7.05 ± 0.78 N·mm. These results support the hypothesis that a more viscous and stronger gel layer was obtained for HPMC matrix tablets in hydro-alcoholic media and are in agreement with the findings of Missaghi et al. [46] and Levina et al. [53].

3.1.6 Relative swelling, dissolution media uptake and erosion

Gravimetric studies were performed to determine relative swelling (RS), dissolution media uptake (DMU) and mass loss (ML) values of the tablets dissolved in 0 % and 40 % ethanol for 2 h (see 5.2.3.11). The results are depicted in Figure 10, Figure 11 and Figure 12 respectively.

Slightly similar values were measured in regard to the RS in both media and amounted approximately 1.7. More interesting were, however, the DMU and ML results. DMU was significantly higher in aqueous media than in hydro-alcoholic ones in regard to all formulations ($p < 0.05$) (Figure 11).

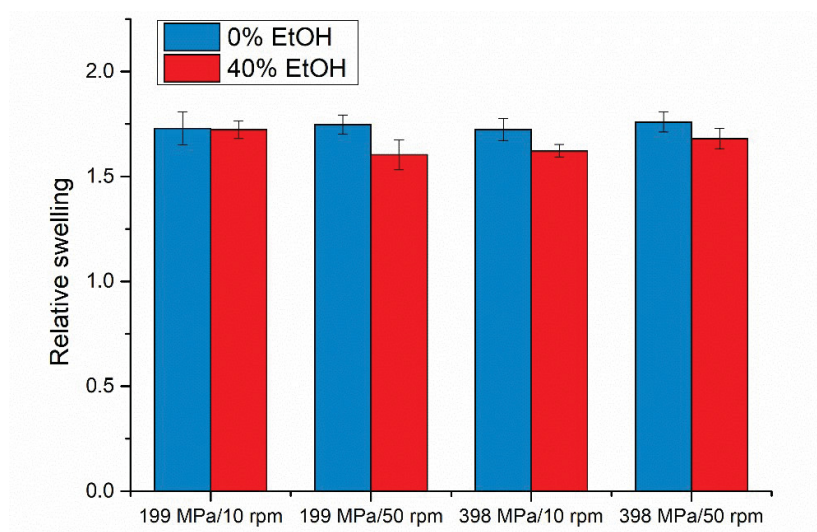


Figure 10: Relative swelling after 2 h dissolution, mean \pm SD (n= 3)

Nevertheless, no significant differences could be detected between the formulations compressed at varied compression pressure and speed. Apart from the high hydrophilicity of HPMC, the higher DMU in hydrous media could be also attributed to the presence of lactose in the RetaLac[®] excipient. Lactose is water soluble and after dissolving upon water ingress into the matrix, is released mainly by the process of diffusion, thus forming porous channels [87, 110, 111]. The increase of water content leads to the dilution of the gel layer and therefore to a weaker gel structure, causing faster erosion and drug diffusion [87]. The ML results are depicted in Figure 12 and may support this hypothesis.

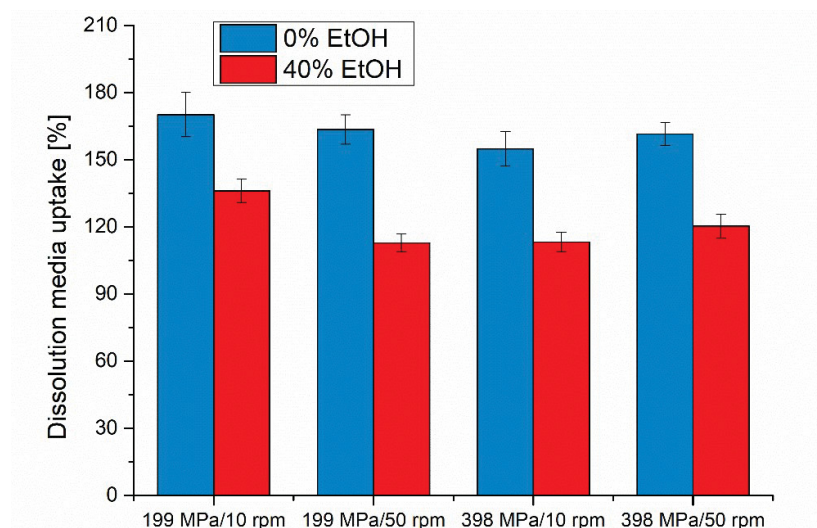


Figure 11: Dissolution media uptake after 2 h dissolution, mean \pm SD (n= 3)

As can be noticed, lower ML values were determined for formulations dissolved in 40 % ethanol. The low lactose solubility in alcohol together with the formation of a more viscous HPMC gel layer may have in this way hindered a fast release of theophylline, which is very soluble in ethanol.

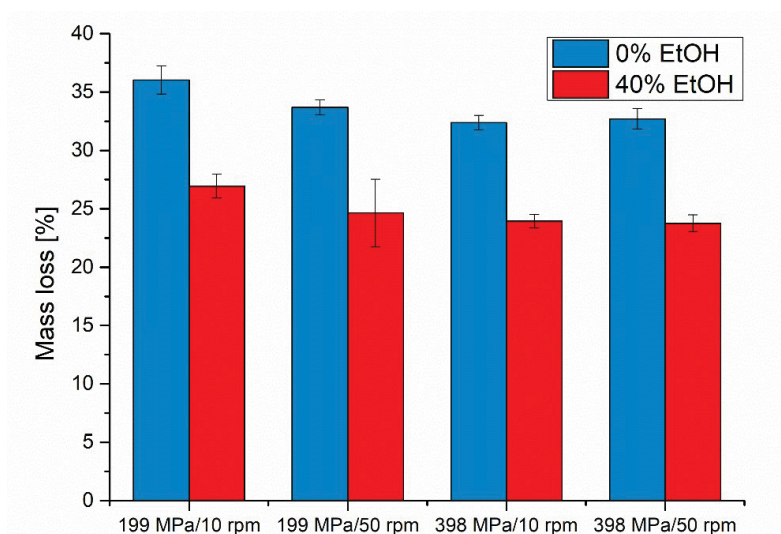


Figure 12: Mass loss after 2 h dissolution, mean ± SD (n=3)

3.1.7 Statistical evaluation

The combination of the factor settings and the results for each response are summarized in Table 4.

Table 4: Values of the factors and responses of the 2^3 full factorial design; mean, n = 3; factors: P = compression pressure, Speed = compression speed, EtOH = ethanol in media; responses: $AUC_{120\text{ min}}$ = area under the curve after 2 h dissolution, RS = relative swelling, DMU = dissolution media uptake, ML = mass loss

Exp. No.	Comp. pressure (P) [MPa]	Comp. speed (Speed) [rpm]	Ethanol (EtOH) [%]	Area under the curve (AUC) [% · min]	Relative swelling (RS)	Dissolution media uptake (DMU) [%]	Mass loss (ML) [%]
1	199	10	0	1843.0 ± 109.8	1.7 ± 0.1	170.2 ± 9.9	36.0 ± 1.2
2	398	10	0	1656.9 ± 50.3	1.7 ± 0.1	154.9 ± 7.8	32.4 ± 0.6
3	199	50	0	1770.0 ± 88.7	1.7 ± 0.0	163.5 ± 6.6	33.7 ± 0.6
4	398	50	0	1659.1 ± 45.4	1.8 ± 0.0	161.5 ± 5.1	32.7 ± 0.9
5	199	10	40	1693.2 ± 56.5	1.7 ± 0.0	136.1 ± 5.3	26.9 ± 1.0
6	398	10	40	1591.3 ± 61.9	1.6 ± 0.0	113.2 ± 4.5	24.0 ± 0.6
7	199	50	40	1646.1 ± 52.6	1.6 ± 0.1	112.8 ± 4.0	24.7 ± 2.9
8	398	50	40	1563.9 ± 56.3	1.7 ± 0.1	120.3 ± 5.3	23.8 ± 0.7

To interpret the statistical power of the performed model, R^2 and Q^2 as model indicators were analyzed and presented as summary of fit plot in Figure 13 [112], whereas the coefficient of determination (R^2) defines how well the regression model can fit the model, the coefficient of prediction (Q^2) describes the goodness of prediction and should be higher than 0.5 for a model which can be considered good [113]. The summary of fit plot pointed to a good model in regard to DMU, ML and released theophylline (AUC), with R^2 values of 0.983, 0.999, 0.947 respectively and Q^2 of 0.876, 0.994, and

0.787. However, the response RS showed a high R^2 of 0.870 but a lack of predictive power with Q^2 of 0.072.

The influence of the investigated factors on the responses is reflected in coefficient plots, which are depicted in Figure 14. The relative swelling resulted to be unaffected by changes in the process variables and, during the dissolution, by the presence of alcohol in the media (Figure 14). Also the interaction between the factors were not significant.

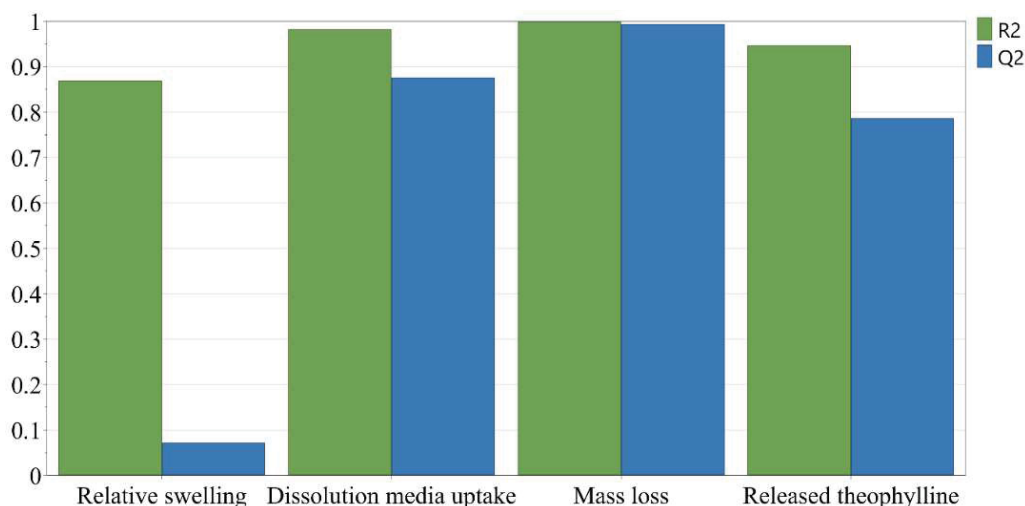


Figure 13: Summary of fit plot for the optimized linear regression model for the responses relative swelling, dissolution media uptake, mass loss (N= 8, DF= 3) and released theophylline (N= 8, DF= 4)

In regard to the response DMU, ethanol resulted to significantly affect it. Thus, by increasing the ethanol concentration in the dissolution medium, lower DMU values were obtained. The compression pressure, speed and ethanol concentration had a negative effect on the ML, where the presence of ethanol had a much greater influence on ML than the other two factors. Also the interaction between compression pressure and ethanol concentration resulted significant.

Finally, the amount of released theophylline during dissolution testing, here represented by the area under the curve (AUC_{120 min}) values, showed to be significantly affected by the compression pressure and ethanol, where both factors led to a negative effect. Interactions between the factors were not significant.

As can be noticed, although the f_2 values were higher than 50 (Table 3), the DoE has shown that alcohol negatively affected the drug release.

As stated by Jedinger et al. [24], “a quantification of the dose-dumping effect is still an open issue without a regulatory decisional framework”, as well as a quantification of a slower drug release effect due to the presence of alcohol in the dissolution media.

Based on this study, beside the similarity factor, the evaluation of an additional strategy should be performed in order to better understand the dissolution behavior of a dosage form in presence of ethanolic media.

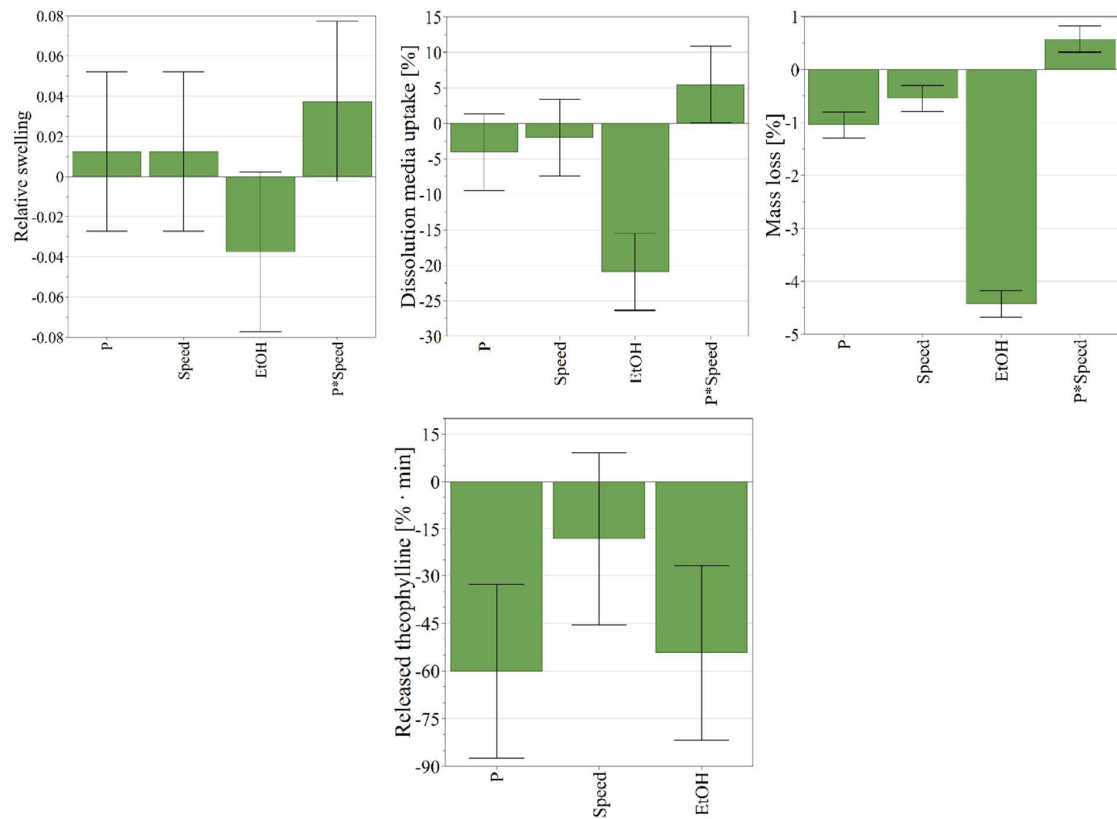


Figure 14: Coefficient plots for relative swelling, dissolution media uptake, mass loss and released theophylline; factors: compression pressure (P), compression speed (Speed), ethanol concentration in the media (EtOH); $\alpha = 0.05$

3.1.8 Summary

Matrix tablets based on theophylline as model API and RetaLac[®], a co-processed excipient made of HPMC K4M and α -lactose monohydrate (1:1), were successfully manufactured by using an uniaxial compaction simulator. A 2^3 full factorial design was performed, where the tableting pressure was varied from 199 MPa to 398 MPa, the simulator speed from 10 rpm to 50 rpm, and afterwards the ethanol concentration was varied from 0 % up to 40 % (v/v) in the dissolution media.

The tablets were first characterized in terms of mechanical properties, as tensile strength and porosity: a slightly higher tensile strength was measured for tablets compressed at higher tableting pressure, and generally, the higher the compression speed the lower the tensile strength. Slightly lower porosity values were in addition determined for the formulation compressed at higher compression pressure.

The influence of the manufacturing process on the tablets dissolution behaviour in acidic media with 0 % and 40 % ethanol was investigated. No alcohol-induced dose dumping occurred, all formulations underwent swelling and showed similar dissolution profiles in both media, with similarity factors $f_2 \gg 50$ and only minimal influences of the manufacturing process could be detected. However, the coefficient plots of the performed DoE showed that alcohol negatively influenced the drug release, indicating that a lower amount of drug was released in 40 % ethanol compared to the hydrous media. Based on these study, the similarity factor f_2 should not be evaluated as the only indicator to assess alcohol-robustness of a drug formulation. An additional strategy should be considered in order to acquire further data at the early stage of drug product development.

Furthermore, swelling, media uptake and erosion of the tablets during dissolution were studied by gravimetrical measurements and image analysis. The tablets swelled anisotropically, where the axial swelling was greater than the radial one. Interestingly, similar radial swelling could be seen in both media, whereas the axial swelling showed slightly different results: after the first hour of dissolution, a slightly higher axial swelling was seen in 0 % ethanol, whereas after the second hour of dissolution more similar results were obtained. Furthermore, the matrices underwent erosion to a higher extent in 0 % alcohol, fact which was confirmed by the higher mass loss values. Texture analysis (TA) was used as tool in order to investigate the gel layer strength in the two media. Thus, if in 40 % a well-defined boundary between the gel layer and the dry core could be visualized, none differentiation could be observed in 0 % alcohol. Interestingly, higher forces had to be applied by the TA probe in order to penetrate the tablets swollen in alcohol, thus demonstrating the formation of a stronger gel layer in this medium. These results were in agreement with Roberts et al. [54], who assumed that in alcohol a stronger interaction with HPMC may take place due to the formation of hydrogen bonding and van der Waals forces. This fact was also confirmed by the lower DMU: as a matter of fact, a stronger gel might have slowed the entry of dissolution medium within the matrix and consequently reduced the dissolution of the drug in the testing media.

3.2 From tablets to mini-tablets: determination of critical attributes to tailor ADD-resistant formulations based on xanthan gum¹

3.2.1 Introduction and Objectives

The development of alcohol resistant multiparticulate dosage forms has become challenging in the last few years. As a matter of fact, multiple unit dosage forms are characterized by a significantly increased surface to volume ratio in comparison to monolithic dosage forms and may therefore show a higher vulnerability against drug release modifications when alcohol is present in the dissolution media [114].

In this study, tablets of 8 mm and mini-tablets of 2 mm were compared in terms of dissolution performance and alcohol resistance, where xanthan gum (XG) was formulated as rate-controlling polymer and theophylline monohydrate as model API. XG was chosen due to its practically insolubility in alcohol [115] and its ability to prevent any initial burst effect in the drug release from hydrophilic matrices [116].

Several authors reported the influence of the polymer particle size on the dissolution rate from matrix tablets [47, 60, 117-119], in particular when the dimensions of the dosage form had been reduced [88]. For these purposes, two particle size fractions of XG were selected, in particular, Xantural[®] 75 and Xantural[®] 180, which are commercially available polymers of pharmaceutical grade. Thus, the particle size of the rate-controlling polymer is a critical attribute, which has to be taken into consideration in the development of hydrophilic matrices. As a matter of fact, it is related to the drug release, since it can affect the entry of the medium into the matrix and consequently the formation of the gel layer which prevents the exit of the drug [47].

It has been shown how the impact of particle size on the dissolution rate is minimized when higher concentration of polymer is used in the formulation [119]. Therefore, in this study, a 2³ full factorial design was performed considering as factors, apart from the polymer particle size (from 75 µm to 180 µm), the XG concentration, which was varied from 30 % (w/w) to 60 % (w/w), and the amount of ethanol in the dissolution media (from 0 to 40 % v/v), in order to assess their influence on the drug release performance and swelling on 8 mm matrix tablets and 2 mm mini-tablets.

3.2.2 Xanthan gum as matrix polymer

Xanthan gum (XG) is a high-molecular mass anionic polymer, gained by the fermentation of carbohydrates by the bacteria *Xantomonas campestris*. Naturally, the bacterium produces the gum in the exocellular compartment, on the cell wall surface, by an enzymatic process and the gum is subsequently released in order to stick to leaves of cabbage-like plants [120, 121]. Commercially,

¹ Results of this chapter have been published in the original paper “*Xanthan gum as a rate-controlling polymer for the development of alcohol resistant matrix tablets and mini-tablets*” (see section List of Publications and Contributions)

xanthan gum is obtained by a multi-step inoculum preparation, then fermentation, pasteurisation and product recovery by alcohol precipitation. After removing the alcohol, the precipitated product is dried, milled, tested and packaged [121]. XG is a polysaccharide and consists of five sugar residues: two glucose units, two mannose units and one glucuronic acid [122, 123] (Figure 15).

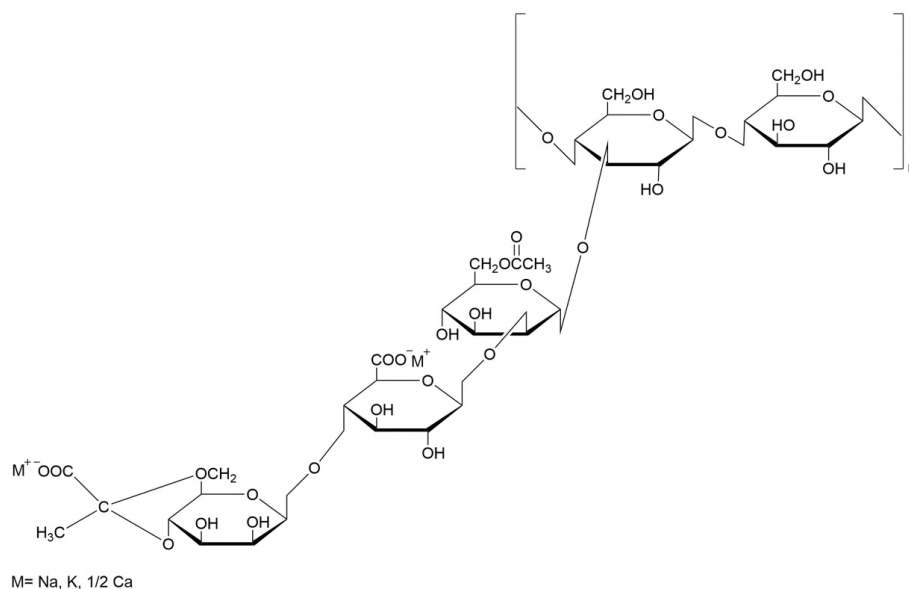


Figure 15: Chemical structure of xanthan gum

Since the polymer backbone contains 1,4-linked β -D-glucose, XG has similar structure to cellulose. However it has trisaccharides side chains (with one glucuronic acid between two substituted mannose units) on alternating anhydroglucose units, which distinguish XG to common cellulose. Once the polymer comes in contact to water, it hydrates rapidly and forms gels. It has been shown that low concentrations of XG lead to highly viscous solutions with shear-thinning properties. For this reason, XG has been widely formulated in food and pharmaceutical products as thickener, stabilizer and emulsifier [120]. Moreover, it has been also employed in the production of solid oral dosage forms in order to tailor controlled drug release [120, 124]. The pharmaceutical grade Xantural[®], manufactured by CP Kelco, met the requirements of USP/NF for pharmaceutical excipients, the Ph. Eur. and the JPE [121]. Furthermore, XG has been classified as generally recognized as safe (GRAS) excipient by the FDA.

Compared to the widely used HPMC, XG offers some advantages, in particular with regard to the production of hydrophilic matrix systems. Talukdar et al. [125], for instance, undertook a comparative investigation to evaluate the performance of XG and HPMC as hydrophilic matrix-forming polymers in regard to compaction properties and *in-vitro* drug release. The authors reported that compaction characteristics were similar within the two polymers, however, in regard to the drug release, XG showed (i) higher drug-retarding ability, (ii) did not lead to initial burst release due to the quick swelling and (iii) tailored zero-order release kinetics [125]. These properties were therefore considered beneficial for a BCS class 1 compound [113], as theophylline. However, the drug release from XG based formulation was influenced by the ionic strength of the medium [61]. Nevertheless, the authors

suggested that this ionic strength dependency should not be seen as a complete failure of XG to control the dissolution [125].

Few works reported the usage of XG to tailor alcohol resistant formulations. Traynor et al. [51] referred to the robustness against alcohol 40 % (v/v) of a commercially available and xanthan gum-based formulation, i.e. Tridural™ extended release tablets (Labopharm Inc., Laval, Québec, Canada), which was incorporating tramadol hydrochloride as drug substance. It consisted of a tablet core made of Contramid®, a cross-linked high-amylose starch, and tramadol hydrochloride, which was surrounded by a Kollidon® SR (spray dried excipient of 80 % polyvinylacetate and 20 % polyvinylpyrrolidone K30)/XG/tramadol coating matrix. The coating was intended to release the drug rapidly, yet in a controlled way, to allow an early pharmacological onset, while the core provided a zero-order drug release for sustained effect [126]. The authors referred to the insolubility of XG, Kollidon® SR and Contramid to explain the alcohol resistance of Tridural™ tablets. More recently, Jedinger et al. [85] developed pellets prepared via an advanced continuous one-step HME, where the drug antipyrine was fed as solution into different molten matrix material, among which XG. It was reported that xanthan pellets swelled and did not dissolve. However, due to their high specific surface area, the pellets did not remain intact during dissolution and released the drug very fast, within 30 min. Therefore this formulation was discharged and not tested further in alcohol.

To our knowledge, no single- and multiple-unit oral dosage forms based on XG as rate-controlling polymer have been tested in alcohol yet. In order to better study the alcohol vulnerability/ robustness of XG, no other polymer was added in the formulations.

3.2.3 Properties of the starting material

The particle size distribution of theophylline and the two size fractions of XG is shown in Figure 16.

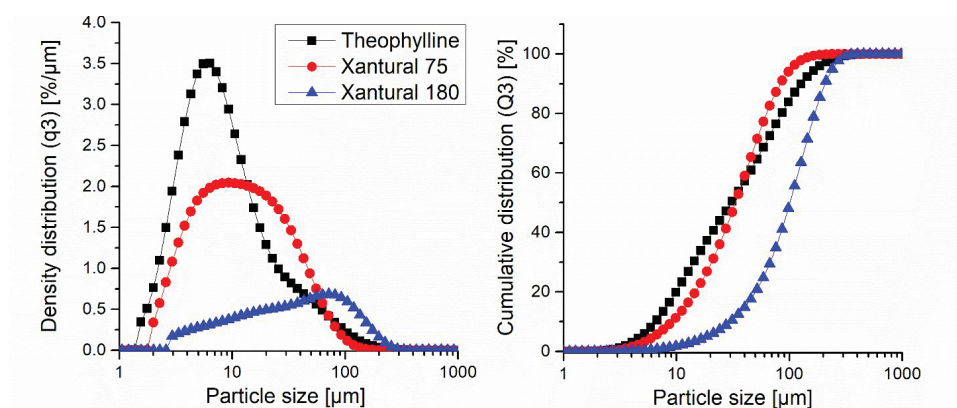


Figure 16: Density distribution (q3) (left) and cumulative distribution Q3 (right) of the starting material (mean ± SD, n = 3)

The x_{10} , x_{50} and x_{90} amounted 6.5 μm, 30.5 μm and 127.0 μm for theophylline, 9.2 μm, 33.2 μm and 83.3 μm for Xantural® 75, 30.0 μm, 101.3 μm and 206.6 μm for Xantural® 180. As can be noticed, the median particle size of theophylline and XG 75 were similar, whereas XG 180 showed higher values. The high x_{90} of theophylline monohydrate can be attributed to the formation of large agglomerates (Figure 17a). In addition, the density distribution (Figure 16) of theophylline depicts a shoulder

corresponding to larger particle sizes, next to a sharper peak, whereas the two Xantural[®] fractions showed broad particle size distributions. Approximately round shaped XG particles were seen at the SEM (Figure 17b-c), a property which might improve the powder flowability and therefore lead to a better processability during compression, in particular during compression of mini-tablets [127].

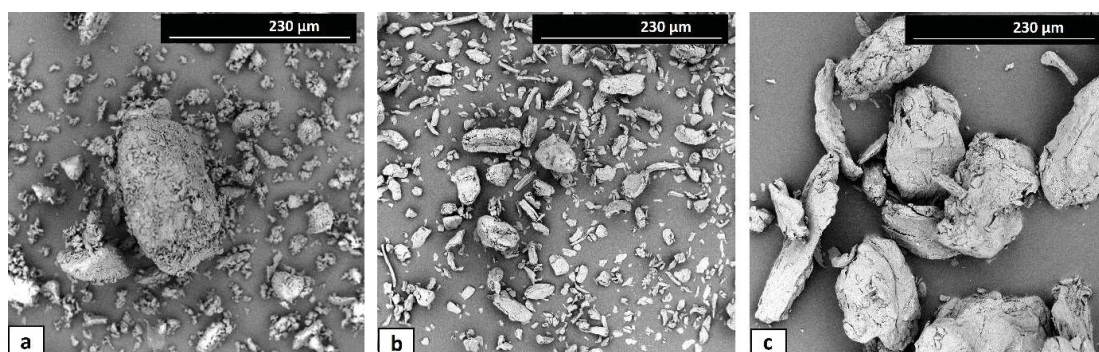


Figure 17: Scanning electron microscope (SEM) images of (a) theophylline monohydrate (b) Xantural[®] 75 and (c) Xantural[®] 180 (used by courtesy of the International Journal of Pharmaceutics, Elsevier [74])

3.2.4 Tablets mechanical properties

The mixtures depicted in Table 29 were directly compressed into 8 mm tablets (single-unit dosage form, “S”) and 2 mm mini-tablets (multiple-unit dosage form, “M”) (see section 5.2.1.1.3) and the tablets mechanical properties were determined.

Table 5: Mass, thickness, tensile strength and porosity values of the XG formulations; 8 mm tablets: mean \pm SD, n = 6; 2 mm mini-tablets: mean \pm SD, n = 10

Formulation	Diameter [mm]	Mass [mg]	Thickness [mm]	Tensile strength [MPa]	Porosity [%]
30% XG 75	8	150.3 \pm 0.9	2.16 \pm 0.1	3.1 \pm 0.2	7.7 \pm 0.2
	2	6.36 \pm 0.33	1.95 \pm 0.03	1.2 \pm 0.5	15.7 \pm 1.9
30% XG 180	8	151.6 \pm 0.6	2.19 \pm 0.01	2.0 \pm 0.1	7.7 \pm 0.3
	2	6.24 \pm 0.17	1.89 \pm 0.03	0.7 \pm 0.3	16.2 \pm 2.1
60% XG 75	8	150.7 \pm 1.0	2.23 \pm 0.01	2.9 \pm 0.1	11.4 \pm 0.3
	2	6.36 \pm 0.21	2.03 \pm 0.04	1.1 \pm 0.2	21.7 \pm 2.4
60% XG 180	8	149.4 \pm 1.1	2.24 \pm 0.01	1.6 \pm 0.1	12.4 \pm 0.3
	2	6.13 \pm 0.16	1.97 \pm 0.05	0.8 \pm 0.3	21.1 \pm 2.1

The mean tensile strength of larger tablets ranged from 1.6 MPa to 3.1 MPa (Table 5). By decreasing the fraction and the particle size of XG, slightly harder tablets were obtained. This phenomenon is explainable by a probable higher specific surface area and therefore a higher available inter-particulate bonding area. Moreover, an increase of the XG fraction led to slightly higher porosities due to the elastic recovery of the polymer (Table 5).

The mini-tablets were characterized by comparable tensile strengths within the batches, with mean values ranging from 0.7 MPa to 1.3 MPa. The porosity resulted higher for the mini-tablets than the 8 mm tablets, due to the lower compression pressures which could be applied. In addition, slightly higher porosity values were calculated with higher fraction of XG.

Mohamed et al. [128] stated that a pore which might be considered small in large tablets may constitute a high proportion of the overall volume within a mini-tablet. Consequently, the porosity may have a significant impact on the dissolution behaviour, when the diameter of the tablet is decreased from 8 mm to 2 mm.

3.2.5 In-vitro drug release

As in chapter 3.1, the dissolution test was performed in a modified version of the USP App. II with the home-manufactured sinkers to avoid the phenomenon of the tablet sticking. The dissolution profiles of 8 mm matrix tablets in alcoholic and non-alcoholic media are depicted in Figure 18.

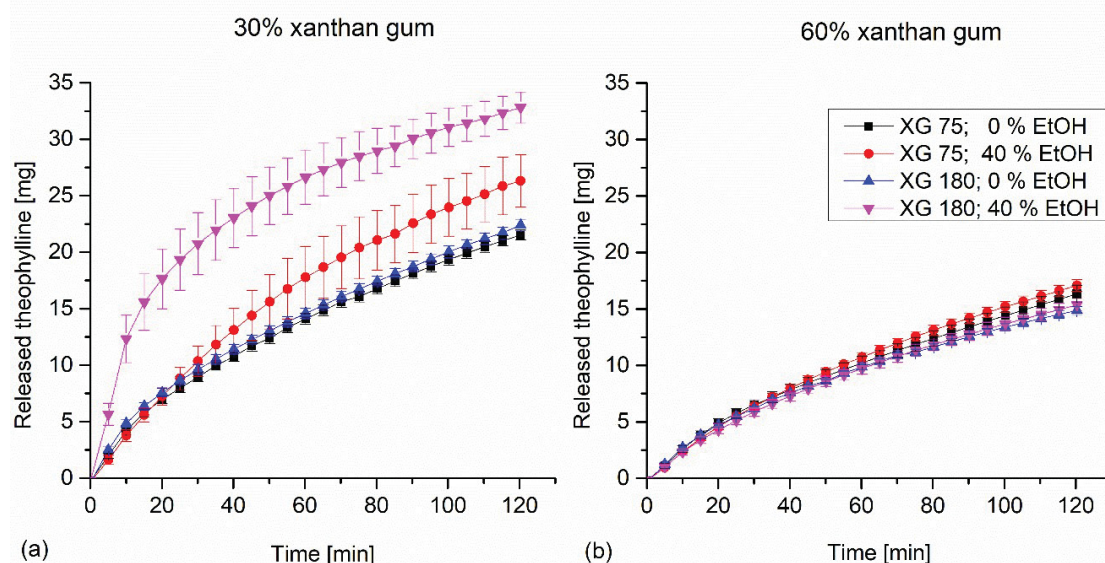


Figure 18: Influence of alcohol and XG particle size on drug release from 8 mm tablets with (a) 30 % XG (102.8 mg API/ tablet) and (b) 60 % XG (57.8 mg API/ tablet); 900 mL 0.1 N HCl with 0 % and 40 % ethanol; USP App. II (paddle, 50 rpm) with sinkers, $37 \pm 0.5^\circ \text{C}$, mean \pm SD, $n = 3$; for the formulation 30% XG 180 in ethanol mean \pm SD, $n = 6$; UV detection at $\lambda = 271 \text{ nm}$ (used by courtesy of the International Journal of Pharmaceutics, Elsevier [74])

All formulations stayed intact and none showed alcohol-induced dose dumping (ADD). However, in alcohol, the coarse fraction of XG 180 at low concentration (S-30% XG180) led to significantly higher amount of drug release in comparison to tablets containing the finer fraction XG 75 (S-30% XG75).

As a matter of fact, after 10 min, 12.3 mg drug were detected in 40 % alcohol, whereas in aqueous media only 4.8 mg drug were released. The similarity factor, which was calculated by comparing these two dissolution profiles in 0 % and 40 % alcohol, amounted 48.3 ($f_2 < 50$), indicating a not similar dissolution behaviour. A risk of dose dumping was therefore recognized. In this case, the 2.8-fold higher solubility of theophylline in 40 % alcohol (Figure 5) might have significantly affected the dissolution of S-30% XG 180. However, once the concentration of XG was increased from 30 % up to 60 %, the effect of the drug solubility and XG particle size appeared to be negligible. As a matter of fact, dissolution profiles with similarity factors of 97.1 and 99.2 ($f_2 > 50$) were determined for the formulations S-60% XG75 and S-60% XG180 respectively, showing that similar profiles could be achieved with both XG particle sizes. Interestingly, the formulations with low polymer content but finer XG particle size (S-30% XG75) were less affected by alcohol and showed more similar results in the two media ($f_2 = 72.4$). The standard deviation values were however higher in presence of alcohol, thus indicating a probable inhomogeneity of the gel layer formed around the tablets.

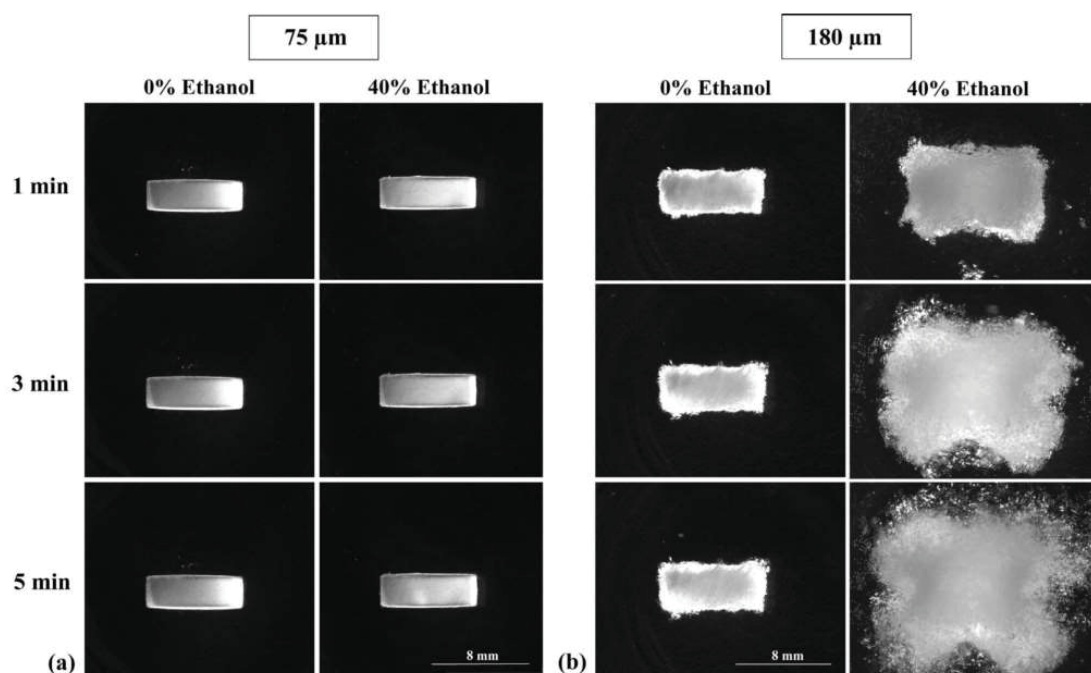


Figure 19: Images of the 8 mm tablets (a) S-30% XG180 and (b) S-30% XG75, acquired using image analysis at 1 min, 3 min and 5 min after coming in contact with 0 % and 40 % alcoholic solutions (used by courtesy of the International Journal of Pharmaceutics, Elsevier [74])

For a better understanding of the tablet swelling process in both media, image analysis was used as a tool to analyse the first 5 min of medium uptake into the formulation with 30 % XG. As can be seen in Figure 19, although S-30% XG75 did not show relevant swelling over the measurement time in both media, S-30% XG180 exhibited a 2-fold increase of the tablet dimensions in both axial and radial directions, however exclusively in presence of alcohol. Except from the drug solubility, ethanol might have influenced the ability of the polymer to hydrate in the media, since XG is practically insoluble in alcohol [115]. Moreover, larger polymer particles are assumed to swell less rapidly than finer ones [47], causing therefore a quick penetration of the media into the tablet, drug solubilisation and a faster

drug diffusion out of the matrix. The percolation theory may also elucidate the different dissolution performances of the formulations S-30% XG75 and S-30% XG180. The percolation theory is a statistical tool, which is applied to study the particle disorder in a lattice sample [128]. According to this theory, a tablet can be recognized as a heterogeneous binary system, which is composed by a drug and an excipient. This theory assumes that each component, including the tablet pores, occupy the sites of the lattice in a random matter. A percolating cluster is formed when the particles of one component, for instance XG, effectively bind to the adjacent XG particles throughout the tablet, thus forming a continuous phase [128]. In our study, it was assumed that larger XG particles at low concentration (below the percolation threshold [129, 130]) do not percolate the system and would therefore not bind effectively with adjacent polymer particles, leading to the formation of a less coherent and more porous gel layer. This fact together with the higher solubility of theophylline in ethanol might have caused the fast drug release. Differently, at the same concentration, finer XG particles were able to percolate the system and allowed the formation of a coherent and strong gel layer. Higher concentrations of polymer with large particles are therefore needed in order to tailor a prolonged drug release.

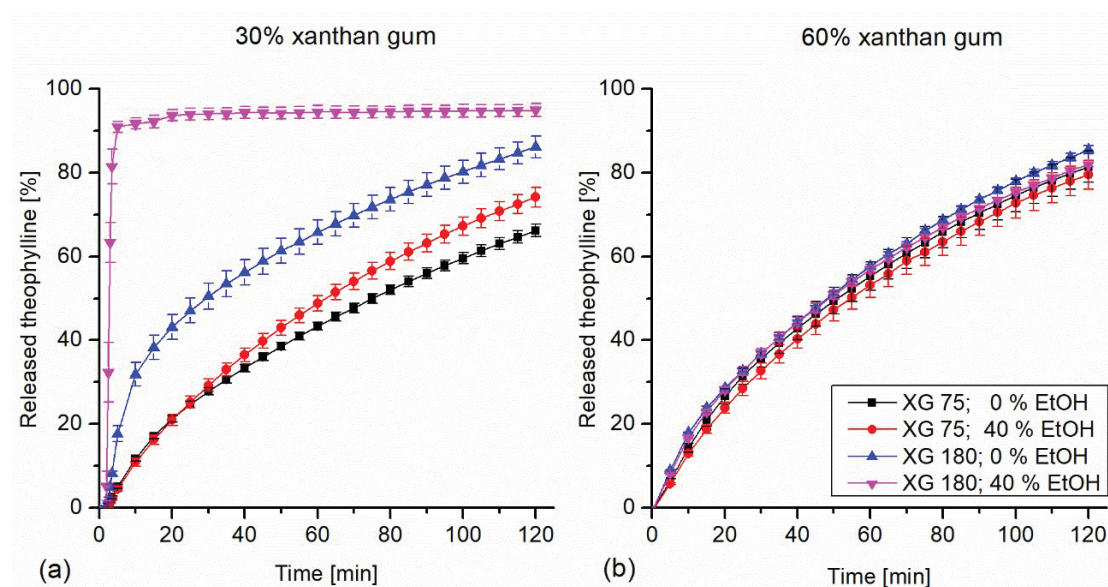


Figure 20: Influence of alcohol and XG particle size on drug release from mini-tablets with (a) 30% XG (4.3 mg API/mini-tablet, 5 mini-tablets in each vessel) and (b) 60% XG (2.4 mg API/mini-tablets, 10 mini-tablets in each vessel); 900 mL 0.1 N HCl with 0 % and 40 % ethanol; USP App. II (paddle, 50 rpm) with sinkers, $37 \pm 0.5^\circ \text{C}$, mean \pm SD, $n = 3$; UV detection at $\lambda = 271 \text{ nm}$ (used by courtesy of the International Journal of Pharmaceutics, Elsevier [74])

The impact of alcohol and polymer particle size was even more pronounced when the diameter of the tablets was reduced from 8 mm to 2 mm. As a matter of fact, mini-tablets are characterized by a higher surface area to volume ratio in comparison to larger tablets and a smaller diffusional pathway is available for the dissolution media to penetrate into the matrix core [128]. The dissolution profiles of the mini-tablets are depicted in Figure 20. The formulation M-30% XG180 underwent disintegration (Figure 21b) and released the entire amount of the embedded theophylline within 5 min, clearly exhibiting ADD ($f_2 = 23.0$). Without alcohol, the same formulation showed an initial fast medium

penetration (Figure 21b) and 17.6 % theophylline was released within 5 min dissolution (Figure 20). Nevertheless, after approximately 20 min a gel layer might have been formed and the drug dissolution rate decreased.

A different scenario was seen when the XG particle size was decreased: only 4.5% theophylline was dissolved within 5 min from M-30% XG75 in 40 % alcohol, and 5% drug was released in 0 % alcohol. Later the dissolution rate in 40 % alcohol was slightly higher than in 0 % alcohol. The similarity factor amounted 62.8, confirming therefore the alcohol resistance of M-30% XG75. Also image analysis supported this finding, exhibiting more similar radial and axial swelling in the two media (Figure 21a).

All formulations containing 60 % XG were robust in alcohol, as already seen for larger tablets, and no influence of the XG particle size could be observed, with $f_2 = 81.2$ for M-60% XG75 and $f_2 = 85.6$ for M-60% XG180. The results are in agreement with several authors, who assumed that at higher concentration of XG, when the percolation threshold has been exceeded, the formation of the gel is consistent and it does not depend on the polymer particle size [60, 129, 131, 132].

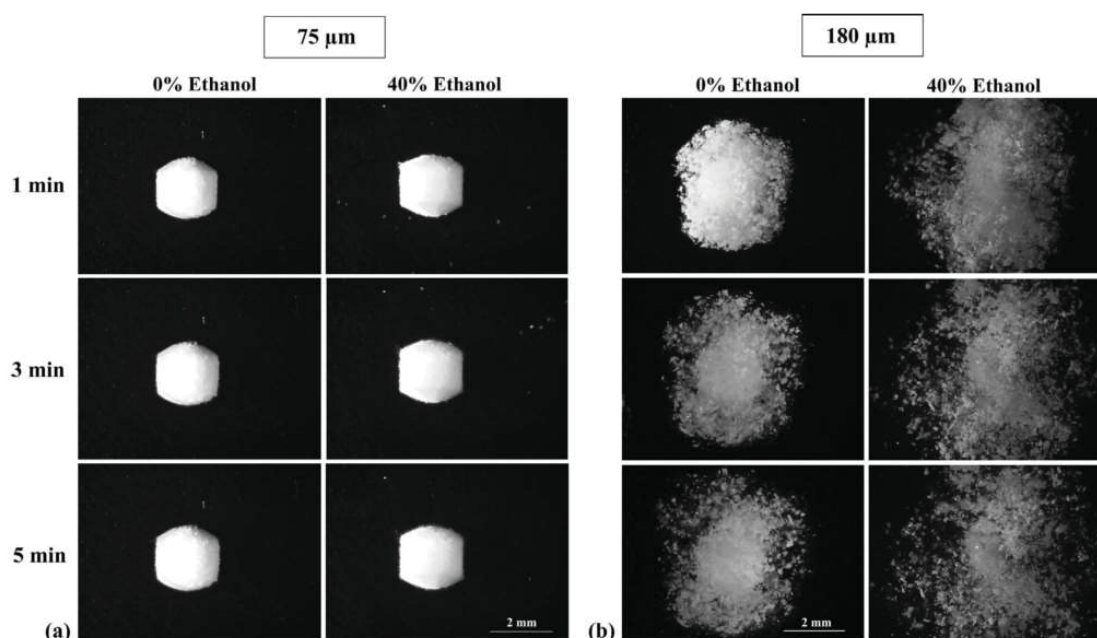


Figure 21: Images of the 2 mm mini-tablets (a) M-30% XG180 and (b) M-30% XG75, acquired using image analysis at 1 min, 3 min and 5 min after coming in contact with 0 % and 40 % alcoholic solutions (used by courtesy of the International Journal of Pharmaceutics, Elsevier [74])

Although no prolonged release could be achieved with 2 mm matrix mini-tablets, it could be shown that all formulations with XG content ≥ 30 % (w/w) were less vulnerable to ethanol when the finer fraction of the polymer was used.

3.2.6 Media uptake, swelling and erosion properties

Gravimetric studies were also performed. However, due to the easier handling, RS, DMU and ML were determined exclusively for the monolithic formulations. The values are listed in Table 6.

Table 6: Relative swelling, dissolution media uptake and mass loss of the 8 mm tablets after 2 h dissolution; media: 0.1N HCl with 0 % and 40 % (v/v) ethanol; USP App. II with sinkers, 37 ± 0.5 °C, 50 rpm mean \pm SD, n = 3

Formulation	Relative swelling		Dissolution media uptake [%]		Mass loss [%]	
	0 % EtOH	40 % EtOH	0 % EtOH	40 % EtOH	0 % EtOH	40 % EtOH
S-30% XG75	2.3 ± 0.0	1.9 ± 0.0	193.9 ± 3.9	151.3 ± 2.9	23.2 ± 0.6	24.1 ± 0.4
S-60% XG75	3.0 ± 0.0	2.3 ± 0.0	289.0 ± 5.4	197.1 ± 4.3	24.2 ± 0.2	21.4 ± 1.1
S-30% XG180	2.4 ± 0.1	2.1 ± 0.2	214.8 ± 13.4	262.7 ± 30.5	22.9 ± 0.5	42.4 ± 2.3
S-60% XG180	3.2 ± 0.0	2.5 ± 0.1	314.4 ± 3.9	217.6 ± 8.0	23.4 ± 0.5	20.7 ± 0.3

Generally, slightly higher RS were observed when the concentration of XG was increased from 30 % to 60 %. However, each formulation exhibited a significantly lower swelling extent (RS) in contact to 40 % ethanol in comparison to hydrous media ($p < 0.05$). DMU results showed the same tendency, with significantly lower values obtained when the tablets were dissolving in ethanolic media ($p < 0.05$). The only exception was represented by the formulation S-30% XG180, which showed a DMU increasing from 214.81 to 262.72 % in 0 and 40 % ethanol respectively. Image analysis studies could confirm these results (see 3.2.5). The same formulation was also characterized by a higher erosion extent in ethanol, with ML increasing from 22.9 to 42.4 % in 0 and 40 % ethanol respectively ($p < 0.05$). Similar ML values were determined for the formulation S-30% XG75, while the 60 % XG-formulations showed slightly lower ML in presence of ethanol.

3.2.7 Viscosity of polymeric solutions

To better understand how alcohol might have affected the rheological properties of polymeric solutions, XG 75 and XG 180 were dissolved in 0.1 N HCl with and without addition of 40 % alcohol, in a concentration of 0.1% polymer.

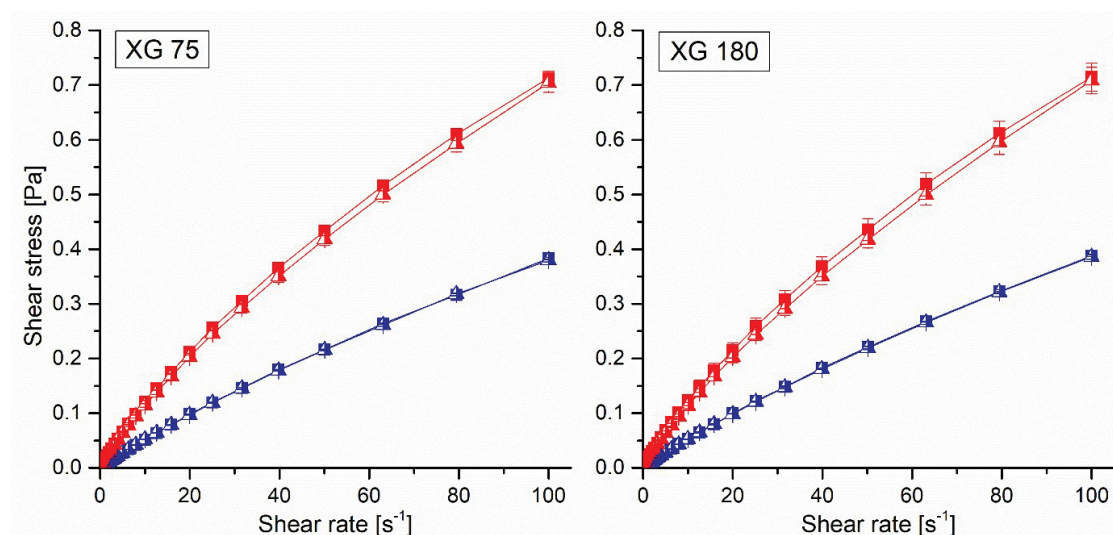


Figure 22: Shear rate ramps of 0.1% XG (75 µm and 180 µm) solutions in 0.1 N HCl with 0 % ethanol (blue curves) and 40 % ethanol (red curves); □ = up curves, △ = down curves; mean \pm SD, n = 3.

Due to the lower solubility of XG in acidic and alcoholic media in comparison to water [115], dispersions with higher concentrations of XG could not be produced, due to the incomplete dissolution of the polymer. The rheograms depicted in Figure 22 show the performed shear rate ramps, with the measured shear stress values depending on the applied shear rate, by using a rotational viscometer equipped with a cone-plate geometry. As in agreement with Katzbauer [133], XG solutions exhibited a pseudoplastic behaviour (Figure 22). To compare the solutions behaviour in hydrous and hydro-alcoholic media, the dynamic viscosities determined at 5 s^{-1} were considered.

As can be seen in Table 7, the dynamic viscosities were obviously independent of the polymer particle size, since the degree of polymerization was the same. However, the presence of alcohol led to a 2.4-fold viscosity increase in the case of all solutions. Due to the anionic nature of XG ($\text{pK}_a = 3.1$), the polymer is predominantly protonated at pH 1.2. The addition of ethanol in the media decreases the dielectric constant and it is therefore assumed that ethanol may act as a cosolvent for the polymer. This effect might increase the interaction of XG with the medium and therefore its viscosity. A stronger gel layer may then form in alcoholic media, which might clarify the lower swelling extent reported in section 3.2.6. Nevertheless, the low hydration rate of XG might still be a crucial factor during drug release.

Table 7: Dynamic viscosities of 0.1% XG solutions; shear rate: 5 s^{-1} ; mean \pm SD, $n = 3$

XG particle size [μm]	Ethanol concentration [%]	Dynamic viscosity [$\text{mPa}\cdot\text{s}$]	
		Up curve	Down curve
75	0	5.5 ± 0.0	5.4 ± 0.1
	40	13.2 ± 0.3	12.7 ± 0.4
180	0	5.7 ± 0.0	5.6 ± 0.1
	40	13.7 ± 1.2	12.7 ± 0.7

3.2.8 DoE: coefficient and contour plots

The Design of Experiments (DoE) represented in Table 34 (see section 5.2.2) was performed for the 8 mm tablets and 2 mm mini-tablets and analysed by the software Modde 12.0. The experimental data exhibited a good fit with the model, where the R^2 values were close to 1. In the case of the monolithic formulations, the factors (i) XG concentration and (ii) ethanol concentration in the dissolution media affected significantly the amount of released theophylline (Figure 23). Specifically, the first had a negative effect on the evaluated response, while the second a positive one.

Furthermore, two two-factors interactions were shown: firstly, the interaction between XG concentration and XG particle size, secondly, the interaction between XG concentration and ethanol concentration in the media. The analysis of these interactions is depicted in the contour plots in Figure 24. As can be noticed, only at low XG concentrations, varying the XG particle size led to different amounts of drug released, while at XG concentration $> 40 \%$ a significant XG particle size effect could not be seen (Figure 24a).

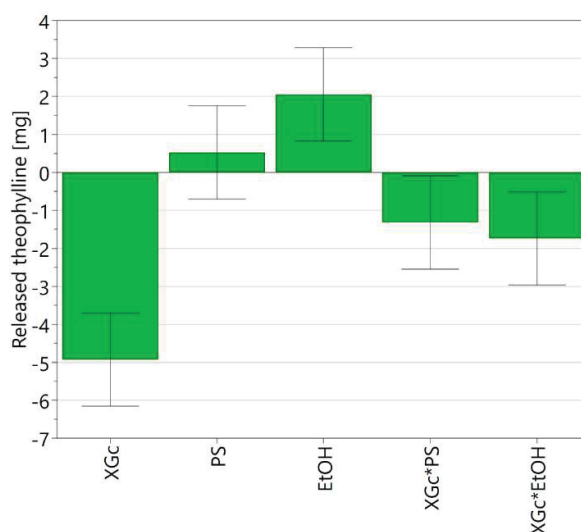


Figure 23: Coefficient plot for the response amount of released theophylline after 2 h dissolution (8 mm diameter tablets); factors: XG concentration (XGc), XG particle size (PS), ethanol concentration (EtOH) ($R^2 = 0.967$, $Q^2 = 0.634$, model validity 0.434, reproducibility 0.988; conf. level = 95%) (used by courtesy of the International Journal of Pharmaceutics, Elsevier [74]).

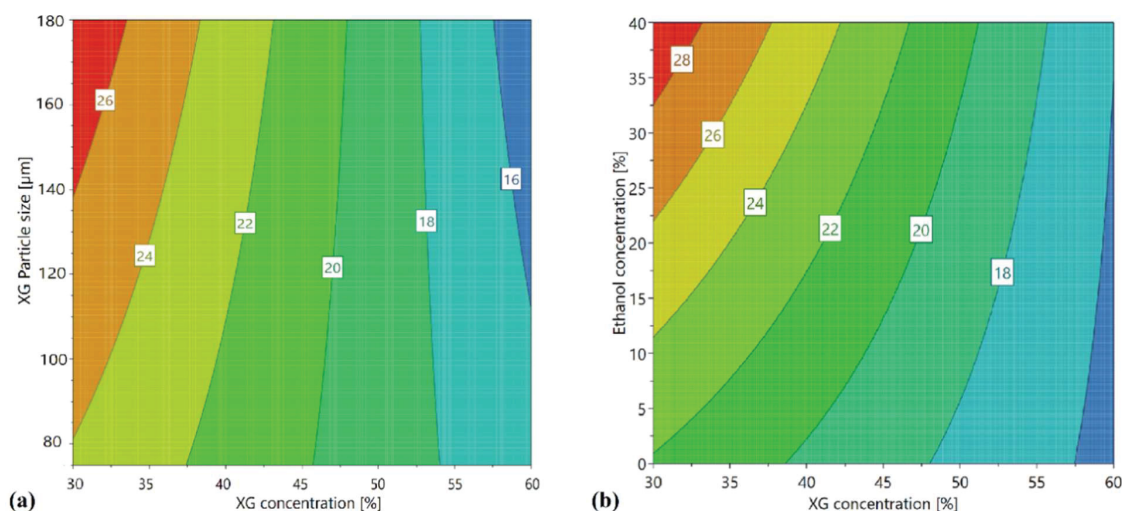


Figure 24: Contour plots for the response amount of theophylline released after 2 h (8 mm tablets) depending on (a) XG concentration and XG particle size (b) XG concentration and ethanol concentration (used by courtesy of the International Journal of Pharmaceutics, Elsevier [74]).

The effect of alcohol was more pronounced by low XG concentration in the formulations (Figure 24b). Consequently, by combining low XG concentration and high concentration of ethanol, a significantly higher amount of theophylline is expected to be released.

The coefficient plot for the response relative swelling (8 mm tablets) is depicted in Figure 25. All considered factors had a significant effect: in particular, XG concentration and XG particle size had a positive effect, whereas the ethanol concentration a negative one. With respect to the mini-tablets, the amount of drug which was released after 1 h was significantly affected only by the XG particle size as factor: specifically, the larger the XG particles the higher the amount of API released (Figure 26).

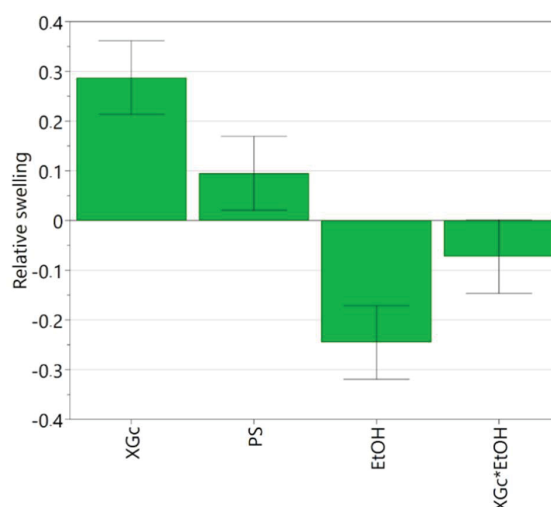


Figure 25: Coefficient plot for the response relative swelling (8 mm tablets); factors: XG concentration (XGc), XG particle size (PS), ethanol concentration (EtOH) ($R^2 = 0.966$, $Q^2 = 0.916$, model validity 0.566, reproducibility 0.984; conf. level = 95%) (used by courtesy of the International Journal of Pharmaceutics, Elsevier [74]).

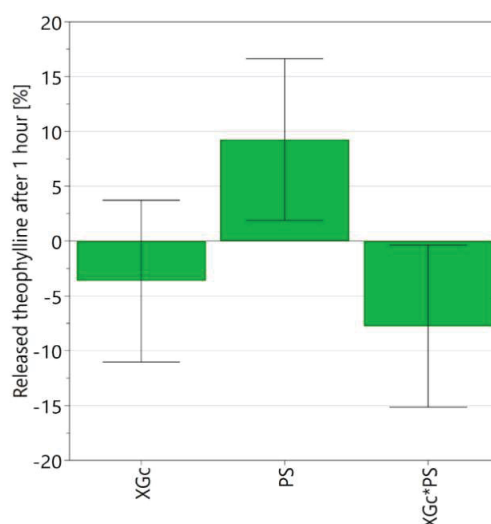


Figure 26: Coefficient plot for the response amount of theophylline released after 1 h dissolution (2 mm mini-tablets); factors: XG concentration (XGc), XG particle size (PS), ethanol concentration (EtOH) ($R^2 = 0.700$, $Q^2 = 0.916$, model validity -0.188, reproducibility 0.995; conf. level = 95%) (used by courtesy of the International Journal of Pharmaceutics, Elsevier [74]).

In addition, the significant interaction between XG concentration and XG particle size was analyzed and the respective contour plot is represented in Figure 27. As already seen for larger tablets, at low XG concentrations the effect of XG particle size resulted significant, with higher release of API by increasing the polymer particle size. Similar dissolution was tailored at higher polymer concentrations. With XG particle approximately $< 120 \mu\text{m}$ similar responses could be obtained at any XG content, while XG particle size $> 120 \mu\text{m}$ led to drug release, dependent of the XG content.

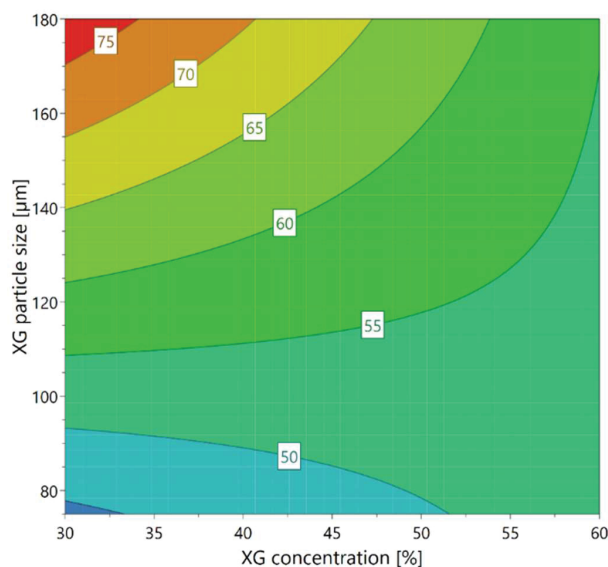


Figure 27: Contour plot for the response released theophylline (2 mm mini-tablets) depending on XG concentration and XG particle size (used by courtesy of the International Journal of Pharmaceutics, Elsevier [74]).

3.2.9 Summary

Matrix tablets (8 mm diameter) and mini-tablets (2 mm diameter) based on theophylline as API and XG as rate-controlling polymer were manufactured by direct compression. Two polymer particle sizes (75 and 180 μm) and two polymer concentrations (30 and 60 % w/w) were utilised to evaluate their influence on the tablet dissolution behaviour and tablet swelling in 0 % and 40 % ethanol (pH 1.2).

The tablets were first characterized in terms of tensile strength and porosity. Larger tablets showed higher tensile strength and lower porosity in comparison to mini-tablets, due to the lower compression pressure which could be applied during the manufacturing of mini-tablets. However, generally, lower XG fraction and finer XG particles led to slightly harder tablets and slightly lower tablet porosity.

Regarding the dissolution behaviour, both tablets and mini-tablets containing 60 % XG stayed intact during the 2 h test and showed similar in-vitro drug release in hydrous and hydro-alcoholic media ($f_2 \gg 50$). In this particular case, the influence of the polymer particle size and the 2.8-fold higher solubility of theophylline in alcohol were negligible. Robustness against alcohol was successfully achieved also by decreasing the polymer concentration from 60 % to 30 % (w/w), however exclusively when finer XG particles were used. As a matter of fact, in the case of larger tablets, 30 % coarse polymer particles led to significantly higher amount of drug release in alcohol ($f_2 < 50$) and a risk of alcohol-induced dose dumping was recognized. Interestingly, mini-tablets of the same composition underwent disintegration and released the entire dose within 5 min, thus exhibiting ADD ($f_2 = 23.0$). Differently, when finer polymer particles were used at lower concentration, a less porous and more coherent gel barrier was formed and both tablets and mini-tablets were not vulnerable to alcohol.

Gravimetric studies were also performed for the monolithic formulations in order to determine relative swelling (RS), dissolution media uptake (DMU) and mass loss (ML) values. Generally, lower RS and DMU were obtained in alcohol in comparison to hydrous media, with the only exception of the

formulation S-30% XG 180. Thus, larger XG particles at lower concentration led to significantly higher DMU, probably due to the less rapid swelling of larger polymer particles in alcohol, which caused a quick penetration of the media into the tablet and a faster drug release. Moreover, the XG concentration was not high enough to exceed the percolation threshold and no infinite percolation cluster could be achieved. The same formulation led consequently to higher erosion extent, with significantly increased ML values. Similar ML were found for all other formulations.

To better understand the influence of alcohol on the rheological properties of XG solutions, rheograms obtained by rotational viscometry were studied. All XG solutions exhibited a pseudoplastic behaviour. As expected, the dynamic viscosities were not influenced by the XG particle size, however, when ethanol was present in the media, a 2.4-fold higher viscosity was measured. A stronger gel layer may have been then formed during dissolution in alcohol, thus hindering ADD in most of the cases. Nevertheless, the slow interaction between the polymer and ethanol remains a crucial factor, especially during the initial phase of the dissolution test.

Additional technological measures should be furthermore adopted in order to decrease the drug release from mini-tablets. Due to the decreased diffusion path length, no prolonged release could be achieved.

3.3 Development of alcohol-resistant multiple-unit dosage forms: screening of polymers processed by direct compression or twin-screw extrusion

3.3.1 Introduction and Objectives

To accomplish alcohol-resistance, the key physico-chemical factors of the formulation components have to be taken into consideration. In this regard, Jedinger et al. [24] considered “(i) solubility, (ii) wettability, (iii) swellability, and (iv) mechanical properties of the active pharmaceutical ingredient (API) and the excipient(s) of the final dosage form”. Based on the results reported in chapters 3.1 and 3.2, the ability of the rate-controlling polymer to swell and form a gel layer around the dosage form is a fundamental factor for the development of alcohol-robust dosage forms.

Thus, a systematic evaluation of suitable polymer candidates was performed. For these purposes, the following hydrophilic polymers were selected: xanthan gum (XG), pregelatinized starch (PGS), microcrystalline cellulose (MCC), hypromellose (HPMC), carbomer and polyethylene oxide (PEO). In addition, also the less hydrophilic polyvinyl acetate (PVAc) has been studied.

Mini-matrices based on theophylline monohydrate as model API were manufactured either by direct compression or wet/hot-melt extrusion and the ability of each polymer to tailor (i) robustness against alcohol and (i) prolonged drug release was investigated.

Furthermore, this chapter will focus on mixer torque rheometry (MTR) as a promising tool to investigate the rheological behaviour of polymer powders wetted by both aqueous and hydro-alcoholic solutions. As a matter of fact, Chatlapalli et al. [134] stated that, during wet massing, the consumed energy depends on “the physico-chemical and mechanical properties of the substrate being wet massed”. Thus, the higher the cohesiveness of the powder particles with increasing liquid amount, the higher the resistance and therefore higher torque on the mixer blades of the MTR [135].

Image analysis was additionally performed on mini-matrices upon contact with the aqueous and hydro-alcoholic media, to macroscopically analyse the swelling of the formulations.

3.3.2 Xanthan gum

In chapter 3.2, mini-tablets based on XG could be manufactured as multiple-unit dosage form. Aim of this part of the work was to produce highly dosed multiple-unit dosage forms based on wet extrusion as alternative manufacturing process to direct compression.

The formulations used in this study are listed in Table 8. F1 was composed solely by theophylline as API and Xantural® 75 as matrix former. To improve the flowability, 0.5 % colloidal silica was added. To ensure resistance against ADD, Schrank et al. [114] incorporated small amounts of alcohol insoluble additives into calcium stearate-based matrices, which had previously shown to be suitable for the development of alcohol resistant formulations. These additives were called “pore blockers” since they were intended to mechanically block the pores, thus regulating the entrance of dissolution media into the formulation, the swelling and eventually the drug release. In this study, the following

additives were selected as suitable pore blockers: dicalcium phosphate anhydrous (DCPA) – soluble in dilute acids but practically insoluble in ethanol –, talc and titanium dioxide (TiO₂) – both practically insoluble in ethanol and water - [115]. These substances were incorporated into the formulations in a concentration of 19.5 % (F2, F3, F4) thus decreasing the XG concentration from 49.5 % to 30 % (w/w).

Table 8: Formulations F1-F4 based on XG and processed by wet extrusion; API: theophylline monohydrate, matrix polymer: xanthan gum; pore blockers: dicalcium phosphate anhydrous, talcum, titanium dioxide; flow-aid: colloidal silica

substance	concentration % (w/w)			
	F1	F2	F3	F4
theophylline monohydrate	50	50	50	50
xanthan gum	49.5	30	30	30
dicalcium phosphate anhydrous	-	19.5	-	-
talcum	-	-	19.5	-
titanium dioxide	-	-	-	19.5
colloidal silica	0.5	0.5	0.5	0.5

Jedinger et al. [66] described the processing of XG as matrix material by hot-melt extrusion and subsequent pelletization. In this regard, the authors faced the following issues: when extruding XG without plasticizers (i.e. water) at process temperatures of 60-85 °C, a non-molten mass, which appeared powdery and brittle, was obtained. Also at temperatures of 80-200 °C the mass failed to melt and the extrudates appeared charred. Only by using temperatures of 60-85 °C and water as plasticizer, smooth, but rather cylindrical pellets could be produced. To our knowledge, no additional work about XG as matrix material in twin-screw extrusion processes (wet and hot-melt extrusion) is present in the literature.

In this study, wet extrusion was the process of choice to manufacture XG-based extrudates, where water was used as granulation liquid. Before performing wet extrusion, the optimal liquid/solid ratio (L/S) had to be determined. Thus, high amount of water leads to sticky extrudates and difficult sample handling, whereas low amount of water leads to high mean torque generated inside the extruder. Therefore, prior to extruding, the rheological behavior of the wet powder masses was investigated to establish a window of granulation liquid needed to achieve a suitable mass consistency for extrusion. Several authors have shown that the rheological properties of wet masses can be successfully monitored by using a mixer torque rheometer (MTR) [134-140].

In this study, MTR was used with the method of multiple addition (see 5.2.3.14), where it was feasible to monitor the changes in mean torque values during the mass kneading dependently on the amount of water which was stepwise added to the powder mass. The rheological profiles are depicted in Figure 28, where the mean torque values were normalized by the mass of each sample.

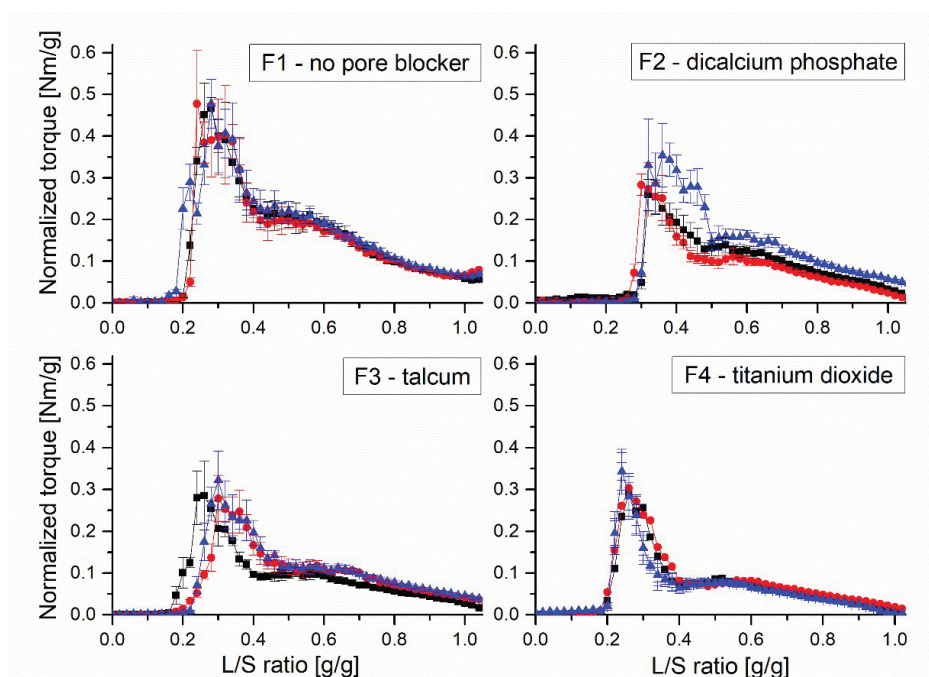


Figure 28: Torque profiles obtained from the multiple addition of water to the powder mixtures; single curves are depicted ($n = 3$), where the mean and SD were calculated considering the torque values over a period of 15 s of mass kneading.

As can be seen, L/S ratio between 0.2 and 0.3 led to a sharp peak of the mean torque for all evaluated mixtures, followed by a torque drop [134], a steady-state region characterized by constant torque values and an additional slow torque drop, due to the over-wetting of the powder mass. F1 showed a 1.6-fold higher torque peak in comparison to the other mixtures, due to the higher amount of XG, whereas F2, F3 and F4 showed comparable profiles. A torque steady-state (0.1 Nm/g) was reached at L/S ratio about 0.5. In light of this, a L/S ratio of 0.5 was tested during extrusion, in order to achieve a compromise between a low torque and a low L/S ratio, thus hindering the production of highly wetted and sticky extrudates.

Wet extrusion of F1-F4 was performed at 25 °C, since higher temperature of 60 °C did not show additional advantages, i.e. in terms of smoother extrudates. A low screw speed of 30 rpm was utilized, in order to achieve a high densification of the wet mass, whereas the powder feed was kept constant at 10 g/min. Wet extrusion of F2, F3 and F4, which contained a lower amount of XG, was feasible at the L/S ratios selected through mixer torque rheometry. By using L/S ratio of 0.5, power consumption values of respectively 17.9 %, 21% and 24.5 % were measured for F2, F3 and F4 respectively. However, when extruding F1, L/S ratio of 0.5 could not be utilized. In Figure 29 the variation of the process parameters (screw speed, powder feed, liquid feed and power consumption) during extrusion of the formulation F1 is depicted. As can be seen, the liquid feed was reduced first from 11 g/min (L/S = 1.1) to 10 g/min (L/S = 1.0), then to 9 g/min (L/S = 0.9) and finally after 1440 s to 8 g/min (L/S = 0.8). When steady-state conditions were reached, the power consumption amounted about 20 %. A further decrease in liquid feed from 8 g/min to 6.5 g/min (L/S = 0.65) led to a drastic increase of the power consumption and the process was stopped. Therefore, L/S ratio of 0.8, which in MTR

corresponded to normalized torque of approximately 0.1 Nm/g, was utilized to produce extrudates from the formulation F1.

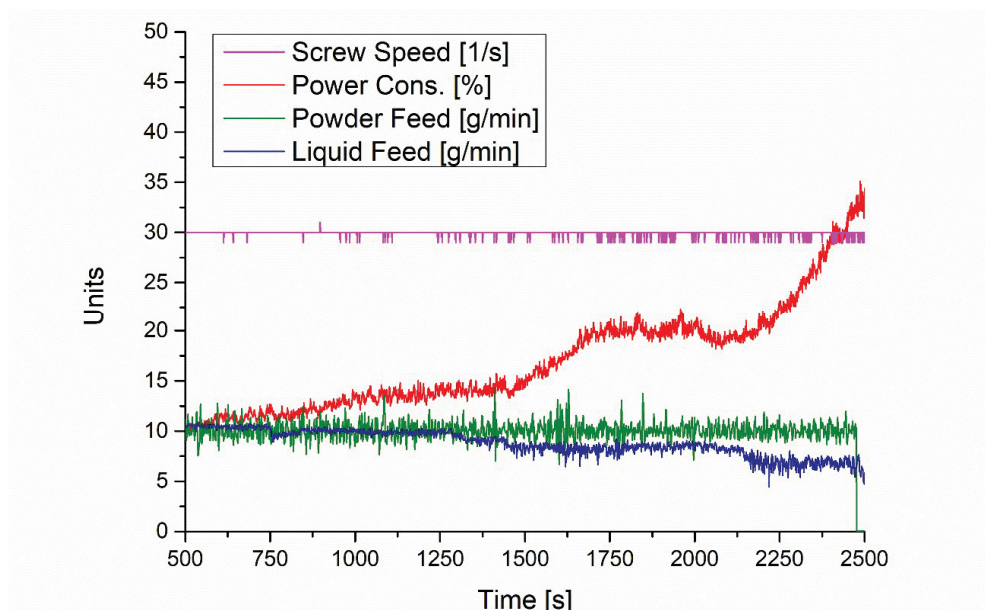


Figure 29: Process monitoring of screw speed, power consumption (reported in the figure as “Power cons.”), powder feed, and liquid feed over time; formulation F1.

The wet mass was forced through the 1.75 mm die and the produced extrudates were dried to constant weight first and then cut in order to reach a length of 3 mm. Extrudates characterized by a rather rough surface were obtained (Figure 30a-b). This may be due to both swelling of the polymer upon contact with water in the extruder and shrinkage of the extrudates during the drying process. As a matter of fact, the presence of XG led to very elastic mixtures within the extruder and the obtained extrudates expanded not uniformly to a wide cross-section after being forced through the die. In addition, it has been generally stated in the literature that the shrinkage is linearly related to the amount of water at the early drying stages [141, 142].

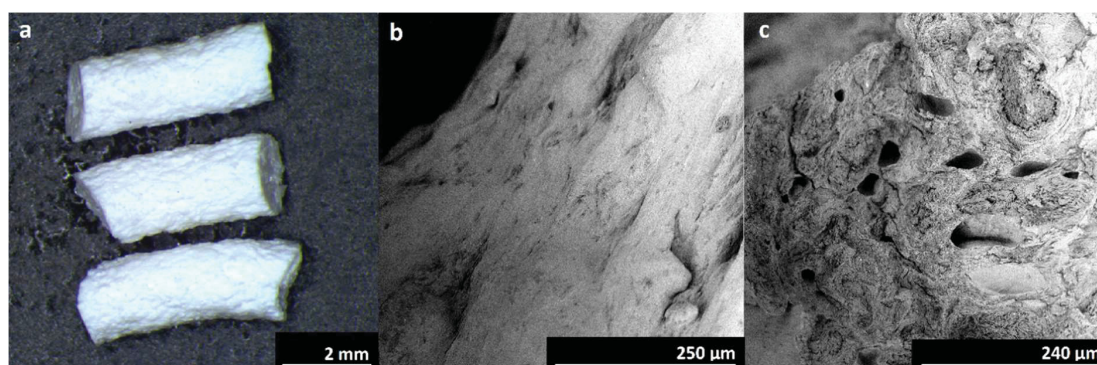


Figure 30: Extrudates containing theophylline monohydrate and xanthan gum (F1): image of the extrudates taken by stereomicroscopy (a), SEM images of the extrudates surface (b) and cross-section of an extrudate (c)

The wet extrudates with higher XG content had a higher water content due to the higher L/S ratio, therefore the extent of shrinking was higher. Indeed, the diameter of the dried extrudates amounted 1.4 ± 0.1 mm ($n = 30$) for F1, whereas F2, F3 and F4 were characterized by slightly larger diameters, 1.6 ± 0.0 mm, 1.5 ± 0.3 mm and 1.6 ± 0.3 mm respectively. The smoothness of the extrudates surface is very important for i.e. solid lipid-based extrudates, since the dissolution is completely diffusion controlled [143]. However, in this case, since hydrophilic matrices are able to swell, a less pronounced effect of the surface roughness on the dissolution behaviour was expected.

Table 9: Porosity values of the extrudates with different pore blockers (F1 = no pore blocker, F2 = dicalcium phosphate anhydrous, F3 = talcum, F4 = titanium dioxide); mean \pm SD, $n = 3$

Formulation	F1	F2	F3	F4
Porosity [%]	23.1 ± 1.5	18.2 ± 0.6	19.8 ± 3.3	20.4 ± 2.3

The porosity data of the extrudates were determined by using the method described in section 5.2.3.7 and the results are listed in Table 9. Due to the fact that higher L/S ratios were used to produce the formulation F1, a higher shrinking of the extrudates and therefore lower porosities were expected for this formulation compared to the other ones. However, similar porosity values were determined.

Dissolution testing was performed in 0.1 N HCl containing 0 % and 40 % ethanol. F1 was in addition tested in media containing 20 % ethanol. The dissolution profiles are represented in Figure 31.

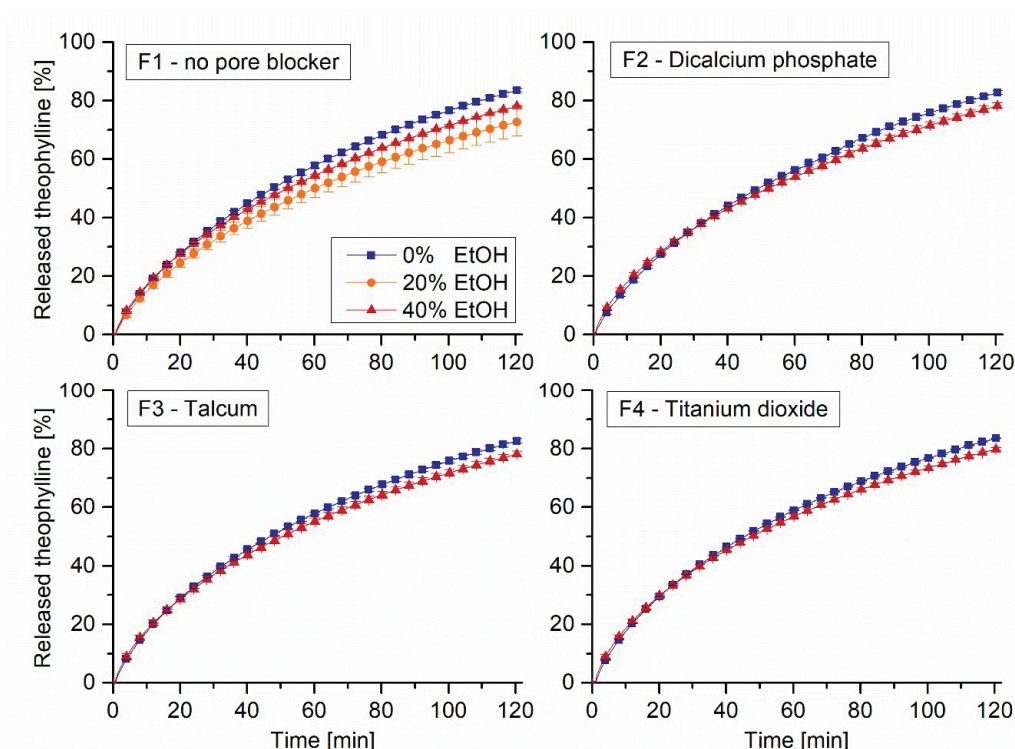


Figure 31: Dissolution profiles of the XG-containing extrudates without (F1) and with the pore blockers dicalcium phosphate anhydrous (F2), talcum (F3) and titanium dioxide (F4) in different media (5 extrudates in each vessel corresponded to approximately 20 mg theophylline); mean \pm SD, $n = 3$.

All matrices underwent swelling in both media and did not dissolve, due to the formation of a highly viscous gel layer which resulted from the uncoiling of the XG structure and the formation of hydrogen bonds with the water molecules [61, 66]. However, despite the formation of a gel layer, the high specific surface area of the extrudates hindered to tailor a rate-controlling effect and 80 % of the embedded drug was released within 2 hours. Nevertheless, alcohol resistance could be achieved and the presence of alcohol did not lead to dose dumping. All similarity factors were higher than 50 and the values increased in the following order: F1 (no pore blocker) < F3 (talcum) < F2 (DCPA) < F4 (TiO₂) (Table 10). Furthermore, the F1 extrudates were robust in 20 % ethanolic media ($f_2 = 55.6$). The addition of pore blockers did not lead to relevant variations in the dissolution profiles and the AUC values were very similar among all formulations, in both media (Table 10). An influence of the initial porosity on the dissolution performances of the extrudates could also not be recognized, as in accordance to the literature regarding swellable matrix systems [60]. In addition, it can be noticed that a decrease in XG concentration (F2, F3, F4) did not cause faster drug release. As a matter of fact, several authors already stated that above the percolation threshold a coherent and homogeneous gel is formed and an increase in the polymer concentration does not lead to a decrease in the release rate in case of highly soluble APIs [47, 87, 144]. As previously seen (3.2.5), fine particles of XG (75 μm) could percolate the system in a concentration of 30 % (w/w) and a uniform and stable rate-controlling gel layer could be formed.

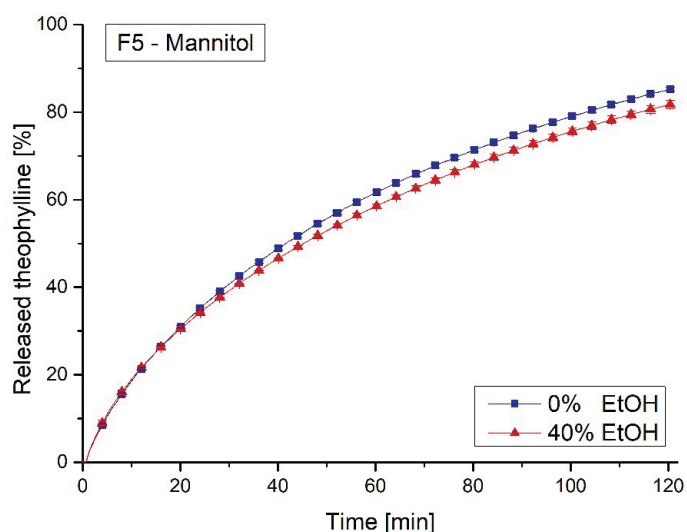


Figure 32: Dissolution profiles of the XG-containing extrudates with β -mannitol (F5) (5 extrudates in each vessel corresponded to approximately 20 mg theophylline) in different media; mean \pm SD, $n = 3$.

In addition, the polyol excipient β -mannitol was investigated as forth additive in the XG-based formulations (F5, 50 % theophylline, 30 % XG, 19.5% β -mannitol, 0.5% colloidal silica) to assess the influence of the additives' solubility on the drug dissolution. Mixtures containing mannitol (Table 8) were wet extruded by using a L/S ratio of 0.5. Rowe et al. [115] reported that the solubility of this polyol in water amounts 1 in 5.5, a value which is decreased to 1 in 83 in ethanol 95%. The drug release was slightly slower in alcohol (Figure 32), as already observed for F1, F2, F3 and F4, and the value f_2 amounted 76.9 (Table 10), thus confirming the similarity between the two dissolution profiles.

However, slightly higher AUC values in both media were calculated for F5 in comparison to the other formulations, in particular, the highest increase was seen in regard to F2 and amounted 6.8 % in 0.1 N HCl and 7.3 % in 40 % alcoholic media. As a matter of fact, the solubility of mannitol was higher in both media compared to DCPA, talcum and TiO₂, therefore mannitol was expected to act as a pore former, thus leading to faster penetration of the dissolution media into the matrices, with consequent dilution of the gel layer and higher amount of theophylline released. However, this was not the case and the polyol affected the dissolution behavior to a very low extent.

Table 11 summarizes the results of the analysis regarding the diffusional release mechanism based on Higuchi and Korsmeyer-Peppas equations. The obtained n_{KP} values amounted 0.69 in 0.1 N HCl and was slightly decreased to 0.65 in both 20 and 40 % alcoholic solutions, thus indicating an anomalous drug transport in all media ($0.45 < n_{KP} < 0.89$) [145]. In addition, the slope of the Higuchi plot was generally decreased by increasing the content of alcohol in the media, and the lowest value could be observed regarding the drug release in 20 % ethanolic media.

Table 10: Dissolution parameters calculated for F1-F5; AUC_{120 min} = area under the curve of dissolution (mean values), f_2 = similarity factor between dissolution data in 0 % and 40 % ethanolic media

Parameters		F1 No pore blocker	F2 DCPA	F3 talcum	F4 TiO ₂	F5 mannitol
AUC [%·min]	0 % ethanol	6458.9	6362.2	6467.7	6564.7	6823.8
	40 % ethanol	6108.8	6058.7	6185.5	6359.5	6537.6
Similarity factor f_2		71.8	77.1	75.8	80.0	76.9

To conclude this part of the work, the extrusion of XG-based mixtures with and without additives was feasible by wet extrusion at the chosen process parameters. No significant influence could however be seen on the drug release by adding either pore blockers or pore former in the formulation. It is assumed that the concentration of XG (30 %) was too high (above the percolation threshold) to observe drug release variations, caused by the different solubility of the here considered additives. The sole swelling ability of XG in the hydrous/ hydro-alcoholic media controlled the dissolution of all formulations and led to alcohol-resistance. Nevertheless, it has to be noticed that lower amount of water as granulation liquid was required for the manufacturing of extrudates containing further additives, fact which can show an advantage in terms of lower duration of the drying step after wet extrusion. Wet extrusion can also result as a valid alternative to direct compression, when poorly flowable mixtures have to be processed into multiparticulate dosage forms, as mini-tablets.

Table 11: Release characteristics for F1; slope (K_H) and R^2 (R^2_H) of the Higuchi plot (for the calculation, dissolution data up to 60 % were evaluated); exponent (n_{KP}), intercept ($\log_{10}k$) and R^2 (R^2_{KP}) of the Korsmeyer-Peppas plot (dissolution data between 10 % and 60 % were evaluated)

Ethanol concentration [%]	Higuchi plot		Korsmeyer- Peppas Plot			Drug transport
	K_H	R^2_H	n_{KP}	$\log_{10}k$	R^2_{KP}	
0	8.44	0.995	0.69	0.54	0.999	anomalous
20	7.37	0.997	0.65	0.57	0.998	anomalous
40	7.76	0.997	0.65	0.54	0.999	anomalous

3.3.3 Microcrystalline cellulose

The second polymer was microcrystalline cellulose (MCC). MCC is widely used in pharmaceuticals, primarily as a binder/diluent in tablets and capsules for oral application [115]. But most of all, MCC is considered the golden standard as extrusion-spheronization aid, due to its good binding properties which give cohesiveness to wetted masses [65]. In addition, due to its ability to absorb and retain a high quantity of water, MCC facilitates extrusion, improves the wetted mass plasticity and enhances spheronization [65, 146-148]. O'Connor et al. [149] reported a delayed release of theophylline from MCC-containing pellets in a drug to polymer ratio of 50 : 50. Instead of disintegrating, the pellets stayed intact, behaving as inert matrices, and exhibited a completed drug release after 2 h of dissolution testing. Several authors reported similar findings [65, 150-153].

Table 12: Composition of the MCC-containing extrudates

component	content [%, w/w]
theophylline monohydrate	50
microcrystalline cellulose (MCC)	49.5
colloidal silica	0.5

In this study, MCC was tested as matrix polymer in extrudates obtained by wet extrusion. The aim was to evaluate its dissolution performance in alcoholic media, since MCC could be used as filler in prolonged release formulations produced by wet extrusion. Few studies are present in the literature regarding behaviour of MCC in alcoholic media, however only taking into consideration MCC as a diluent in matrix tablets containing polymers as HPMC [53, 154] and PEO [155], used as matrix formers. Thus, the behaviour of solely API/ MCC formulations in alcoholic media has not been completely investigated yet.

Wet extrusion of the formulation listed in Table 12 was performed by using the following parameters: 50 rpm screw speed, 10 g/min powder feed, 9 g/min liquid feed (L/S ratio of 0.9) and 25 °C temperature. During the process, a power consumption value of 16.9 % was reached in the steady-state conditions. Differently from the XG-based extrudates, MCC-based extrudates were characterized by a smoother surface (Figure 33), by a diameter of 1.3 ± 0.3 mm ($n = 30$) and a porosity of 18.8 ± 1.6 %.

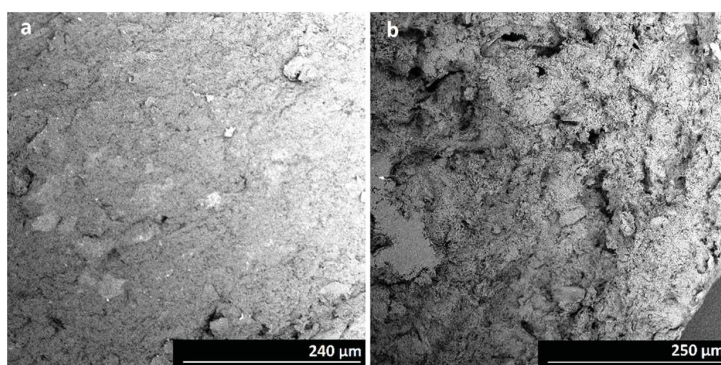


Figure 33: Extrudates containing theophylline monohydrate and MCC: SEM images of the extrudates surface (a) and extrudates cross-section (b)

The dissolution profiles of theophylline from the MCC extrudates are depicted in Figure 34. In all media, the dissolution resulted biphasic, with sudden increase of drug release after 8 min, 19 min and 79 min in 0, 20 and 40 % ethanolic media respectively. The presence of ethanol in the media had a significant influence on the dissolution behaviour: if the AUC amounted 9756 % min and 8744 % min in 0 % and 20 % alcohol respectively, by increasing the alcohol concentration up to 40 % ethanol the AUC was considerably decreased to 7140 % min. The similarity factor f_2 between the dissolution curves in 0 % and 40 % ethanol amounted 30.6, thus indicating that alcohol was influencing the drug release and not similar profiles were obtained.

To better clarify the process of medium penetration into the matrix, image analysis was performed. The resulting images are depicted in Figure 35. In 0.1 N HCl the extrudates absorb water much faster than in 40 % ethanol, and after 10 min multiple ruptures were visible within the extrudates matrix. These ruptures led to the erosion of the polymer matrix and therefore to the aforementioned faster drug release (Figure 34). Another scenario was seen in presence of 40 % ethanolic media: the extrudates maintained their shape throughout the observation time and swelled to a lower extent in comparison to hydrous media. However, after 25 min slight ruptures could be seen also in 40 % ethanol, in particular at the edges of the extrudates.

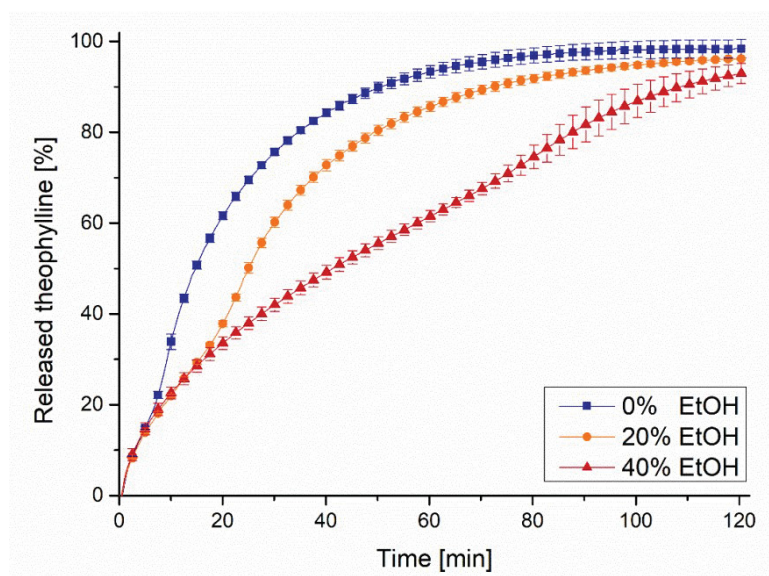


Figure 34: Dissolution profiles of theophylline from the MCC-containing extrudates (5 extrudates in each vessel which corresponded to approximately 15 mg theophylline) in different media; mean \pm SD, $n = 3$.

Several authors studied the swelling abilities of MCC in solvents with different polarities, in order to examine the extrusion-spheronization performance of MCC by using alternative granulation liquids to water [156-159]. It was found that MCC fibres can swell due to the combined effect of (i) absorption of the solvent into its micro-fibril and (ii) absorption of the solvent into the micro-fibril cell wall [160]. However, based on the studies of Sarkar et al. [156], only liquids with high polarity are more effective in interacting with the amorphous ends of MCC and in breaking the hydrogen bonds, whereas less polar solvents/solutions, as water-ethanol mixtures, induced a de-aggregation of the MCC particles to a lower extent. Similarly, Ferrari et al. [158] showed that the disintegration properties of MCC tablets

during dissolution in solvents with different polarities were enhanced by more polar solvents due to the swelling of MCC in these solvents. Our findings seem to be well in accordance with these studies.

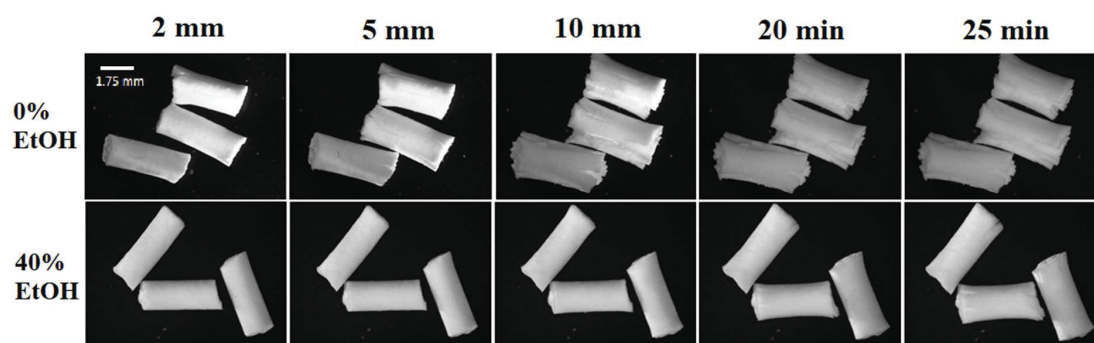


Figure 35: Images of the MCC extrudates taken by image analysis at different time points during dissolution in 0.1 N HCl with 0 % ethanol (upper row) and 40 % ethanol (lower row).

Due to the different behaviour of MCC in ethanolic solutions and, obviously, its very low ability to prolong the drug release, no further investigations were conducted with MCC.

3.3.4 Polyvinyl acetate

Polyvinylacetate (PVAc) is a homopolymer synthesized from vinylacetate monomer via a technique of free radical polymerization. Although characterized by water-insolubility, PVAc is a slightly hydrophilic polymer, which is able to absorb water to a certain extent [161, 162]. PVAc has already been reported as release-controlling carrier for drug delivery systems prepared by both direct compression and hot melt extrusion. It is commercially available in pharmaceutical grade as a spray-dried co-processed excipient in combination with polyvinylpyrrolidone (PVP K30) (ratio 8:2), with the trade name of Kollidon® SR. In this excipient, the amorphous nature of PVAc combined with the low glass transition temperature leads, upon compression, to the formation of a matrix block with releases the embedded drug through channels generated by the gradual leaching of the water-soluble PVP [163].

The influence of alcohol on the dissolution of Kollidon® SR-based mini-tablets (section 5.2.1.1.5) was evaluated. In this study, mini-tablets were the dosage form of choice due to the good flowability properties of Kollidon® SR and the consequently easy manufacturing by direct compression. Mass, tensile strength and porosity of the manufactured mini-tablets are reported in Table 13. Due to the high plastic deformation and compactability of PVAc [164], coherent matrices of sufficient mechanical properties could be produced at 114 MPa compression pressure.

Table 13: Mass, tensile strength and porosity of the manufactured mini-tablets; mean \pm SD, n = 6.

Formulation polymer	Mass [mg]	Tensile strength [MPa]	Porosity [%]
Kollidon® SR	6.60 \pm 0.09	4.5 \pm 0.5	15.4 \pm 1.2
PVP K30	7.04 \pm 0.24	1.3 \pm 0.3	14.1 \pm 1.9
PVP 90F	6.69 \pm 0.13	0.5 \pm 0.3	21.0 \pm 2.8
PVAc	6.55 \pm 0.40	1.9 \pm 0.9	11.4 \pm 3.6

The dissolution data are depicted in Figure 36. The area under the curve (AUC) value amounted 4433 %·min in 0 % ethanol, which was increased up to 5918 %·min in 40 % ethanol, probably due to the higher solubility of theophylline in 40 % ethanol (Figure 5). Furthermore, also the solubility of PVAc was probably affected by ethanol: being an amorphous polymer with a solubility parameter of 19.4 MPa^{1/2}, PVAc dissolves in solvents with similar solubility parameters, e.g. acetone ($\delta = 20.4$ MPa^{1/2}) [165]. The solubility parameters of ethanolic solutions were calculated by Ruidiaz et al. [166] and amounted 47.9 MPa^{1/2}, 40.2 MPa^{1/2} and 35.1 MPa^{1/2} for hydrous solutions containing 0, 20 and 40 % ethanol respectively. Based on these parameters, it is plausible that the solubility of PVAc was increased by increasing the concentration of ethanol in the media. However, in 20 % ethanol the drug release was significantly slower than in 0 % and 40 % ethanol and the AUC amounted 3352 %·min. The release characteristics of the mini-tablets are reported in Table 14 and the n_{KP} values indicated an anomalous drug transport. By increasing the ethanol content, an increase of the exponent n_{KP} was observed, which indicated the higher contribution of the erosion process on the drug release [167]. The slope of the Higuchi plot was affected by the presence of alcohol and the maximal values were calculated from the dissolution data in 40 % alcoholic solutions. Interestingly, however, Kollidon® SR led to decreased drug release rate in hydrous media, where ca. 50 % drug was released within 2 hours dissolution.

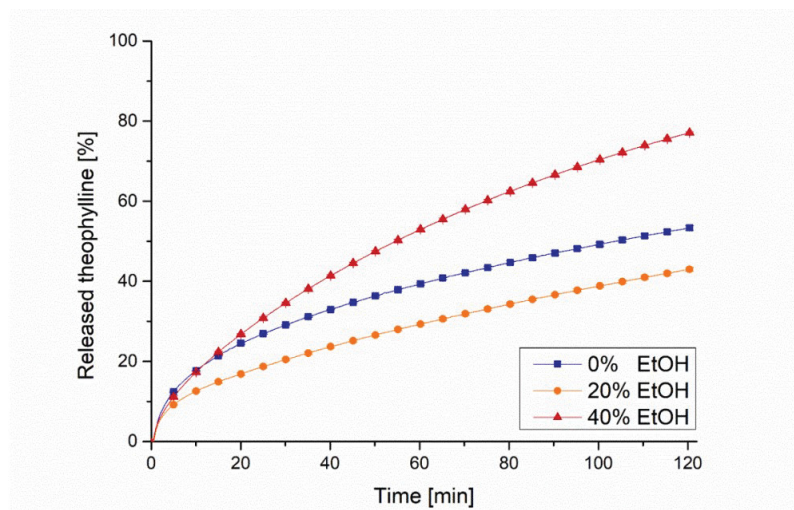


Figure 36: Dissolution profiles of the mini-tablets based on Kollidon® SR in 0.1 N HCl with 0, 20 and 40 % ethanol; in each vessel 8 mini-tablets, which corresponded to ca. 15.6 mg theophylline; mean \pm SD, $n = 3$

By further analysing the dissolution data, the drug release resulted similar to the reference (0 % ethanol) in presence of 20 % ethanol ($f_2 = 51.5$), however differed when the concentration of alcohol was increased up to 40 % ethanol ($f_2 = 41.5$). The behaviour of mini-tablets in 20 % ethanol cannot be explained by the solubility of theophylline in this medium (21.92 mg/mL, see Figure 5), since a slightly faster drug release would be then expected in comparison to hydrous media. Similar results have already been reported in the literature with regard to tramadol hydrochloride-containing matrices based on Kollidon® SR [168-170]. The authors assumed that the decreased drug release in 20 % ethanol may have resulted by an inter-play of swelling of PVAc and leaching of PVP out of the matrix in the different media. However, no further explanation was provided regarding the influence of 20 % alcohol on the dissolution testing.

To better elucidate this behaviour, mini-tablets consisting, firstly, of API/PVP K30, and secondly, of API/PVAc were manufactured by direct compression. The mechanical properties are depicted in Table 13. Significantly lower tensile strengths were measured for both formulations compared to Kollidon® SR -mini-tablets, whereas similar porosities were determined.

Table 14: Release characteristics for Kollidon® SR mini-tablets; slope (K_H) and R^2 (R^2_H) of the Higuchi plot (for the calculation, dissolution data up to 60 % were evaluated); exponent (n_{KP}), intercept ($\log_{10}k$) and R^2 (R^2_{KP}) of the Korsmeyer-Peppas plot (dissolution data between 10 to 60 % were evaluated for 20 and 40 % ethanol, data between 10 and 54 % in 0 % ethanol)

EtOH [%]	Higuchi plot		Korsmeyer- Peppas Plot			Drug transport
	K_H	R^2_H	n_{KP}	$\log_{10}k$	R^2_{KP}	
0	4.65	0.997	0.47	0.73	0.999	anomalous
20	4.15	0.998	0.56	0.44	0.999	anomalous
40	7.67	0.998	0.64	0.57	1.000	anomalous

The solubility of PVP K30 was drastically affected by the presence of ethanol and the mini-tablets showed faster dissolution in 40 % ethanol ($f_2 = 40.1$) and similar profiles to the reference (0 % ethanol) in 20 % ethanol ($f_2 = 73.7$) (Figure 37). PVP is a polymer of amphiphilic character: it is composed of (i) the dipolar imide groups on the pyrrolidone rings and (ii) the methane and methylene groups of the backbone, and the methylene groups in the ring, both of hydrophobic character [171]. Thus, it is considered that organic cosolvents, whose molecules consist of a polar and a non-polar group, i.e. ethanol, are most likely to interact with PVP, through both hydrogen bonding and hydrophobic forces [171]. In light of this, a possible explanation for the decreased drug release in 20 % ethanol is that PVP could interact with 20 % ethanol to a higher extent, thus leading to the formation of a gel, which was more viscous than in 0.1 N HCl. However, when the ethanol concentration was further increased up to 40 %, a faster drug release was achieved. It is assumed that the higher solubility of theophylline in 40 % ethanol (Figure 5) mainly influenced the dissolution in this media.

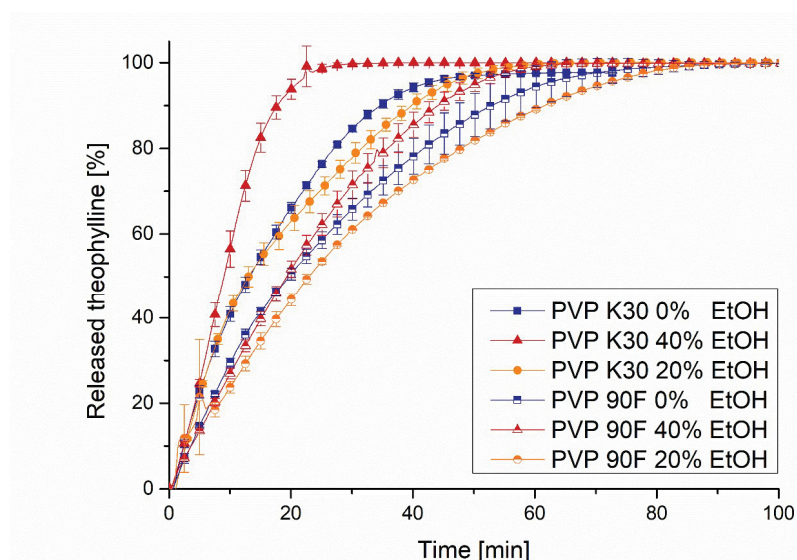


Figure 37: Dissolution profiles of the mini-tablets based on PVP K30 (filled symbols) and PVP 90F (partially filled symbols) in 0.1 N HCl with 0, 20 and 40 % ethanol; in each vessel 8 mini-tablets, which corresponded to ca. 15 mg theophylline; mean \pm SD, $n = 3$

Based on these observations, it is plausible that the drug release from Kollidon[®] SR-mini-tablets (Figure 36) was influenced by the slower leaching of PVP in 20 % ethanol, due to the more viscous PVP gel layer, which led to significantly slower drug release from the matrices.

In addition, PVP 90F, which is characterized by a higher viscosity than PVP K30, was evaluated as suitable excipient for the preparation of physical mixture in combination with PVAc. The results in Figure 37 showed that PVP 90F was less vulnerable against alcohol and showed similar profiles to the reference data in 20 % ($f_2 = 62.9$) and 40 % ethanol ($f_2 = 68.9$). Interestingly, it has to be noticed that both viscosity grades of PVP released the API less rapidly in 20 % ethanol than the other media, probably due to the formation of a more viscous gel layer in this medium, which partially blocked the matrices pores.

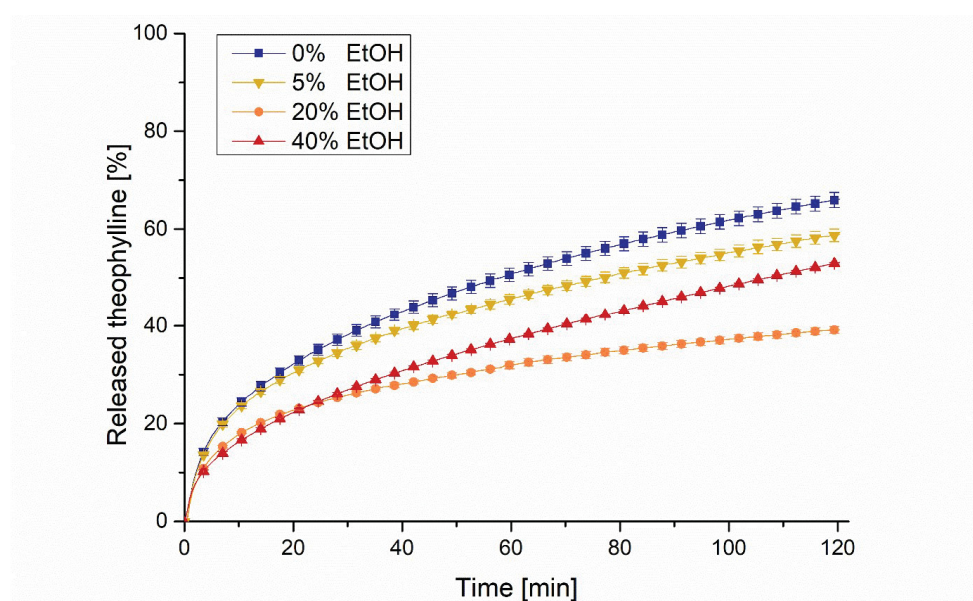


Figure 38: Dissolution profiles of the mini-tablets based on PVAcetate in 0.1 N HCl with 0, 5, 20 and 40 % ethanol; in each vessel 8 mini-tablets, which corresponded to ca. 15 mg theophylline; mean \pm SD, $n = 3$

Table 15: Release characteristics for PVAc mini-tablets; slope (K_H) and R^2 (R^2_H) of the Higuchi plot (for the calculation, dissolution data up to 60 % were evaluated); exponent (n_{KP}), intercept ($\log_{10}k$) and R^2 (R^2_{KP}) of the Korsmeyer-Peppas plot (dissolution data between 10 to 60 % were evaluated). The amount of drug released in 20 % ethanol was too low (< 60 %) to perform the analysis.

EtOH [%]	Higuchi plot		Korsmeyer- Peppas Plot			Drug transport
	K_H	R^2_H	n_{KP}	$\log_{10}k$	R^2_{KP}	
0	5.90	0.997	0.47	0.85	0.997	anomalous
5	4.71	0.993	0.43	0.87	0.995	fickian
40	4.77	0.999	0.50	0.67	0.999	anomalous

The PVAc-based mini-tablets showed completely diverse dissolution profiles (Figure 38). The matrices stayed intact throughout the dissolution time in all media (Figure 39). However, the reference drug release (0 % ethanol) was similar only to the drug release in 5% ethanol ($f_2 = 60.8$). When considering the dissolution in 20 and 40 % ethanol as test, the similarity factor was decreased to 34.9 and 43.7 ($f_2 < 50$) respectively. The exponent n of the Korsmeyer-Peppas plot indicated that the drug

release was controlled by Fickian diffusion ($n \leq 0.45$) in 5%, and by anomalous diffusion in 0, 20 and 40 % ethanol (Table 15).

To better understand the polymer-liquids interaction, MTR measurements were conducted with powder of PVAc as substrate and water without and with 20 % and 40 % ethanol as moistening liquids. The temperature of the chamber and the liquids was set at 37 °C to simulate the temperature during dissolution testing. The MTR results are depicted in Figure 40.

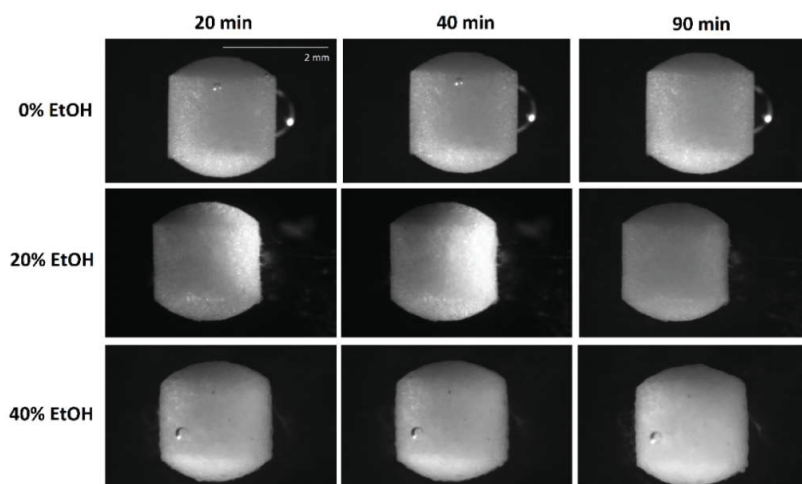


Figure 39: Swelling of the PVAc-based mini-tablets in 0.1 N HCl with 0, 20 and 40 % ethanol, over a time of 90 min; the images were taken by using stereomicroscopy.

PVAc is characterized by a low T_g of 39.3 °C (onset at 37.1 °C) (Figure 42), therefore it is assumed that it underwent a transition from a glassy to a rubbery state, readily after coming in contact with the dissolution medium. It can be observed that PVAc could interact with 0, 20 and 40 % ethanol and a sudden torque increase was seen at L/S ratio of 0.04 [g/g] when moistened by all solutions. As a matter of fact, it has been already reported in the literature that PVAc is also able to interact with sole water, despite its insolubility in this solvent [161, 162]. However, in alcoholic media, further addition of liquid led to the kneading of a softer mass (lower torque), therefore it is plausible that a gel-like mass was formed (Figure 41).

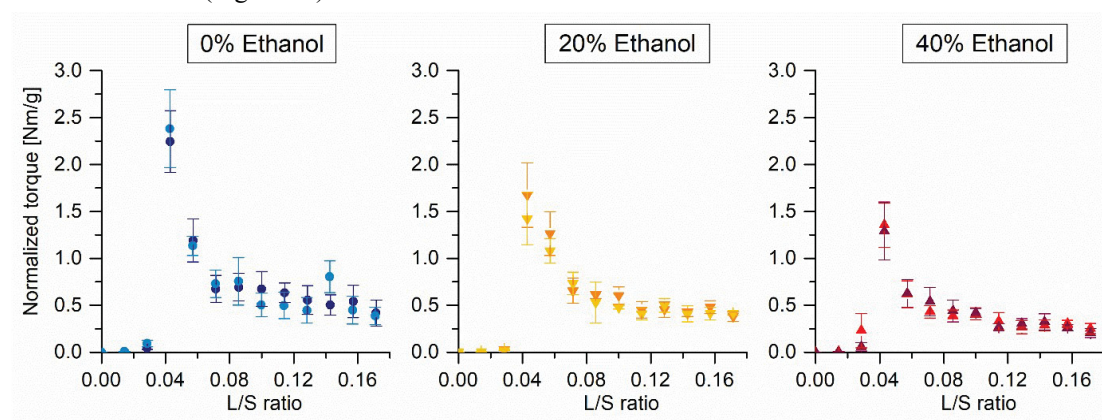


Figure 40: Torque profiles of PVAc using water (blue circles) and water-ethanol mixtures containing 20 % ethanol (yellow point-down triangles) and 40 % ethanol (red point-up triangles) as moistening liquids; shaft speed: 5 rpm; temperature of measuring chamber and medium: 37 °C; the single curves are depicted; $n = 2$.

As a matter of fact, the solubility of PVAc was increased by increasing the concentration of ethanol in the media and ethanol interacted with the polymer chains, thus leading to polymer entanglement and the formation of a polymer gel. The created gel layer might have increased the tortuosity within the matrix, thus lowering the release of theophylline in 20 and 40 % ethanol. In addition, the drug release in 40 % ethanol resulted slightly increased in comparison to that in 20 % ethanol due to the 2.8-fold higher drug solubility in this media.



Figure 41: Kneading knives of the mixer torque rheometer covered by the swollen PVAc, by using water (left) and 40 % ethanol (right) at a temperature of 37 °C, after the measurement time

Slightly faster drug release was seen in 0 % ethanol, due to the practically insolubility of PVAc in hydrous media, however, when 5 % ethanol was added, it is assumed that the formation of a gel decreased the dissolution rate.

In the second part of the study regarding PVAc, hot-melt extrusion (HME) was performed with theophylline/ PVAc-containing mixture (5.2.1.2), in order to tailor prolonged drug release. First, the thermal behaviour of the pure substances, theophylline monohydrate and PVAc, were investigated *via* DSC (Figure 42). For theophylline monohydrate, a sharp endothermic peak at 271.1 °C was recorded during the first heating cycle, which corresponded to the melting peak of the drug.

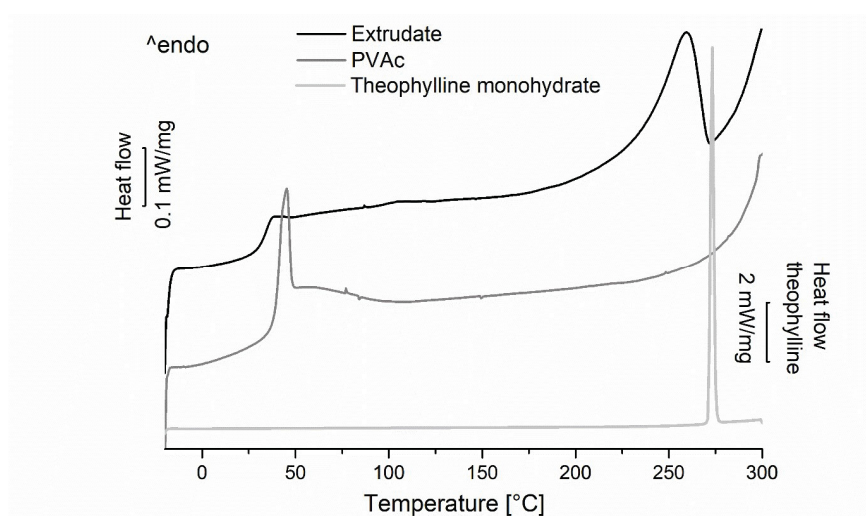


Figure 42: DSC thermograms (first heating cycle) of theophylline monohydrate, polyvinyl acetate and the extrudates produced by HME at 130 °C

The DSC scan of PVAc showed a slightly broad endothermic event (onset at 38.6 °C) in the first heating cycle, which corresponded to the polymer relaxation peak, followed by a broad shoulder due to the moisture evaporation. Upon reheating (not shown in Figure 42), an endothermic event, which corresponded to the polymer glass transition temperature (T_g), was detected at 39.3 °C (onset at 37.1 °C). As a matter of fact, PVAc is an atactic amorphous polymer [165] due to its acetate ester side chain and the T_g is relatively low due to the highly flexible backbone structure [162].

PVAc matrices could be successfully prepared by HME and a process temperature of 130 °C was used. The power consumption amounted 19%. The produced extrudates were also analysed *via* DSC and showed two endothermic events at the first heating cycle (Figure 42): firstly, a T_g at 31.9 °C (onset 27.4 °C) and secondly, a wide endothermic peak at 259.0 °C (onset at 234.3 °C), which corresponded to the melting peak of theophylline. The extrudates were characterized by a smooth surface and theophylline was mainly dispersed into the matrix rather than dissolved (Figure 43a).

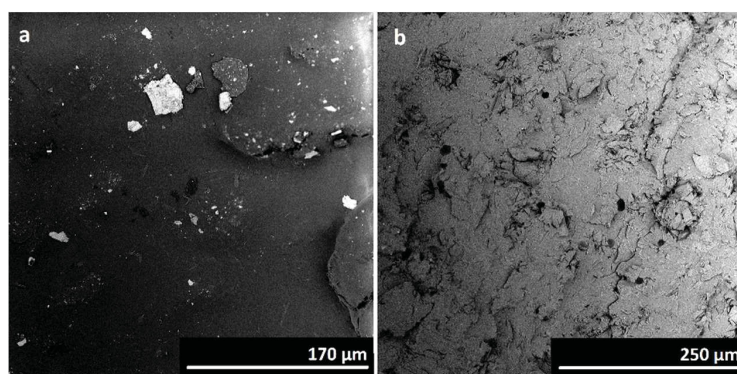


Figure 43: SEM images of the PVAc extrudates surface (a) and cross sections (b)

Dissolution test was performed and media containing 0, 5, 20 and 40 % ethanol were evaluated. The PVAc mini-matrices maintained their shape throughout the all dissolution test, however only in 0 % and 5 % ethanol. In presence of 20 and 40 % the extrudates attached together and formed a sticky gum-like mass. PVAc was in a rubbery state during the dissolution test since the onset of the glass transition was registered at 37.1 °C. As can be seen in Figure 44, not even 10 % API was released in 0% ethanol after 2 hours. In addition, increasing the ethanol concentration up to 5 and 20 % did not lead to significantly higher drug release. However, a trend which was in accordance to the increased solubility of theophylline in the different hydro-alcoholic media (see Figure 5) could be recognized. Differently, in 40 % alcohol much faster drug release could be achieved and 60 % theophylline was released after 2 h. The exponent n of the Korsmeyer-Peppas plot amounted 0.49 ($R^2 = 0.987$) thus indicating anomalous drug transport due to the swelling and erosion of PVAc in 40 % alcohol, which is slightly soluble in ethanolic solutions.

In addition, the significantly increased theophylline solubility in 40 % ethanol contributed to the faster release in this media. Özgüney et al. [172] hot-melt extruded powder mixtures containing theophylline and Kollidon® SR. The authors investigated the effect of process temperature (from 80 to 90 °C) and drug loading (from 25 to 35%) on the drug release and stated that theophylline release rate decreased when (i) the extrusion temperature increased and (ii) the drug load decreased. As a matter of fact, a “big jump” [172] in theophylline release was seen when the drug loading was increased from 25 to

35% and explained by the presence of isolated drug particles within the matrix with 25 % API load. In this case, the release of the drug particles took place primarily through the matrix and not through pores generated by the dissolved drug particles as with 35% drug loadings. It is obvious now, how the temperature chosen for this study was probably too high and led to very dense matrices. In addition, it is assumed that 30 % drug loading was below the percolation threshold in this matrix system and the drug release was therefore drastically decreased.

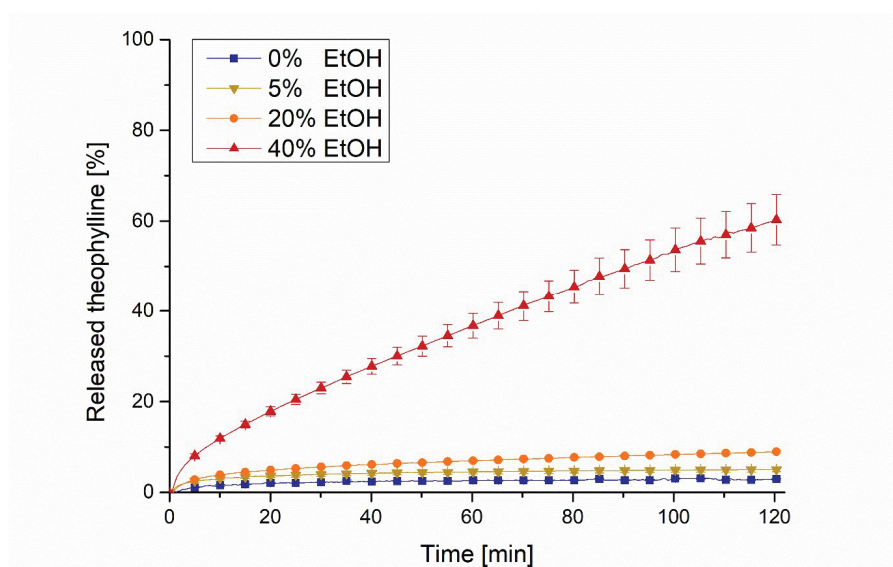


Figure 44: Dissolution profiles of the extrudates based on PVAc in 0.1 N HCl with 0, 5, 20 and 40 % ethanol; in each vessel 8 mini-tablets, which corresponded to ca. 15 mg theophylline; mean \pm SD, n = 3

Due to the highly variable dissolution behaviour of PVAc-based mini-tablets and extrudates against different concentrations of alcohol, only hydrophilic rate-controlling polymers will be tested and discussed in the following sections. Moreover, for the experiments reported below, mini-tablets have been chosen as the dosage form of choice, since wet extrusion was not expected to bring further advantages in terms of dissolution performances of the resulting mini-matrices.

3.3.5 Hypromellose

In chapter 3.1, it has been shown that a co-processed excipient based on HPMC could lead to resistance against alcohol. Aim of this study was to assess the ability of sole HPMC to prolong the release of theophylline from 2 mm mini-tablets (5.2.1.1.5). HPMC with different viscosity grades were tested, in particular HPMC K4M and HPMC K100M, in order to evaluate the influence of the polymer viscosity on the drug release rate in 0 % and 40 % ethanol.

Table 16: Mass, tensile strength and porosity of mini-tablets based on HPMC K4M and HPMC K100M

Polymer	Mass [mg]	Crushing strength [N]	Tensile strength [MPa]	Porosity [%]
HPMC K4M	6.62 \pm 0.14	14.3 \pm 2.0	2.1 \pm 0.3	14.7 \pm 1.4
HPMC K100M	6.92 \pm 0.14	13.4 \pm 2.8	1.9 \pm 0.4	38.6 \pm 1.1

The mini-tablet mass, tensile strength and porosity values are shown in Table 16. As can be seen, the mini-tablets were characterized by acceptable crushing strength values, which were higher than the acceptable value of 7 N [173] and not significantly affected by the polymer viscosity. By analysing the porosity values, an increase in viscosity grade resulted in an increase in porosity of the mini-tablets. This phenomenon was already described by Nokhodchi et al. [174, 175], who assumed that lower viscosity grade of HPMC can deform more easily in order to fill inter-particulate void.

HPMC is referred to as a polymer, which undergoes a rapid hydration after coming into contact with water and the polymer chains form a viscous gel layer by polymer cross-linking [176]. To assure that a failure of the matrix system does not occur, a fast hydration of the polymer is mandatory.

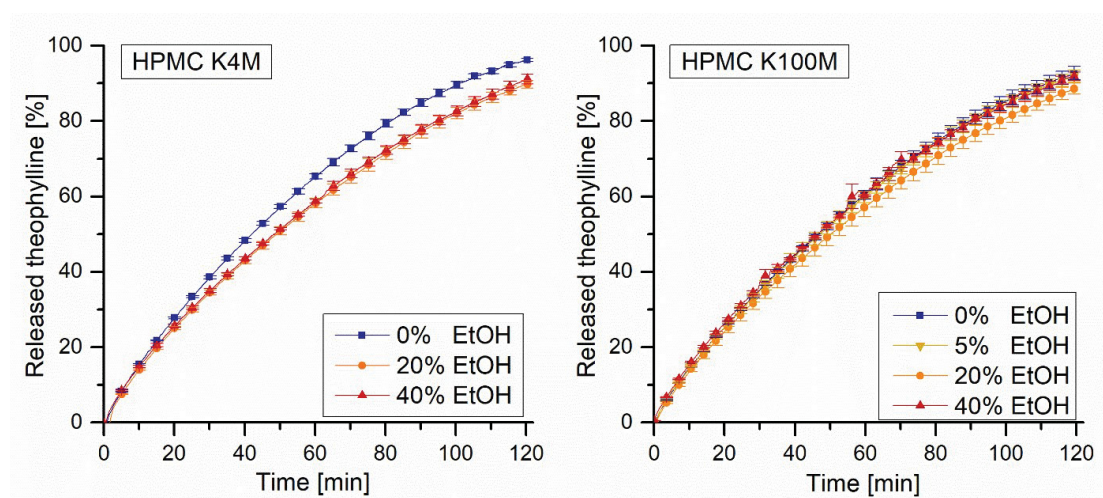


Figure 45: Dissolution profiles of the mini-tablets based on HPMC K4M (left) and HPMC K100M (right) in 0.1 N HCl with 0 %, (5 %), 20 % and 40 % ethanol; in each vessel 8 mini-tablets, which corresponded to ca. 15.6 mg theophylline; mean \pm SD, n = 3.

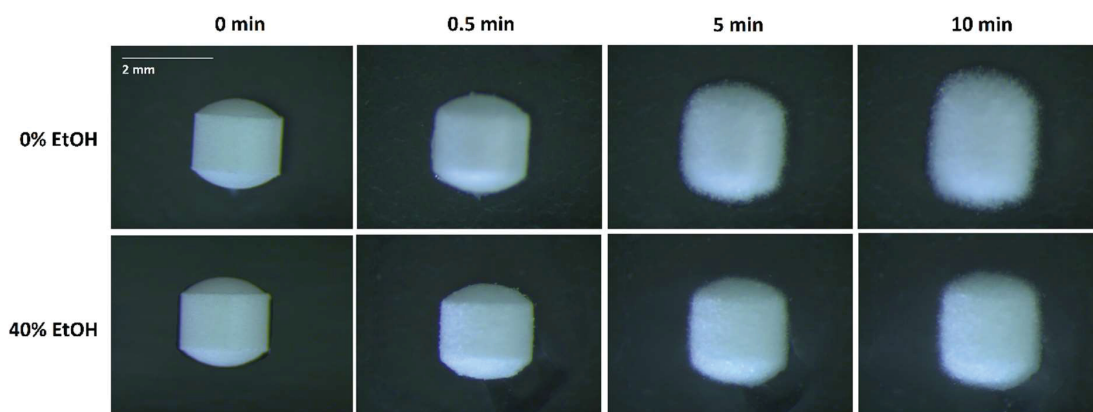


Figure 46: Swelling of the HPMC K100M-based mini-tablets in 0.1 N HCl with 0 % and 40 % ethanol, over a time of 10 min; the images were taken by using stereomicroscopy.

Figure 45 (left) illustrates the dissolution of HPMC K4M-based mini-tablets. No ADD occurred and the dissolution showed similar profiles in 0, 20 and 40 % ethanol, with calculated similarity factors f_2 of 61.7 and 64.1, when comparing the dissolution data in 0 % as reference and those in 20 and 40 %

alcohol as test respectively. However, when the ethanol concentration in the medium was increased, the amount of released drug was slightly decreased, as demonstrated by the decreased AUC values in Table 17. As already seen in chapter 3.1 for RetaLac[®]-based matrices, the presence of alcohol in the medium might have induced an increase in the viscosity of the HPMC gel layer which surrounds the mini-tablets, phenomenon which was also reported by Missaghi et al. [46]. These findings are in accordance with several authors, who reported the effect of ethanol on HPMC large tablets [4, 5, 27, 28, 94, 95].

When the viscosity grade of HPMC was increased from 4,000 to 100,000 mPa·s, the dissolution profiles were only slightly affected (Table 17). The results are shown in Figure 45 (right). Similarity factors were higher than the values calculated for HPMC K4M-based mini-tablets and amounted 97.9 (0 % vs. 5 % ethanol), 75.0 (0 % vs. 20 % ethanol) and 92.9 (0 % vs. 40 % ethanol), showing similar release profiles in all ethanol concentrations.

Table 17: Area under the curve (AUC_{120 min}) values calculated from the mean dissolution curves of mini-tablets based on different viscosity grade of HPMC, in 0, 20 and 40 % ethanol in the dissolution media

Polymer	AUC _{120 min} [%·min]		
	0 % EtOH	20 % EtOH	40 % EtOH
HPMC K4M	7203	6518	6608
HPMC K100M	6781	6422	6806

In Figure 46 the swelling of the mini-tablets with HPMC K100M upon contact with 0 % and 40 % alcohol is shown. The mini-tablets underwent a higher swelling extent in media without alcohol, especially in the axial plane, however, they were able to swell also in presence of alcohol. As already seen for larger tablets (3.1.5), the mini-tablets expansion was higher in the axial plane than in the radial one, which is assumed to result from the release of the tablet compression forces during the dissolution [94]. The obtained n_{KP} values (Table 18) indicated an anomalous non-Fickian transport in 0, 20 and 40 % ethanol, obviously due to the swelling and erosion of the matrix in all media. Very good correlation of the dissolution data with the Korsmeyer-Peppas plot was observed.

Table 18: Release characteristics for the HPMC K4M/ K100M mini-tablets; slope (K_H) and R^2 (R_H^2) of the Higuchi plot (for the calculation, dissolution data up to 60 % were evaluated); exponent (n_{KP}), intercept ($\log_{10}k$) and R^2 (R_{KP}^2) of the Korsmeyer-Peppas plot (dissolution data between 10 % to 80 % were evaluated)

EtOH [%]	HPMC type	Higuchi plot		Korsmeyer- Peppas Plot			Drug transport
		K_H	R_H^2	n_{KP}	$\log_{10}k$	R_{KP}^2	
0	K4M	9.51	0.983	0.77	0.44	0.999	anomalous
	K100M	9.04	0.981	0.79	0.37	0.999	anomalous
20	K4M	8.94	0.988	0.76	0.42	1.000	anomalous
	K100M	8.77	0.984	0.78	0.37	0.999	anomalous
40	K4M	8.61	0.985	0.77	0.39	0.999	anomalous
	K100M	8.67	0.983	0.79	0.37	0.998	anomalous

Rheological measurements were performed on the two HPMC viscosity grade powders, to study the polymers swelling ability, by using mixer torque rheometry (MTR). In this study, the torque was evaluated as an indirect value for the polymer swelling in 0 % and 40 % ethanol, since it describes the cohesive strength of the wet mass [156]. Pure polymer was used for these investigations to exclude the influence of further excipients present in the formulation. As a matter of fact, such excipients may enhance or hinder the swelling ability of the polymer within the matrix microenvironment due to their solubility and interaction. The torque profiles are depicted in Figure 47 and Figure 48 for HPMC K4M and HPMC K100M respectively.

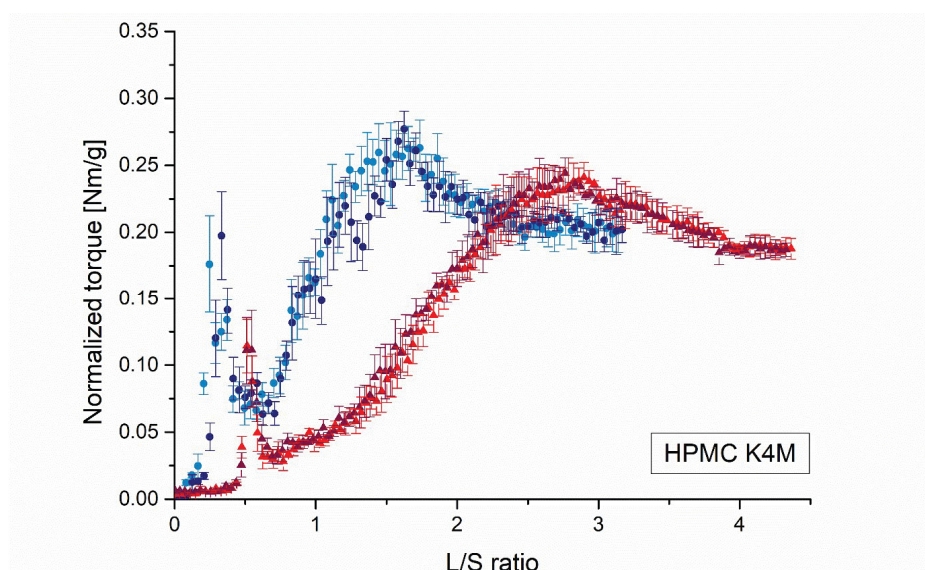


Figure 47: Torque profiles of HPMC K4M using water (blue circles) and water-ethanol mixtures containing 40 % ethanol (red triangles) as moistening liquid; the single curves are depicted; $n = 2$.

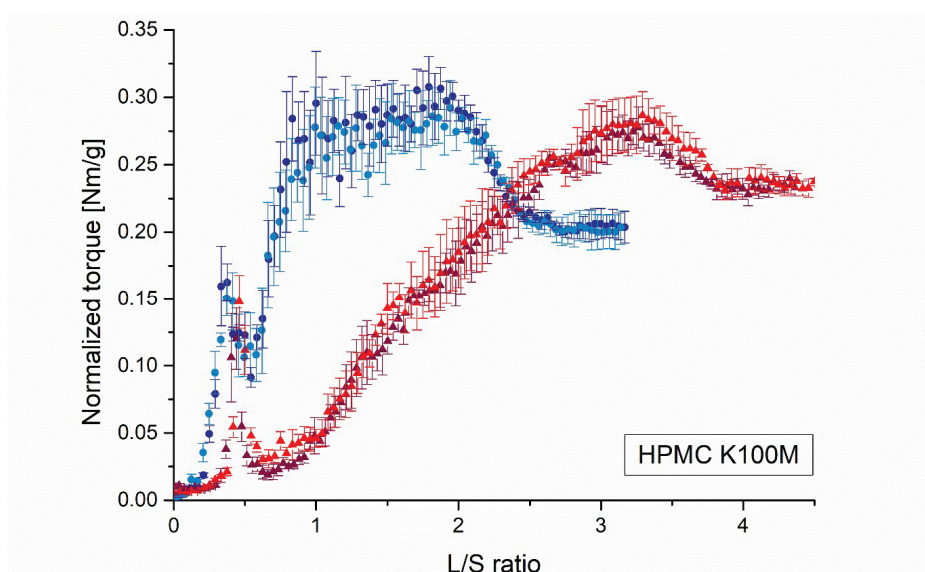


Figure 48: Torque profiles of HPMC K100M using water (blue circles) and water-ethanol mixtures containing 40 % ethanol (red triangles) as moistening liquid; the single curves are depicted; $n = 2$.

The torque recorded while mixing the polymer wetted with both media initially rose up to a first peak, to which a sudden torque drop followed. To clarify these findings, a short overview about particle agglomeration in wet state follows. At the initial wetting stage, the addition of liquid to the dry polymer causes the formation of liquid bridges between the solid particles till a pendular agglomerate is formed. By further increasing the amount of liquid, the number and extent of liquid bridges increase and the funicular state is achieved [135]. When the liquid has filled all inter-particulate voids, the agglomerates held together by strong capillary forces (capillary state) cause the onset of a maximum torque recorded by the rheometer. The further addition of liquid leads to a rapid torque reduction, due to the overwetting of the mass. Several studies regarding the agglomeration process of wet powders have been performed in wet granulation research [177, 178].

Interestingly, similar maximum torque were recorded at the capillary state (first peak) for both polymers in both media and amounted 0.19 ± 0.01 Nm/g in 0 % ethanol and 0.11 ± 0.00 Nm/g in 40 % ethanol for HPMC K4M and 0.16 ± 0.01 Nm/g in 0 % ethanol and 0.13 ± 0.02 Nm/g in 40 % ethanol for HPMC K100M. However, higher L/S ratio were needed to reach the capillary state for HPMC K4M wetted with 40 % ethanol (0.29 ± 0.06 g/g in water vs. 0.53 ± 0.02 g/g in ethanolic liquid). HPMC K100M showed a torque peak at L/S ratio of 0.37 ± 0.00 g/g in water and 0.45 ± 0.01 g/g in 40 % ethanol, thus indicating more similar results. Nevertheless, the most interesting results of this study were shown at higher L/S ratios. As can be noticed, the overwetting of the masses led to the swelling of the polymers, to which a gradual increase in the mean torque corresponded. It has been already reported that HPMC can retain a relatively large quantity of moistening liquid [134]. The flat and extended peak, especially in the case of HPMC K100M- water system, indicates that this polymer could interact strongly with the medium [179]. Large differences can be observed regarding the polymer swelling in the two media: both HPMC viscosity grade underwent swelling, however, significantly higher L/S ratio were needed with alcohol to reach a state of wet mass with maximal cohesive strength. A gradual torque decrease was observed at higher L/S ratio, followed by a plateau, where an increase of liquid did not result in torque variations. In addition, when comparing the two viscosity grades, slightly more cohesive masses were obtained by wetting HPMC K100M with both media. In light of these data, it can be indicated that both viscosity grades were able to swell, also in the presence of alcohol. However, both viscosity grades needed more liquid to agglomerate and swell, thus indicating that the interaction polymer-water was higher than the interaction polymer-ethanol. Nevertheless, it has to be taken into account that the amount of liquid used in the dissolution testing was significantly higher than that considered in this test. Therefore, a complete swelling is expected to take place during the dissolution test in both media, thus leading to similar drug release as seen above (Figure 45).

3.3.6 Pregelatinized starch

Most native starches consist of two polysaccharides, the essentially linear amylose and the branched amylopectin, in different amounts. Since native starches do not swell extensively in cold water, physically or chemically modified starched have been used in sustained release tablets, due to their swelling ability in cold-water and gel layer formation [101]. Rak et al. [180] and Van Aerde and Remon [181] evaluated to use thermally modified starches for controlled drug release. Herman and

Remon [182] stated that only fully pregelatinized starch (PGS) with low amount of amylose ($\leq 25\%$) could be used to form a strong gel which controls the drug release. As a matter of fact, amylose molecules are assumed to decrease the gel cohesion and accelerate the erosion of the gel barrier [183]. Studies regarding cross-linked high amylose starch, commercially available as Contramid[®], were also performed by Traynor et al. [51]. Partially pregelatinized maize starches are usually formulated as binder-disintegrants in immediate drug release tablets [184] and not in prolonged release applications, due to their very limited ability to form a gel on the tablet surface [185]. It is also well known that PGS is also one of the most commonly used fillers in the development of HPMC-based matrix tablets [53, 101]. PGS is insoluble in alcohol [51] and to our knowledge, no data are available regarding exclusively PGS-formulations in combination with hydro-alcoholic media. Thus, in this study, PGS was formulated into 2 mm mini-tablets (5.2.1.1.5) to establish a possible vulnerability or robustness of the polymer against alcohol.

The mass, tensile strength and porosity of the mini-tablets were the following: 6.70 ± 0.14 mg, 0.3 ± 0.1 MPa and $21.8 \pm 1.4\%$. The dissolution behaviour of the produced PGS- based mini-tablets is depicted in Figure 49. As can be seen, the formulation was not alcohol resistant and showed ADD in both 20 and 40 % ethanol. As can be seen in Figure 50, the mini-tablets fully disintegrated after coming in contact with the ethanolic media and within few minutes the entire dose was released ($f_2 = 11.5$). Differently, in 0 % ethanol the mini-tablets swelled (Figure 50) and a slower drug release was achieved. It is assumed that the vulnerability against alcohol is due to the practically insolubility of PGS in alcohol.

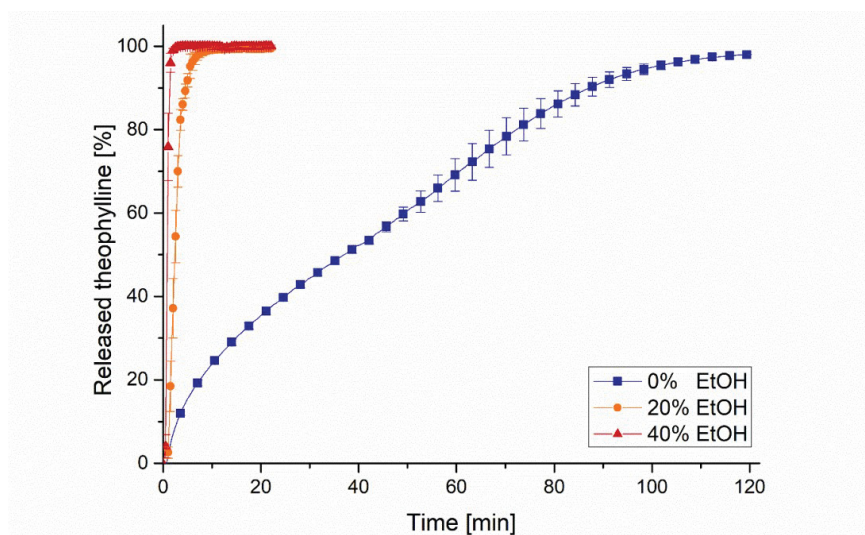


Figure 49: Dissolution profiles of the mini-tablets based on pregelatinized starch in 0.1 N HCl with 0, 20 and 40 % ethanol; in each vessel 8 mini-tablets, which corresponded to ca. 15.6 mg theophylline; mean \pm SD, n = 3.

The dissolution without alcohol was characterized by a slightly sigmoidal profile (Figure 49). During the test, it was observed that the mini-tablets first swelled, and then, after approximately 60 min, a rupture within the matrix occurred, which caused the observed slightly higher drug release rate. This rupture, however, did not lead to a dose dumping. The described phenomenon might be due to the partial elastic deformation of the tablets at the end of the compression process, which leads to (i) very

low crushing strengths of 2.25 ± 1.01 N and (ii) a network, which is easy to be penetrated by the medium during dissolution [186]

Stoltenberg et al. [173] reported that good compactability properties of the powder mixtures are required to produce mini-tablets, due to the fragility of the mini-tableting tools and the lower compression pressures which can be therefore applied. The authors considered acceptable crushing strengths ≥ 7 N. Not sufficient mechanical properties could be achieved at the selected compression force, by using PGS.

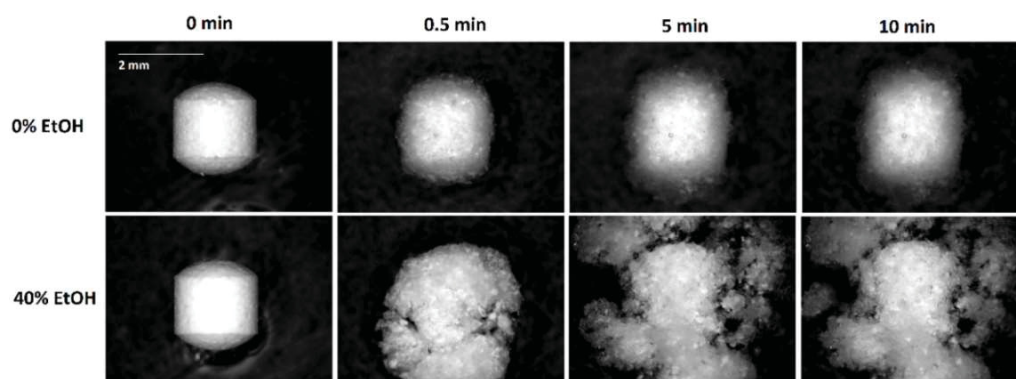


Figure 50: Swelling of the pregelatinized starch-based mini-tablets in 0.1 N HCl with 0 % and 40 % ethanol, over a time of 10 min; the images were taken by using stereomicroscopy.

Due to the lack of consistent swelling and gelation of PGS in hydro-alcoholic media, the usage of PGS should be recommended only in combination with rate-controlling polymers, which are able to swell in alcohol. Thus, the insolubility of PGS in alcohol did not allow to tailor alcohol-resistance.

3.3.7 Carbomer

Due to their hydrophilic nature and tightly cross-linked structure, polyacrylic acid resins, also known as carbomer or Carbopol[®], are widely used in the development of oral controlled-release dosage forms [24, 187-189]. Carbomers have been reported to be able to swell upon hydration in water but also in polar solvent, as alcohol [24], which leads to the formation of a hydrogel. Therefore, in this study, a high viscosity grade of carbomer, Carbopol[®] 980 NF (40,000-60,000 mPa·s, 0.5% wt polymer at pH 7.5) was used to prepare mini-tablets (5.2.1.1.5). The mass, tensile strength and porosity of the mini-tablets were the following: 3.98 ± 0.14 mg, 4.3 ± 0.8 MPa, 28.9 ± 2.4 %. The blend was characterized by poor flowability, which hindered the complete filling of the die, thus leading to mass values lower than 6.5 mg.

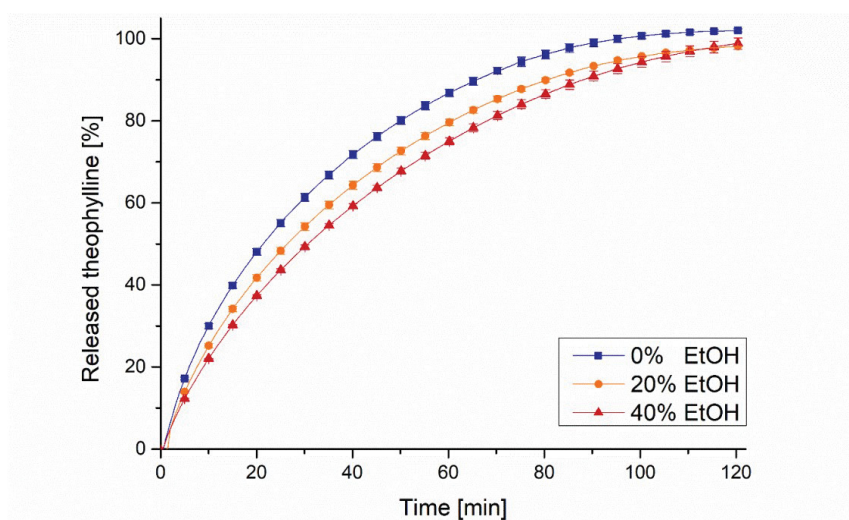


Figure 51: Dissolution profiles of the mini-tablets based on Carbopol® 980 NF in 0.1 N HCl with 0, 20 and 40 % ethanol; in each vessel 13 mini-tablets, which corresponded to ca. 15 mg theophylline; mean \pm SD, $n = 3$

The results of the dissolution testing in hydro-alcoholic media are illustrated in Figure 51. The mini-tablets underwent swelling in all media and no disruption of the mini-matrices was observed (Figure 52). Similarity factor amounted 59.2 when considering the drug release in 0 % (reference) and 20 % ethanol (test), thus showing similarity between the dissolution profiles, however, when adding 40 % ethanol in the media, f_2 decreased to 48.3, due to the decreased dissolution rate in presence of alcohol. Although alcohol resistance was achieved, low f_2 were calculated.

Carbomer has a pK_a of 6.0 ± 0.5 [115]. Therefore, as already seen for the anionic xanthan gum (Figure 22), it is plausible that at lower pH carbomer is not fully swollen [24] and alcohol might have functioned as a cosolvent for the polymer, thus leading to the formation of a gel of higher strength. The usage of MTR was avoided in order to study the swelling ability of carbomer in hydrous and hydro-alcoholic media. As a matter of fact, the experiments should have been performed at $pH = 1.2$ due to the pH-dependency of this polymer to swell. However, the metallic walls of the measuring chamber of the MTR might have been damaged by acid corrosion.

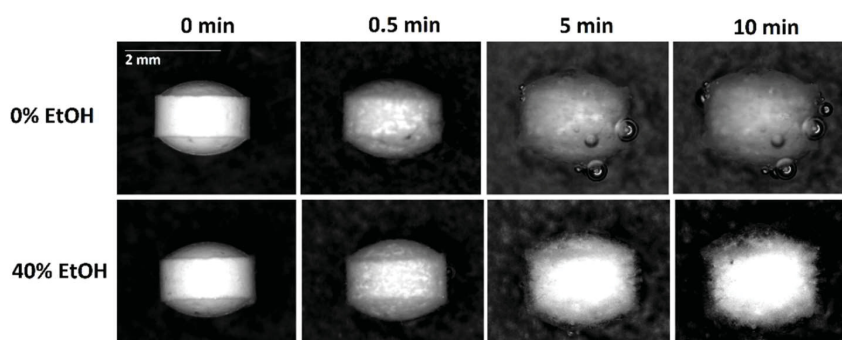


Figure 52: Swelling of the carbomer-based mini-tablets in 0.1 N HCl with 0 % and 40 % ethanol, over a time of 10 min; the images were taken by using stereomicroscopy.

Rahim et al. [190] studied the effect of ethanolic media (buffered and acidic media) on the swelling and drug release of carbomer matrix tablets, which incorporated differently soluble model APIs and viscosity grades of polymer (Carbopol® 971P and 974P). The results revealed that no alcohol-induced dose dumping occurred. However, the drug release rate and mechanism was significantly influenced by the presence of alcohol, due to the affected solubility of the drugs, the polymer viscosity grade and the medium pH together with alcohol.

Table 19: Release characteristics for carbomer mini-tablets; slope (K_H) and R^2 (R_H^2) of the Higuchi plot (for the calculation, dissolution data up to 60 % were evaluated); exponent (n_{KP}), intercept ($\log_{10}k$) and R^2 (R_{KP}^2) of the Korsmeyer-Peppas plot (dissolution data between 10 % to 80 % were evaluated)

EtOH [%]	Higuchi plot		Korsmeyer- Peppas Plot			Drug transport
	K_H	R_H^2	n_{KP}	$\log_{10}k$	R_{KP}^2	
0	12.19	0.993	0.66	0.79	0.993	anomalous
20	11.24	0.995	0.72	0.63	0.991	anomalous
40	10.60	0.991	0.70	0.64	0.996	anomalous

The kinetics of the drug release (Table 19) was in addition analysed and n_{KP} values were above 0.45 and below 0.89 in all media, suggesting that the dissolution was controlled by an anomalous transport. The n_{KP} values for theophylline in 20 % ethanol was the highest. In addition, $n_{KP} = 0.66$ calculated for the mini-tablets in 0.1 N HCl indicates that the drug diffusion and erosion controlled the release process of theophylline in equal parts [167].

3.3.8 Polyethylene oxide

High-weight polyethylene oxide (PEO) is a polymer, which is soluble in water, however insoluble in most alcohols [115]. Therefore Jedinger et al. [24] and Bartholomaeus et al. [55] reported that PEO could be used as suitable polymer for the development of ADD resistant formulations. Palmer et al. [155] investigated the influence of ethanol on the hydration and swelling properties of compacts prepared with three viscosity grades of PEO and showed that all compacts underwent swelling and did not exhibit any disruption of the matrix. To our knowledge, no data regarding multiple-unit dosage forms with PEO as rate-controlling polymer have been published in the literature until now.

The high viscosity grade of PEO (Polyox™ WSR-303 LEO NF, 7,000,000 g/mol) was used to produce matrix mini-tablets (5.2.1.1.5). Mass, tensile strength and porosity of the produced PEO mini-tablets were the following: 6.40 ± 0.12 mg, 1.2 ± 0.2 MPa and 10.3 ± 1.3 % respectively. Upon compression, PEO underwent plastic deformation, however, due to its viscoelastic behavior and large axial expansion [191], PEO led to mini-tablets of slightly low tensile strength. Nevertheless, crushing strengths of 8.0 ± 1.4 N ($F \geq 7$ N) were measured, indicating that the mini-tablets were characterized by acceptable mechanical properties.

The dissolution profiles of PEO-mini-tablets are shown in Figure 53. Interestingly, similar profiles in 0, 20 and 40 % ethanol could be tailored, with similarity factors of 62.3 and 76.3, considering the drug release profiles in respectively 20 and 40 % ethanol as test and in 0 % ethanol as reference.

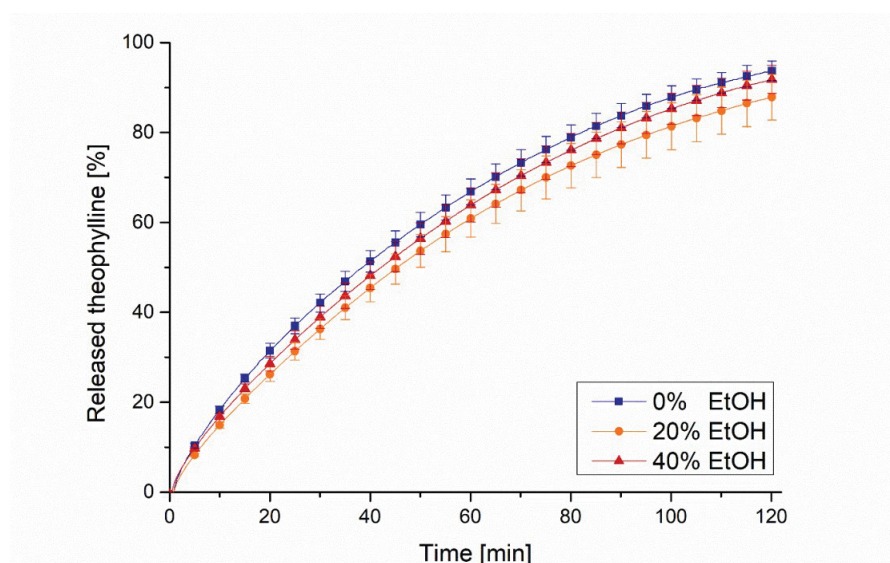


Figure 53: Dissolution profiles of the mini-tablets based on PEO in 0.1 N HCl with 0, 20 and 40 % ethanol; in each vessel 8 mini-tablets, which corresponded to ca. 15.6 mg theophylline; mean \pm SD, $n = 3$

The transport of the drug through the matrices was slightly influenced by alcohol, with slightly increased exponent n of the Korsmeyer-Peppas- equation in alcoholic media (Table 20). n_{KP} values were between 0.45 and 0.89, thus indicating that the drug transport was anomalous (non-fickian) and therefore controlled by both polymer erosion and diffusion of the theophylline through the gel layer [145]. Furthermore, by increasing the ethanol content in the media the n_{KP} slightly increased.

Table 20: Release characteristics for PEO mini-tablets; slope (K_H) and R^2 (R^2_H) of the Higuchi plot (for the calculation, dissolution data up to 60 % were evaluated); exponent (n_{KP}), intercept ($\log_{10}k$) and R^2 (R^2_{KP}) of the Korsmeyer-Peppas plot (dissolution data between 10 % between 80 % were evaluated)

EtOH [%]	Higuchi plot		Korsmeyer- Peppas Plot			Drug transport
	K_H	R^2_H	n_{KP}	$\log_{10}k$	R^2_{KP}	
0	9.53	0.990	0.70	0.58	0.998	anomalous
20	9.02	0.984	0.74	0.47	0.997	anomalous
40	8.95	0.986	0.75	0.45	0.998	anomalous

The swelling of PEO-mini-tablets was monitored and the resulting images are depicted in Figure 54. In comparison to HPMC (Figure 46), PEO led to a less anisotropic swelling, thus increasing their size also on the radial plane. PEO led to a fast swelling in both 0 % and 40 % ethanol. Slightly higher swelling can be observed in hydrous liquids, however a rate-controlling gel layer could be formed in 40 % ethanol, which counteract the high solubility of theophylline in this medium.

The swelling ability of PEO was in addition studied in hydrous and hydro-alcoholic media by using mixer torque rheometry. Also in this case, the rheological behavior of the PEO powder masses, moistened by water and alcoholic media, was characterized by multiple liquid addition technique. The resulting profiles are represented in Figure 55. In comparison to HPMC, PEO showed a more rapid increase in normalized torque at lower L/S ratio, between 0.2 and 0.3 g/g, using both water and 40 % alcohol as moistening liquids. At higher L/S ratio the torque decreased and a steady-state region was

achieved at torque values which ranged between 0.3 Nm/g and 0.4 Nm/g. The extended plateau, which could be seen, indicates that PEO was able to retain both water and alcoholic solutions to a high extent. Based on these observations, it is therefore plausible that the ability of PEO to swell was not influenced by the presence of alcohol in the media. These findings are in alignment with the literature: Palmer et al. [155] evaluated the effect of alcohol on swelling of compacts made of different viscosity grade of PEO. They performed gravimetric studies and reported that all PEO tablets underwent swelling and gelation in hydro-alcoholic media, without any disruption within the matrix.

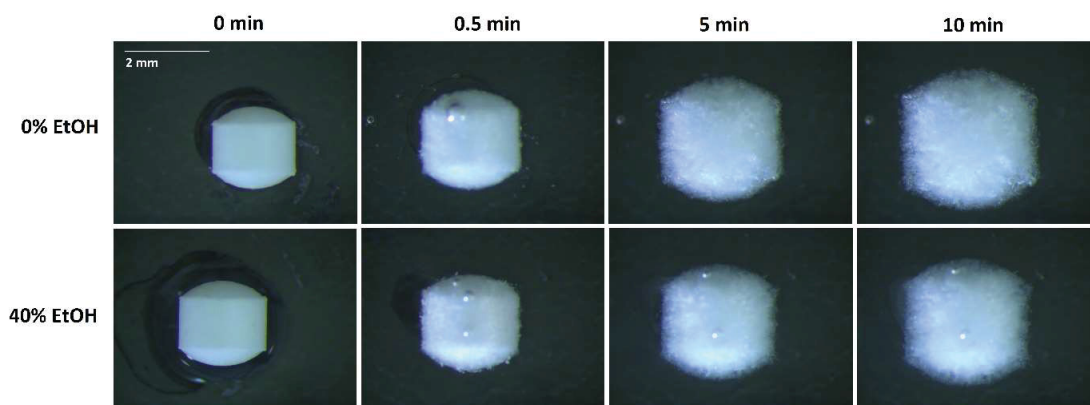


Figure 54: Swelling of the PEO-based mini-tablets in 0.1 N HCl with 0 % and 40 % ethanol, over a time of 10 min; the images were taken by using stereomicroscopy.

In accordance to these studies, PEO has demonstrated to be a suitable candidate for the development of ADD-resistant matrix tablets, due to its fast and consistent swelling ability, which could minimize the risk of dose dumping. In chapter 3.4, further studies will be shown regarding the influence of the dissolution medium composition on relative swelling, dissolution media uptake and mass loss of differently sized PEO matrix tablets.

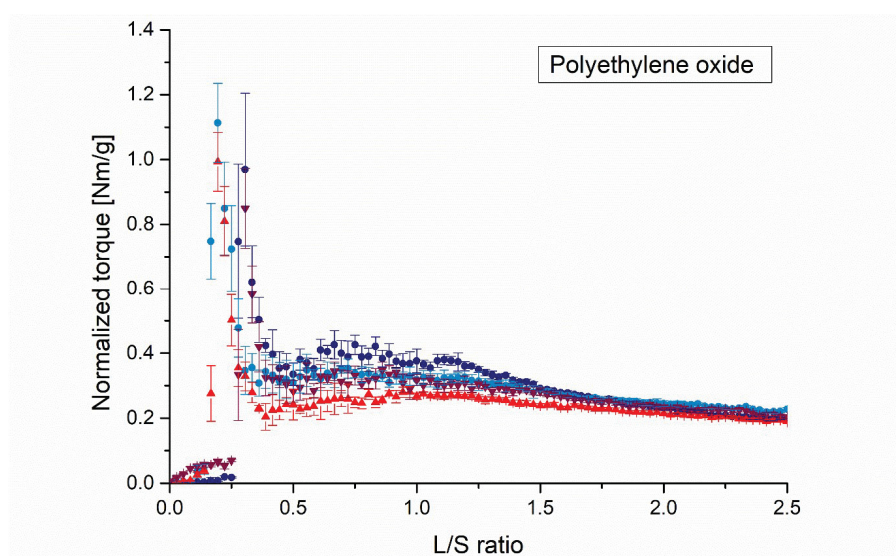


Figure 55: Torque profiles of PEO using water (blue circles) and water-ethanol mixtures containing 40 % ethanol (red triangles) as moistening liquid; the single curves are depicted; $n = 2$.

3.3.9 Summary

A screening of polymers suitable for the development of alcohol-resistant mini-matrices has been performed. Hydrophilic polymers such as XG, HPMC (K4M and K100M), carbomer (Carbopol® 980 NF) and PEO (7,000,000 g/mol) were able to swell in 0, 20 and 40 % ethanolic dissolution media and formed a rate-controlling gel around the mini-matrices. Consequently, alcohol resistance could be tailored with all aforementioned polymers. Despite the higher solubility of the model API theophylline in alcohol, a slightly lower amount of drug was released in 40 % ethanol from XG-, HPMC K4M- and carbomer-based mini-matrices. Furthermore, very high similarity factors were determined in regard to HPMC K100M- and PEO-mini-tablets, thus indicating the high suitability and robustness of these polymers against ADD, when theophylline is incorporated as drug.

Moreover, the commonly used additives MCC and PGS were investigated. Interestingly, MCC led to decreased drug release rates in 40 % alcohol, whereas PGS led to ADD in both 20 and 40 % ethanol.

The rheological behaviour was successfully monitored by MTR in regard to the two viscosity grade of HPMC and PEO. Interestingly, both HPMCs needed more liquid to form a wet mass with maximal cohesive strength in presence of ethanol, thus indicating that the interaction polymer-water was higher than the interaction polymer-ethanolic solutions. However, it is assumed that during dissolution, both polymer grades underwent swelling in 0 % and 40 %, which was also confirmed by the image analysis results. PEO showed very similar torque profiles in water and 40 % ethanol by MTR and slightly higher swelling in 0 % alcohol by image analysis.

Also Kollidon® SR resulted to be a promising polymer to achieve both prolonged drug release and alcohol resistance. The drug release rate was significantly decreased in 0.1 N HCl in comparison to the formulations with hydrophilic polymers. However, in 20 % ethanol, the drug release rate was further decreased, while in 40 % ethanol it was strongly increased. As a matter of fact, the PVP contained in Kollidon® SR is assumed to be more soluble in 20 % ethanol than 0.1 N HCl, which led to more viscous gels and less polymer leaching in 20 % ethanol. The EMA requirements, which recommend to perform the dissolution test in a maximal ethanol concentration of 20 % (v/v) [5] were met by the Kollidon® SR mini-tablets. However, further excipients are needed in the formulation to overcome the faster drug release in 40 % ethanol and to meet the requirements of the FDA.

Surprisingly, PVAc-mini-tablets showed a completely different behaviour and similarity of the dissolution profiles was achieved only in 5% ethanol. Based on MTR results, it is assumed that a PVAc gel was formed in 20 and 40 % ethanol, which led to decreased drug release rates. HME of PVAc-based mixtures led to high mass densification and not even 10 % drug was released in 2 h in 0, 5 and 20 % ethanol. However, faster drug release was seen in 40 % ethanol, due to the higher solubility of both API and PVAc in this media.

3.4 Influence of the tablet size on the dissolution properties of PEO matrix tablets

3.4.1 Introduction and Objectives

In chapter 3.3 it has been seen that prolonged drug release could not be tailored by using either 2 mm mini-tablets or extrudates of 3 mm length based on hydrophilic polymers, as HPMC, PEO and carbomer. Due to the short diffusion pathway, the slightly soluble theophylline was completely released within approximately 2 to 3 hours dissolution testing, dependent on the physico-chemical characteristics of the rate-controlling polymer in hydrous and hydro-alcoholic media.

Therefore, the aim of this study was to assess the influence of the matrix tablet diameter on the drug release kinetic. Thus, the geometry, i.e. diameter, thickness and shape, of the matrix tablet is a critical factor, which has to be taken into account in order to tailor the desired drug release profile [47].

It is already known in the literature that the surface area of the matrix has a relevant influence on the dissolution behaviour, in particular the higher the surface area of the matrix in contact with the dissolution medium the higher the drug dissolution rate which results [192]. Siepmann et al. [193] evaluated the influence of the tablet radius to height ratio and the size of cylindrical matrices on drug dissolution for diffusion-controlled systems. The authors stated that, due to the high specific surface area (equal to the absolute surface area to absolute volume ratio, SA/V), smaller tablets led to faster dissolution than large cylindrical tablets. In addition, Skoug et al. [194] reported that halving a sustained release tablet leads to an increase in SA/V of 16 % in comparison to the whole tablet. Consequently, the authors observed that the drug release from the two halves was faster than from the entire tablet.

It is therefore clear that the SA/V is a relevant parameter which has to be evaluated when developing prolonged release matrix tablets [195]. According to Reynolds et al. [195], HPMC matrix tablets of similar shape (flat-faced round tablets) and similar SA/V lead to comparable drug release, with similarity factor f_2 higher than 70. However, when varying the SA/V but keeping the surface area of the tablet constant, the dissolution behaviour results are significantly affected.

For this study, matrix tablets were manufactured by using theophylline as API and PEO as a hydrophilic rate-controlling polymer. PEO was chosen due to its fast and consistent swelling ability, as reported in section 3.3.8. Different tablet diameters were evaluated, in particular 2 mm, 6 mm, 8 mm, 10 mm and 12 mm, to investigate the impact of the tablet size on the dissolution kinetics in phosphate buffer. In addition, the influence of 0.1 N HCl with and without ethanol on the dissolution kinetics, dissolution media uptake and mass loss of the differently sized tablets was studied.

3.4.2 Mechanical properties and tablets dimensions

The tablets were characterized in terms of mass, dimensions, tensile strength and porosity. The values are summarized in Table 21. Similar results were determined regarding porosity and tensile strength, due to the constant compression pressure which was applied during tableting. By holding the tablet thickness approximately constant and increasing the tablet diameter and weight, both surface area and

volume resulted increased (Table 21). Moreover, by increasing the tablet diameter, both tablet specific surface area (SSA), i.e. the ratio between the tablet mass and surface area, and surface to volume ratio (SA/V) clearly decreased (Table 21). In particular, on the one side, the SA/V ratios increased from 1.1 mm⁻¹ to 1.4 mm⁻¹ by decreasing the tablet diameter from 12 mm to 6 mm. On the other side, a 2.7-fold increase of the SA/V ratio was observed when the tablet diameter was decreased from 12 mm to 2 mm, showing values ranging from 1.1 mm⁻¹ to 2.8 mm⁻¹ respectively. Reynolds et al. [195] studied the influence of surface area to volume ratio of HPMC-based matrices on drug release and stated that the SA/V ratio has a greater impact on drug release from hydrophilic matrices than the sole tablet surface area [195]. Therefore, in the following studies, the SA/V ratio was evaluated as potential influencing factor during dissolution.

Table 21: Mass (m), thickness (h), tensile strength (σ), porosity (ϵ), surface area (SA), specific surface area (SSA), volume (V) and surface to volume ratio (SA/V) of the PEO- tablets; tablets ≥ 6 mm: mean \pm SD, n = 6; 2 mm mini-tablets: mean \pm SD, n = 10

d	m	h	σ	ϵ	SA	SSA	V	SA/V
[mm]	[mg]	[mm]	[MPa]	[%]	[mm ²]	[mm ² /g]	[mm ³]	[mm ⁻¹]
2	6.40 \pm 0.12	2.1 \pm 0.0	1.2 \pm 0.2	10.3 \pm 1.3	15.5 \pm 0.2	2.4 \pm 0.0	5.5 \pm 0.1	2.8 \pm 0.0
6	89.9 \pm 0.6	2.9 \pm 0.0	1.1 \pm 0.1	14.6 \pm 0.3	110.4 \pm 0.2	1.2 \pm 0.0	80.8 \pm 0.3	1.4 \pm 0.0
8	151.6 \pm 0.6	2.6 \pm 0.0	1.0 \pm 0.0	11.6 \pm 0.4	166.0 \pm 0.4	1.1 \pm 0.0	131.5 \pm 0.7	1.3 \pm 0.0
10	241.5 \pm 0.5	2.8 \pm 0.0	1.0 \pm 0.0	14.7 \pm 0.4	243.3 \pm 0.6	1.0 \pm 0.0	217.1 \pm 0.2	1.1 \pm 0.0
12	357.4 \pm 1.9	2.8 \pm 0.0	1.0 \pm 0.0	11.7 \pm 0.2	328.8 \pm 0.6	0.9 \pm 0.0	310.4 \pm 1.8	1.1 \pm 0.0

3.4.3 In-vitro drug release

In this study, phosphate buffer pH 6.6 was used as dissolution medium to analyse the dissolution kinetic of the matrices over a test time of 16 hours (5.2.3.9). Figure 56 depicts the dissolution profiles from the tablets with different diameters but constant initial theophylline loading (30 % w/w), where the amount of drug release was expressed in mg (absolute amount of drug released) (Figure 56a) and percentage (relative amount of drug released) (Figure 56b). As can be seen, by increasing both diameter and weight of the matrices, the initially incorporated absolute amount of theophylline increased, resulting in higher absolute amounts of drug released versus time (Figure 56a). However, as according to Siepmann et al. [193], from a tablet designer's point of view, the relative amounts of drug released are of higher importance to tailor a certain shape of release profile. The profiles of the relative amount of drug release are illustrated in Figure 56b. Here, it could be observed that the drug dissolution was dramatically influenced by decreasing the tablet diameter to 2 mm: if the $t_{80\%}$ amounted 8.7 h, 9.5 h, 11.5 h and 13.3 h for tablet diameters of 6, 8, 10 and 12 mm respectively, a $t_{80\%}$ of 1.4 h was determined in the case of 2 mm mini-tablets (Figure 56b). In addition, only larger tablets could tailor a prolonged drug release, whereas mini-tablets released the entire drug dose within 3 h dissolution time. On the one hand, one possible explanation for the prolonged drug release from

tablets with diameter ≥ 6 mm might be found in the thicker gel layer which forms on large tablets and through which the drug has to diffuse [193, 196, 197].

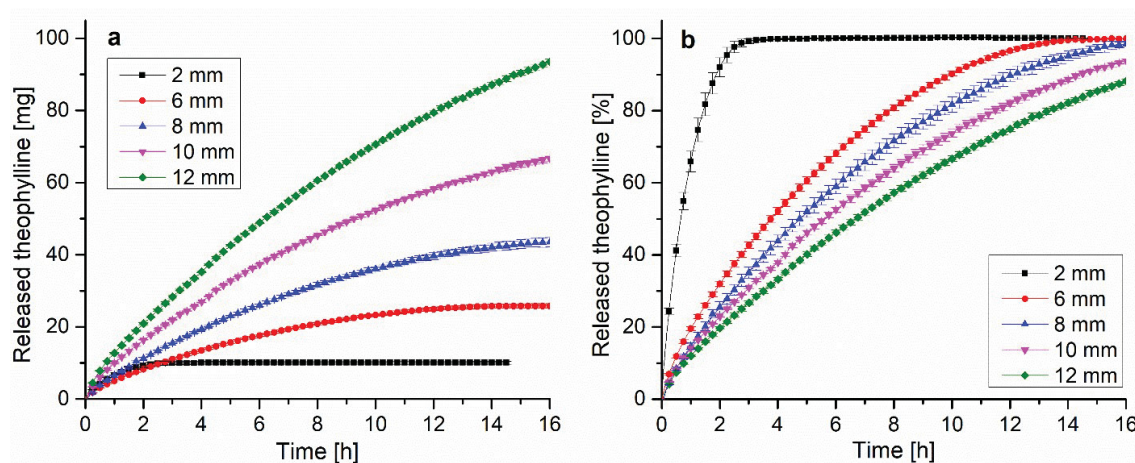


Figure 56: Influence of the tablet size on the theophylline release (mean \pm SD, $n = 3$), where the amount of released drug is expressed in (a) mg and (b) percentage; in each vessel 8 mini-tablets, which corresponded to ca. 10 mg theophylline; the drug load amounted 27 mg for 6 mm tablets, 45 mg for 8 mm tablets, 72 mg for 10 mm tablets, 107 mg for 12 mm tablets; medium: phosphate buffer pH 6.6.

On the other hand, this phenomenon might be due to the fact that the relative surface area (SA/V) of the tablets is significantly decreased by increasing the tablet diameter [193], as already seen in Table 21.

The data depicted in Figure 56b were plotted versus the square root of time to calculate the slope of the linear regions. Interestingly, a linear correlation between the slope values, i.e. relative diffusional drug release rate, for each formulation and the SA/V ratio was found ($R^2 = 0.9988$). The graph is depicted in Figure 57a.

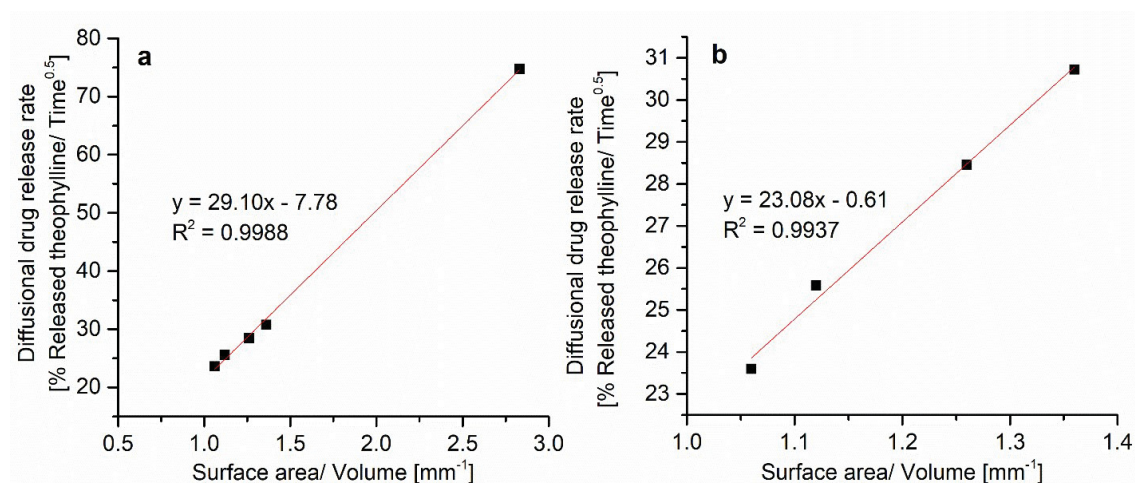


Figure 57: Diffusional drug release rate versus tablet surface area to volume ratio (SA/V) for theophylline from PEO matrix tablets: (a) plot for the tablets of 2 mm, 6 mm, 8 mm, 10 mm and 12 mm diameter, (b) plot for the tablets of 6 mm, 8 mm, 10 mm and 12 mm diameter.

Due to the fact that the data points which refer to larger tablets ($d \geq 6$ mm) are proximal in the graph, a correlation regarding the aforementioned data points was evaluated (Figure 57b). As can be seen, a good correlation was obtained with $R^2 = 0.9937$. These findings are in accordance with the Higuchi equation adapted by Lapidus and Lordi for HPMC swellable matrices [198] (Equation 1):

$$\frac{M_t}{M_0} = 2 \left(\frac{SA}{V} \right) \left(\frac{D_{eff} t}{\pi} \right)^{0.5}$$

Equation 1

where M_t is the amount of drug released at time t , M_0 is the drug dose in the initial tablet, SA/V the tablet surface area to volume ratio and D_{eff} is the effective matrix drug diffusion coefficient.

Moreover, the ratio between absolute amount of theophylline release and the tablet surface area (M_t/A or Q) was plotted versus the dissolution time (Figure 58a). Interestingly, it can be seen that the dissolution profiles slopes, which represent the drug release rate, are similar for tablets with diameter ≥ 6 mm. Differently, the slope of the dissolution profile of the 2 mm mini-tablets was significantly higher.

In particular, when fitting the dissolution data in the Higuchi equation, thus plotting Q against the square root of time \sqrt{t} (5.2.3.10), the diffusional drug release rate D_k could be determined as the slope in the linear regions of the Higuchi plots (Figure 58b). Interestingly, D_k values of 0.0093, 0.0071, 0.0075, 0.0074 and 0.0075 $\text{g} \cdot \text{cm}^{-2} \cdot \text{h}^{-0.5}$ were determined for tablets with diameter of 2, 6, 8, 10 and 12 mm respectively. The coefficient of determination R^2 of the linear regressions depicted in Figure 58b resulted higher than 0.985 in all cases, thus showing very good correlations. As can be noticed, the drug release was proportional to the square root of time, however the D_k resulted higher for mini-tablets than for larger tablets, which showed comparable results.

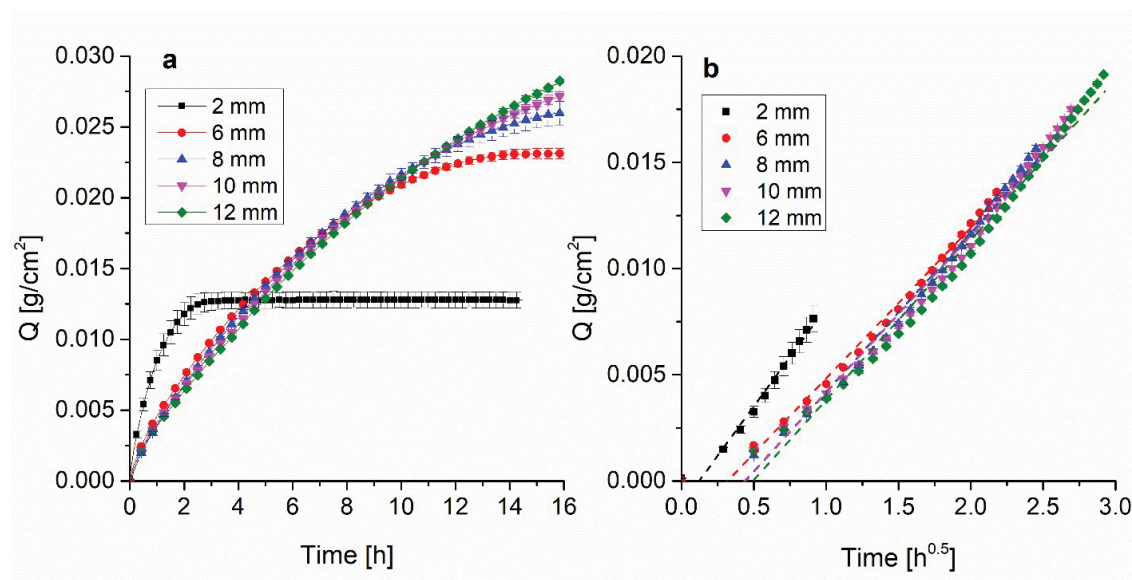


Figure 58: Analysis of the dissolution kinetics in phosphate buffer pH 6.6. (mean \pm SD, $n = 3$): (a) drug release per tablet surface unit (Q) of the differently sized tablets, where the initial Q amounted 0.013 g/cm^2 , 0.024 g/cm^2 , 0.027 g/cm^2 , 0.03 g/cm^2 and 0.033 g/cm^2 for tablets of 2 mm, 6 mm, 8 mm, 10 mm and 12 mm diameter respectively (b) fit of the dissolution data (≤ 60 % drug released) into the Higuchi equation

The dissolution data were further evaluated using the Korsmeyer-Peppas equation in order to analyse the diffusional drug release mechanism from the polymeric matrices. The exponent n_{KP} and the logarithm of the slope ($\log_{10}k$) of the Korsmeyer-Peppas plots are listed in Table 22. It can be seen that the release exponents n_{KP} are approximately constant and were not affected by the size of the tablets. The n values indicated an anomalous transport and all dissolution data were in good agreement with the matrix-controlled release mechanism, with $R^2 > 0.998$. In addition, the logarithm of the slope $\log_{10}k$ decreased by increasing the tablet diameter. As a matter of fact, this constant incorporates the structural and geometric characteristic of the matrix device, as in accordance with Siepmann and Peppas [197].

Table 22: Release characteristics for PEO-matrix tablets with different tablet diameter; R^2 for Korsmeyer-Peppas (R^2_{KP}) plot, the exponent (n_{KP}) and logarithm of the slope ($\log_{10}k$) of Korsmeyer-Peppas plots; for calculation of KP plots, drug release data between 10 % and 80 % were evaluated.

Tablet diameter [mm]	Korsmeyer- Peppas Plot			Drug transport
	n_{KP}	$\log_{10}k$	R^2_{KP}	
2	0.71	1.82	0.998	anomalous
6	0.69	1.30	0.999	anomalous
8	0.71	1.23	0.999	anomalous
10	0.71	1.17	0.999	anomalous
12	0.73	1.09	0.999	anomalous

At last, in-vitro dissolution tests were conducted in 0.1 N HCl with 0 % and 40 % ethanol for 2 hours, as in accordance to the FDA guidelines [5], to evaluate the impact of alcohol on the dissolution of larger PEO tablets.

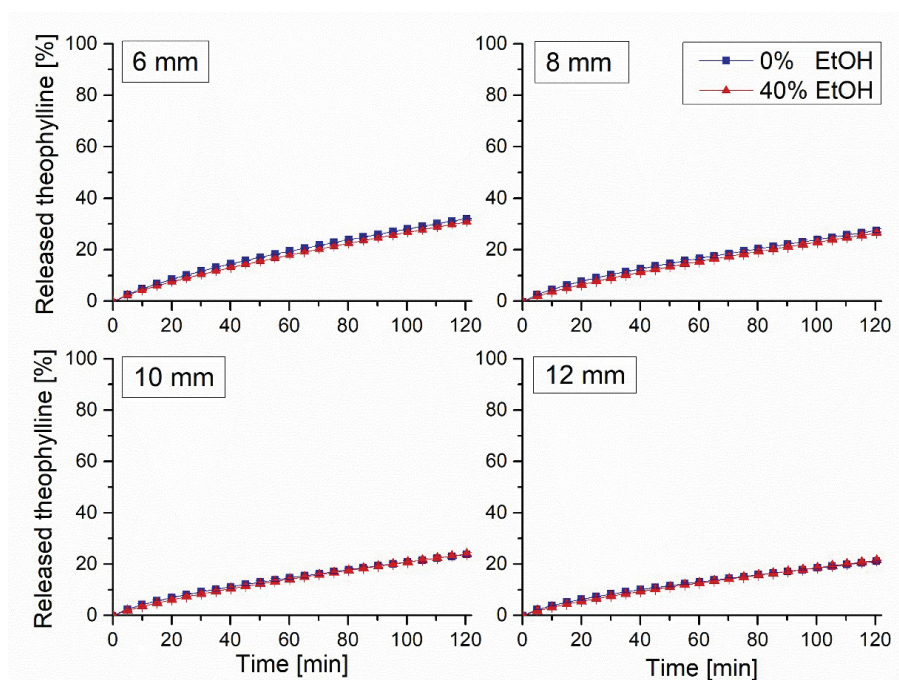


Figure 59: Dissolution profiles of the large tablets based on PEO in 0.1 N HCl with 0 % and 40 % ethanol; mean \pm SD, $n = 3$

The drug release of PEO mini-tablets has been shown already in section 3.3.8 (Figure 53). As can be seen in Figure 59, alcohol did not lead to either dose dumping or drug release variation with regard to larger tablets. The similarity factor f_2 was calculated and resulted increased by increasing the tablet diameter: in particular, values of 76.3, 89.5, 91.4, 97.5 and 97.7 were determined for tablets of 2, 6, 8, 10 and 12 mm diameter respectively. It can be therefore observed that the influence of 40 % alcohol in the dissolution media on drug release was decreased by increasing the tablet radius.

3.4.4 Media uptake and erosion properties

The results regarding (i) relative swelling (RS), (ii) dissolution media uptake (DMU) and (iii) mass loss (ML) after 2 h dissolution in 0.1 N HCl without and with 40 % ethanol are depicted in Figure 60, Figure 61 and Figure 62 respectively. An increase in the tablets diameter led to significantly decreased RS, DMU and ML in both 0 % and 40 % ethanol. In particular, RS, DMU and ML values determined in alcohol were generally lower than those in 0.1 N HCl.

The media uptake and erosion properties of the 2 mm mini-tablets after dissolution could not be determined in 0 % ethanol due to the high erosion of the mini-matrices and therefore the difficult handling. However, these studies could be conducted on the mini-tablets in 40 % ethanol, since they stayed more intact after 2 h dissolution.

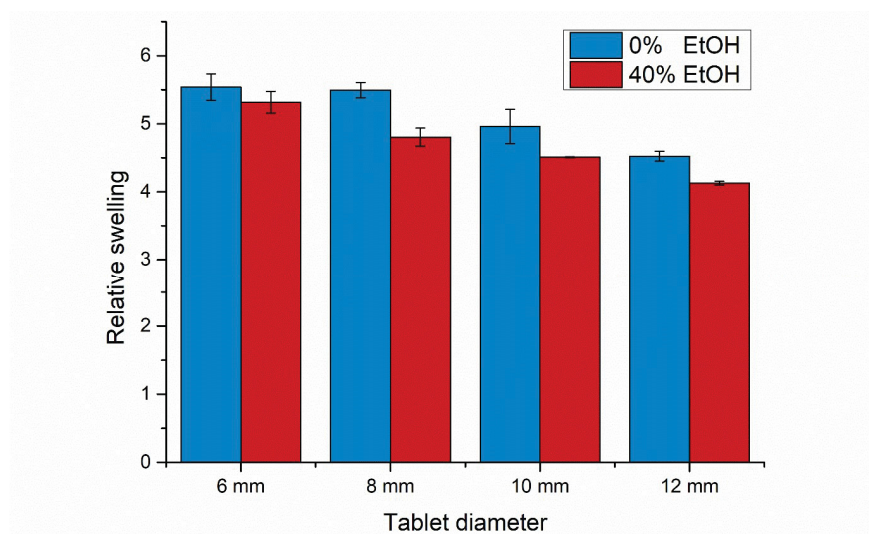


Figure 60: Relative swelling of the PEO-based tablets depending on the presence of alcohol in the dissolution media and the tablet size; mean \pm SD, $n = 3$.

With regard to the mini-tablets in alcoholic media, RS amounted 8.3 ± 0.2 , DMU 1229.1 ± 17.6 % and ML 37.7 ± 0.3 %. It can be noticed that media uptake and erosion in 40 % ethanol were drastically increased for mini-tablets in comparison to larger tablets. In particular, DMU was 3.5-fold higher for mini-tablets than 12 mm-tablets and ML was 4.5-fold increased. As a matter of fact, the diffusion pathway for both media and dissolved drug through the matrix structure is much shorter for mini-tablets [77], which caused higher media penetration into the matrix, and consequently (i) faster drug release (Figure 53) and (ii) erosion to an higher extent.

By analysing larger tablets, RS, DMU and ML regarding the 6 mm tablets resulted similar in both media. However, by increasing the tablet diameter, significantly different gravimetrical values were determined depending on the dissolution media. As already seen in section 3.3.8, PEO matrices are able to swell in alcoholic media, however to a lower extent in comparison to aqueous media. The gravimetrical analysis which were here conducted could therefore give further evidences to support the hypothesis reported in chapter 3.3.

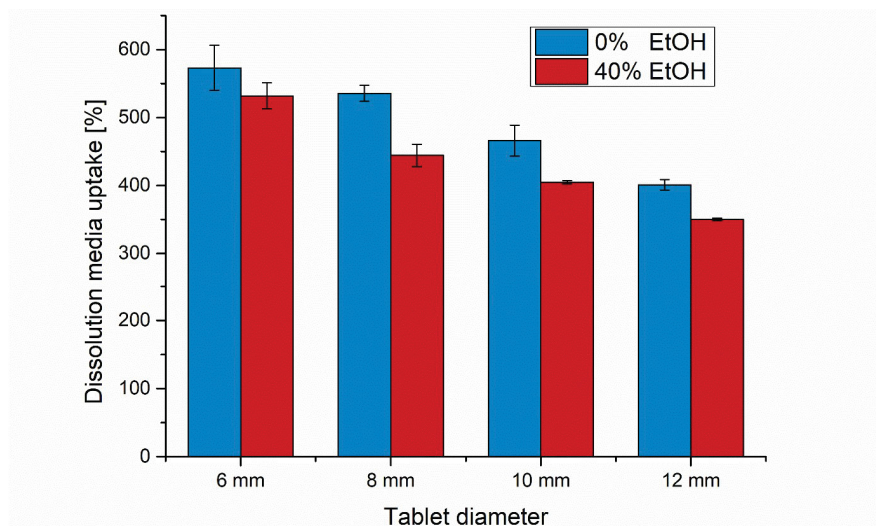


Figure 61: Dissolution media uptake of the PEO-based tablets depending on the presence of alcohol in the dissolution media and the tablet size; mean \pm SD, $n = 3$.

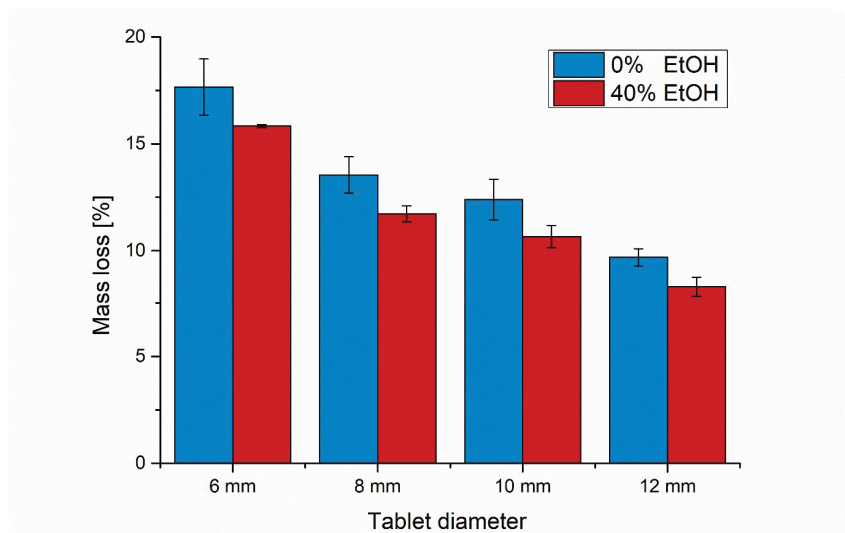


Figure 62: Mass loss of the PEO-based tablets depending on the presence of alcohol in the dissolution media and the tablet size; mean \pm SD, $n = 3$.

Moreover, the absolute tablet swelling values were calculated (see section 5.2.3.11) in order to evaluate whether the swelling extent was influenced by the tablet surface. The resulting values are reported in Table 23. Generally, the values were decreased by adding alcohol in the dissolution media,

as previously seen. The mini-tablets in 0 % ethanol underwent a high erosion, therefore the values could not be determined. However, in 40 % ethanol, the mini-tablets were more intact probably due to the lower erosion of PEO in alcoholic media. The absolute tablet swelling of mini-tablets in 40 % ethanol was lower than that calculated for tablets with $d \geq 6$ mm: an explanation for this might be found in the fact that mini-tablets were completely swollen after 2 h dissolution testing and no additional medium could be further uptaken. Differently, the tablets with $d \geq 6$ mm showed more similar values: as a matter of fact, the concentration of polymer was constant within the differently sized tablets and a similar weight gain per surface unit was determined, which led to similar drug release per surface unit.

These results support the hypothesis that the swelling extent was not dependent on the surface area. However, in case of mini-tablets, the dissolution media completely penetrated the mini-tablets, the drug was fully solubilized and could be released faster from mini-tablets than from larger tablets. Differently, larger tablets ($d \geq 6$ mm) probably maintained a diffusion front (see section 1.6) intact during dissolution and the drug release could be prolonged further.

Table 23: Influence of the tablet diameter on the absolute tablet swelling and absolute tablet mass loss values in 0.1 N HCl with 0 % and 40 % ethanol; mean \pm SD, n = 3.

tablet diameter	absolute tablet swelling [mg/cm ²]	
	0 % EtOH	40 % EtOH
2 mm	-	298.1 \pm 20.7
6 mm	364.6 \pm 19.8	349.7 \pm 11.5
8 mm	410.3 \pm 10.2	346.8 \pm 12.7
10 mm	392.9 \pm 24.6	348.8 \pm 1.8
12 mm	383.1 \pm 6.8	338.4 \pm 1.4

3.4.5 Summary

The influence of the PEO tablet size on the drug release kinetics was evaluated firstly, in phosphate buffer for 16 hours and secondly, in hydro-alcoholic media for 2 hours. The results indicate that the surface to volume ratio of the matrices was a key factor to control the drug release, and a linear correlation was found between the SA/V ratio of the differently sized tablets and the diffusional drug release rate of the obtained drug release profiles. The dissolution data were in good agreement with the Korsmeyer-Peppas plot ($R^2 > 0.998$), where the exponent n was approximately 0.7 for all formulations, thus indicating anomalous transport, independently from the tablet size, whereas the logarithm of the slope k resulted decreased when the tablet diameter was increased. In addition, the data were fitted in the Higuchi plot and interestingly the slope values, i.e. D_k , were similar for the drug release of tablets with diameter ≥ 6 mm, however resulted increased for 2 mm mini-tablets. It became therefore clear that mini-tablets based on hydrophilic polymer are not a suitable dosage form to tailor a prolonged drug release for theophylline as API (drug load 30 % w/w).

Furthermore, the influence of alcohol on the dissolution behaviour of differently sized tablets was studied. It was shown that by increasing the tablet diameter more similar drug release profiles could be achieved, which was confirmed by the increased similarity factor f_2 . In addition, gravimetric studies were performed to determine RS, DMU and ML. Mini-tablets did not stay sufficiently intact in 0 % ethanol, due to the fast erosion, however it was possible to perform the analysis on mini-tablets after dissolution in 40 % ethanol. Interestingly, all three parameters resulted decreased in both media by increasing the tablet diameter and, generally, lower RS, DMU and ML values were observed in 40 % ethanol than in 0 % ethanol. A possible explanation could be found in the slightly lower capability of PEO to swell in presence of alcohol (see section 3.3.8). However, a drastic increase in DMU and ML was seen with regard to the 2 mm mini-tablets in 40 % ethanol. In particular, 3.5-fold higher DMU and 4.5-fold higher ML were determined for mini-tablets when compared to 12 mm larger tablets. As a matter of fact, the shorter diffusion pathway which characterized the mini-tablets and the significantly higher surface area to volume ratio probably led first to higher dissolution media uptake and second to higher erosion and therefore higher mass loss values.

According to these studies, the surface area/volume ratio can be utilized to develop tablets with drug release profiles with prolonged-release characteristics. It was demonstrated that the development of prolonged release matrix mini-tablets was not possible, although ADD robustness could be achieved. However, an increase of the matrix system size would enable to tailor both aims of interest.

4 SUMMARY AND CONCLUSIONS

This work focused on development, manufacturing and characterization of oral prolonged release matrix dosage forms intended to achieve robustness against alcohol-induced dose dumping (ADD). Theophylline was chosen as a model drug, due to its narrow therapeutic index, which, in case of formulation vulnerability against ethanol, can lead to critical side effects or even fatality. Furthermore, the solubility of theophylline is increased in the presence of ethanol (up to 40 %, v/v), which can potentially lead to an increased drug release from a dosage form in the presence of ethanol in the gastro-intestinal tract.

Firstly, single-unit matrix tablets were produced by directly compressing a mixture of theophylline and the HPMC-based co-processed excipient RetaLac® (ratio 1:1), using an uniaxial compaction simulator. A 2³ full factorial design of experiment (DoE) was performed in order to evaluate the influence of the manufacturing process parameters on dissolution behaviour of the matrices. For this purpose, the tableting pressure was varied from about 200 to 400 MPa and the simulator speed from 10 to 50 rpm. The resulting tablets were further characterized in terms of (i) mechanical properties and (ii) *in-vitro* drug release in acidic media without and with 40 % (v/v) ethanol. All formulations underwent swelling and exhibited similar dissolution profiles in both media ($f_2 \gg 50$), despite the increased solubility of the drug in ethanol and the mechanical properties being slightly affected by the manufacturing process. However, despite the similarity of the dissolution curves ($f_2 \gg 50$), the DoE coefficient plots showed that ethanol negatively affected drug release, dissolution media uptake and mass loss of the tablets. These results have therefore revealed that the f_2 value should not be the only indicator which has to be considered to assess the dissolution similarity in the development of ADD resistant formulations.

To explain the decrease in drug release from the RetaLac® matrices in 40 % ethanol, texture analysis was performed on the swollen tablets after 2 h dissolution testing. The results led to the hypothesis that a gel of higher strength was formed in 40 % ethanolic media than in hydrous one, probably due to the decreased matrix erosion in hydro-ethanolic media. Evidences for this were given by both gravimetric studies and image analysis.

In the second chapter of this thesis, xanthan gum (XG) was evaluated as a suitable polymer candidate for avoiding ADD from single-unit ($d = 8$ mm) and multiple-unit ($d = 2$ mm) matrix tablets. Moreover, the influence of polymer particle size and polymer concentration on the dissolution behaviour in aqueous and hydro-alcoholic media was evaluated. For these purposes, a full factorial 2³ DoE was conducted. Both tablets and mini-tablets with higher amount of XG stayed intact in both 0 and 40 % ethanolic media and showed similar drug release ($f_2 \gg 50$). For these formulations, the influence of XG particle size and the amount of ethanol in the media was negligible. Nevertheless, if decreasing the polymer content, robustness against ADD could be achieved, however only with finer polymer particles. As a matter of fact, in alcohol, larger polymer particles led to significantly increased drug release from larger tablets and a risk of ADD was observed ($f_2 < 50$). Mini-tablets with the same composition, however, led to complete disintegration within 5 min of dissolution test, thus exhibiting ADD ($f_2 = 23.0$). Differently, when finer polymer particles were used even at a lower concentration, mini-tablets were robust in alcohol, due to the formation of a more coherent and less porous gel layer. Furthermore, the influence of alcohol on the rheological properties of XG solutions was studied: the

results showed that 40 % alcohol led to a 2.4-fold higher dynamic viscosity than in aqueous media. Therefore, it is assumed, that a stronger gel layer was formed in the presence of alcohol, thus hindering ADD in most of the cases. However, the slow swelling process of the hydrophilic XG in contact with alcoholic media may be a crucial factor affecting dissolution, especially in the initial phase of the test, when using larger polymer particles.

In the third chapter, wet extrusion was chosen as an alternative manufacturing process to direct compression, in order to produce XG-based mini-matrices. With the purpose of prolonging the drug release, dicalcium phosphate anhydrous, talcum and titanium dioxide were added to the mixtures and potential pore-blocking effect of these excipients was evaluated. Extrudates of 1.75 mm diameter were successfully produced at L/S ratios, which were previously determined by using mixer torque rheometry (MTR). The obtained extrudates were cut afterwards in 3 mm mini-matrices in order to increase the diffusion path length for the API in comparison to the 2 mm mini-tablets. However, more than 80 % theophylline was released within 2 h dissolution test with and without pore blockers, thus no prolonged release characteristics could be achieved. Nevertheless, the extrudates showed alcohol-resistant properties and similarity factors higher than 50 were determined.

Since no relevant advantages in terms of dissolution performance of the extrudates were observed, direct compression was further applied to study the performance of selected hydrophilic (HPMC K4M, HPMC K100M, PEO, carbomer) and hydrophobic polymers (Kollidon® SR and PVAc) for the development of alcohol-robust mini-tablets. All evaluated hydrophilic polymers led to similar drug release in 0, 20 and 40 % ethanolic media. Interestingly, despite the higher solubility of theophylline in hydro-alcoholic media, a slightly slower drug release was observed in ethanolic media.

A mixer torque rheometer was for the first time successfully applied for characterization of the swelling properties of PEO and two viscosity grades of HPMC, in 0 and 40 % ethanol. Interestingly, both HPMCs needed more liquid to form a mass of maximal cohesive strength in presence of ethanol, thus indicating that the interaction polymer-ethanolic solutions was weaker than the interaction polymer-water. However, both polymer grades underwent swelling in media with and without ethanol during dissolution, which was confirmed by image analysis. The torque profiles were not affected by the presence of ethanol when characterizing PEO with MTR, however a slightly higher swelling of the mini-tablets was seen in 0 % ethanol by image analysis.

When hydrophobic polymers were used for the preparation of mini-tablets (Kollidon® SR and PVAc), the drug release was affected by the presence of varying concentrations of alcohol in the media. Kollidon® SR resulted to be a promising polymer to achieve both prolonged drug release and robustness against alcohol, however only in 20 % ethanol. This formulation therefore met the requirements of the EMA. In order to fulfil the “more strict” FDA requirements, which consider a maximal ethanolic concentration of 40 %, further advancements of the formulation are needed.

With the exception of Kollidon® SR and PVAc, prolonged drug release from mini-tablets could not be achieved with the evaluated rate-controlling polymers and > 80 % drug was released within 2 h. To evaluate the influence of the tablet size on dissolution performance, matrix tablets based on PEO as a swellable polymer, with a diameter of 2, 6, 8, 10, as well as 12 mm were directly compressed. In this study, by applying the Higuchi equation, a linear correlation between surface area to volume ratio and diffusional drug release rate was found. Furthermore, it was shown that by increasing the tablet

diameter, the influence of alcohol on tablet dissolution behaviour was less pronounced. With other words, tablets with higher diameter exhibited higher similarity factors, when comparing the dissolution curves in 0 % and 40 % ethanol. Moreover, by increasing the tablet diameter, relative swelling, dissolution media uptake and mass loss were decreased in both media, however, in 40 % ethanol the above mentioned parameters generally showed lower values compared to hydrous media.

To conclude, matrix formulations based on certain hydrophilic polymers provided a promising platform for the production of alcohol-robust single-unit and multiple-unit oral dosage forms. In those formulations, the drug release was only slightly affected by the presence of alcohol, despite the influence of ethanol on API and polymer solubility. It was shown that a matrix represents a complex system, where several key factors, such as drug solubility, polymer particle size, polymer concentration, polymer solubility and swellability can play an essential role in the final formulation properties. However, one to one formulation transfer from single-unit matrix systems towards mini-matrices was demonstrated to be challenging, due to the different drug release properties. For this reason, the application of film coatings with ethanol-resistant and controlled release properties can represent a successful approach for prolonging the dissolution kinetics from multiple-unit dosage forms in the future.

5 EXPERIMENTAL PART

5.1 Materials

Table 24: The model drugs

substance	batch no.	source of supply
Theophylline monohydrate	287031AX20	BASF, Germany
Theophylline anhydrate	973391AX10	BASF, Germany

Table 25: Excipients used for the direct compression of tablets and mini-tablets

substance	name/grade	source of supply
colloidal silicium dioxide	Aerosil [®] 200	Evonik, Germany
hydroxypropyl methylcellulose (HPMC)	Methocel [™] K4M Premium	Colorcon, UK
	Methocel [™] K100M Premium	Colorcon, UK
HPMC/lactose co-processed polymer	RetaLac [®]	Meggle Pharma, Germany
magnesium stearate	Parateck [®] LUB MST	Merck, Germany
polyacrylic acid (carbomer)	Carbopol 980 NF	BF Goodrich, Belgium
polyethylene oxide (PEO)	Polyox [™] WSR-303 LEO NF	Colorcon, UK
polyvinyl acetate (PVAc) M _w = 65,000 g/mol	Vinnapas [®] B 60 sp	Wacker, Germany
polyvinyl acetate/ polyvinylpyrrolidone co-processed polymer	Kollidon [®] SR	BASF, Germany
polyvinylpyrrolidone K30 (PVP K30)	Kollidon [®] 30	BASF, Germany
polyvinylpyrrolidone K90 (PVP 90F)	Kollidon [®] 90 F	BASF, Germany
pregelatinized starch (PGS)	Spres [®]	GPC, USA
xanthan gum (XG)	Xantural [®] 75	CP Kelco, UK
	Xantural [®] 180	CP Kelco, UK

Table 26: Excipients used for the extrusion processes

substance	name/grade	source of supply
colloidal silicon dioxide	Aerosil® 200	Evonik, Germany
dicalcium phosphate anhydrous (DCPA)	Di-Cafos® A7	Budenheim, Germany
β-mannitol	Pardeck® M 100	Merck, Germany
microcrystalline cellulose (MCC)	Vivapur® 101	JRS Pharma, Germany
polyvinyl acetate (PVAc) M _w = 65,000 g/mol	Vinnapas® B 60 sp	Wacker Chemie AG, Germany
talcum	Talkum Pharma G	Erbslöh HG, Germany
titanium dioxide (TiO ₂ , Anatase)	Kronos 1171	Kronos International, Germany
xanthan gum (XG)	Xantural® 75	CP Kelco, UK

Table 27: Substances used for the analytics

substance	source of supply
demineralized water	-
dibasic potassium phosphate, reagent grade	Merck, Germany
ethanol, reagent grade	-
hydrochloric acid, 1 M	VWR International GmbH, Germany
liquid nitrogen	-
sodium hydroxide, 1 M	Fisher Chemical

5.2 Methods

5.2.1 Manufacturing methods

5.2.1.1 Tableting

5.2.1.1.1 Preparation of the powder blends

To prepare the physical mixtures each component of the evaluated formulations except magnesium stearate was weighted and blended for 10 min by using a Turbula® mixer (T2F, W.A. Bachofen, Basel, Switzerland) at 49 rpm rotation speed. When large agglomerates were present, the powders were sieved through a 315 µm mesh aperture sieve prior weighing. The lubricant was then added to the

premixture and it was blended for other 2 min. The batch size varied between 10 g (manual filling) and 200 g (filling shoe).

5.2.1.1.2 RetaLac[®] tablets²

To investigate the influence of the compression force and tableting speed on the dissolution properties from RetaLac[®]-based tablets (chapter 3.1), the prepared mixtures (Table 28) were directly compressed into 260 mg tablets on a Style'One Evo single stroke multi-layer tablet press (Romaco Kilian, Karlsruhe, Germany), by using a gravity feed shoe.

Table 28: Composition of all HPMC-based formulations

component	content [%, w/w]
anhydrous theophylline	49.7
RetaLac [®] (HPMC: lactose, 50:50)	48.7
magnesium stearate	1.1
colloidal silica	0.5

The tableting instrument Styl'One Evo is also known as uniaxial compaction simulator [199] and in this study, it was used for the hybrid modelling of the Kilian Pressima-16 station tablet press. The machine was equipped with EU B 8 mm round flat-faced punches (Ritter Pharma-Technik, Stapelfeld, Germany). Prior tableting, a metal gauge block of 5 mm height was used to measure the punch deformation and a 1 mm high gauge block to calibrate the punch displacement. The die filling height was adjusted to 9.9 mm and the compaction height was regulated to achieve compression forces of 10 and 20 kN. In addition the simulator speed was set at 10 rpm and 50 rpm. 100 tablets per batch were produced. The temperature and humidity conditions were kept constant at 21 °C and 35 % RH during the experiments.

5.2.1.1.3 XG tablets and XG mini-tablets

The XG-containing mixtures (Table 29) (chapter 3.2) were manually filled into the die and directly compressed into 150 mg flat-faced tablets on a instrumented rotary tablet press (Pressima MX-EU-B/D, IMA Kilian, Germany) equipped with punches of 8 mm diameter. To manufacture the 6.3 mg mini-tablets, a 19 mini-tableting tool (Ritter Pharma-Technik GmbH, Stapelfeld, Germany) was used. A compression force of 10 kN, which resulted in a compression pressure of 199 MPa, was applied to prepare the 8 mm tablets, whereas a compression force of 7.5 kN, which resulted in a compression pressure of 107 MPa, was applied for the mini-tablets. The turret speed was set at 10 rpm. The produced tablets and mini-tablets were finally dedusted for 2 min by using an air jet sieve (Hosowaka Alpine, Augsburg, Germany) with a nominal mesh width of 125 and 500 µm and a pressure of 600 and

² The manufacture of the RetaLac[®] tablets by Style'One Evo was carried out by Dr. Carola Hanl at Romaco Kilian GmbH, Köln, Germany.

2,800 Pa for the mini-tablets and the 8 mm tablets respectively. The temperature and relative humidity of the room were kept constant at values of 21 °C and 45 % RH during the tableting process.

Table 29: Formulations of the evaluated 8 mm tablets (S) and 2 mm mini-tablets (M) based on XG as rate-controlling polymer

COMPONENTS	CONTENT (% w/w)			
	S-/M-30%	S-/M-60%	S-/M-30%	S-/M-60%
	XG75	XG75	XG180	XG180
theophylline	68.5	38.5	68.5	38.5
Xantural® 75	30	60	-	-
Xantural® 180	-	-	30	60
magnesium stearate	1	1	1	1
colloidal silica	0.5	0.5	0.5	0.5
compression forces (kN)	8 mm tablets		10	
	2 mm mini-tablets		7.5	

5.2.1.1.4 PEO tablets

The PEO-containing mixtures (chapter 3.4) (Table 30) were directly compressed into tablets of different diameters on an instrumented rotary tablet press with the filling shoe (Pressima MX-Eu-B/D, IMA Kilian, Köln, Germany). 6, 8, 10 and 12 mm diameter round flat-faced punches (Ritter Pharma-Technik GmbH, Stapelfeld, Germany) were used and a compression pressure of 114 MPa was applied. The produced tablets weighted respectively 90, 151, 241 and 357 mg. In order to significantly vary the tablet surface/volume ratio, the tablet thickness was kept constant at 2.8 ± 0.1 mm. After at least 24 h storage at 21 °C/ 45 % RH, all batches were dedusted for 2 min in an air jet sieve (Hosowaka Alpine, Augsburg, Germany) with a nominal mesh width of 500 µm and a pressure of 2,800 Pa.

Table 30: Composition of (i) PEO large tablets and (ii) mini-tablets based on PEO and other hydrophilic polymers

component	content [%, w/w]
theophylline monohydrate	30
polymer (PEO, PVAc, PVP K30, PVP 90F, PGS, HPMC K4M/ K100M, carbomer)	65.5
magnesium stearate	3
colloidal silica	1.5

5.2.1.1.5 Mini-tablets with other polymers

To produce the biconvex 6.5 mg mini-tablets, 2 mm, 19 tip mini-tableting tool (Ritter Pharma-Technik, Stapelfeld, Germany) was utilised after manually filling the die, on an instrumented rotary tablet press (see section 5.2.1.1.4). A compression pressure of 114 MPa was applied for all batches

and the turret speed was kept at 10 rpm. The composition of the directly compressed mini-tablets manufactured for the polymer screening in chapter 3.3 are listed in Table 30.

The room conditions were kept at 21 °C/ 45 % RH during the entire processes. After at least 24 h storage at the same room conditions, all batches were dedusted for 2 min in an air jet sieve (Hosowaka Alpine, Augsburg, Germany) with a nominal mesh width of 125 µm and a pressure of 600 Pa.

5.2.1.2 Co-rotating twin-screw extrusion

Twin-screw wet extrusion of the mixtures listed in Table 8 and Table 12 (chapter 3.3) was performed with a Pharmalab 16 extruder (Thermo Fisher Scientific, Karlsruhe, Germany), with screws of 16 mm diameter (D). The length of the screws was 40 D (640 mm). The components of each blend were mixed for 15 min at 25 rpm in a laboratory-scale blender (LM 40, L.B. Bohle, Ennigerloh, Germany) and prior extrusion, manually transferred into a loss-in-weight powder feeder (K-CL-24-KT 20, K-Tron, Niederlenz, Switzerland). The powder feeder was calibrated before each process. The powder feed-rate was set at 10 g/min during the experiments, unless otherwise indicated. Demineralized water was used as granulation liquid and added by a micro annular gear pump (MZP 7205, HNP-Mikrosysteme, Schwerin, Germany) through an own built nozzle with the inner diameter of 0.12 mm into the extruder barrel, directly in front of the first kneading zone. To record the gravimetric feed-rate, the pump was connected to a coriolis mass flow measurement (Proline Promass 80A, Endress+Hausner, Weil am Rhein, Germany). To avoid the blockage of the solid feeding port in the first zone due to the polymer swelling, the liquid feeding port was located in the zone 3 along the barrel (Figure 63). The liquid/ solid ratio (L/S) and screw speed were adjusted depending on each formulation whereas the temperature of the extruder cylinder was set at 25 °C. The used screw configuration is depicted in Figure 63 and described in Table 31.

The wet mass was extruded through a 1.75 mm diameter die and the resulting extrudates were then transported by a conveyor belt (model 846102.001, Brabender, Germany) in front of the extruder. After reaching the steady state, extrudates were collected and dried to constant weight in a vacuum drying oven (Heraeus VT6025 Vacutherm, Germany) at a temperature of 70° C and a pressure < 200 mbar. Extrudates of approximately 3 mm length were finally cut manually using a surgical disposable scalpel (B. Braun, Tuttlingen, Germany).

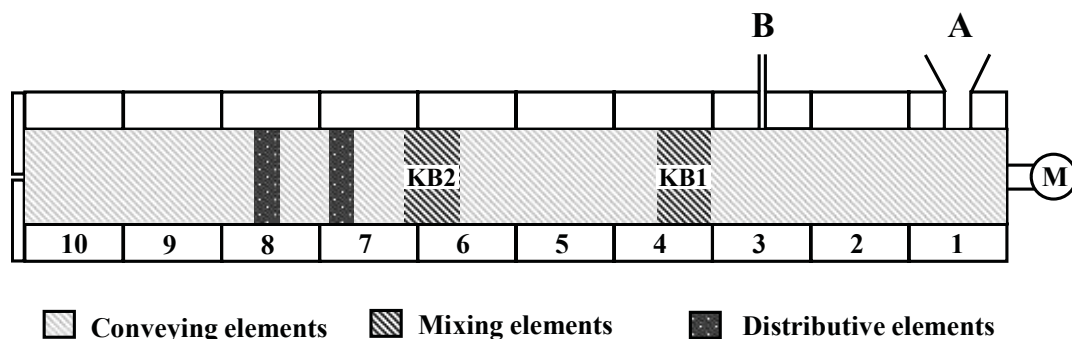


Figure 63: Screw configuration for the wet and hot-melt extrusion, from feeder (right) to die (left); A: loss-in-weight feeder, B: liquid feed, KB: kneading block

Table 31: Utilized screw configuration for wet and hot-melt extrusion

4 D	Conveying elements (helix 3/2 L/D)	
8 D	Conveying elements (helix 1 L/D)	
2.25 D	Kneading block 1 (KB1) (1/4 L/D)	KB 1: S(0°) - F(30°) - S(30°) - S(60°) - S(60°) - F(90°) - S(90°) - F(90°) - S(90°)
8 D	Conveying elements (helix 1 L/D)	
2.25 D	Kneading block 2 (KB2) (1/4 L/D)	KB 2: S(0°) - F(30°) - F(60°) - F(60°) - F(60°) - F(60°) - F(60°) - F(60°) - S(30°)
2 D	Conveying elements (helix 1 L/D)	
1 D	Distributive flow (1 L/D)	
2 D	Conveying elements (helix 1 L/D)	
1 D	Distributive flow (1 L/D)	
8 D	Conveying elements (helix 1 L/D)	
0.5 D	Conveying elements (helix 1 L/D)	
1 D	Conveying elements (helix 1 L/D)	

To perform hot-melt extrusion (HME) of the mixture in Table 32, the powder dosing was set at 8 g/min, the screw speed 20 rpm, and the temperature was set at 30 °C in the first barrel segment, 130 °C along the barrel length and at 10 °C at the die segment. The screw configuration described above was used also in HME.

Table 32: Composition of the mixture processed by HME

component	content [%, w/w]
theophylline monohydrate	30
PVAc	69.6
colloidal silica	0.4

5.2.1.3 Ultra-centrifugal mill

The particle size reduction of polyvinyl acetate (PVAc) beads was performed by grinding in an ultra-centrifugal mill (ZM 100, Retsch GmbH, Haan, Germany), where the mill was equipped with a 12 wedge-shaped rotor teeth. Stainless steel ring sieve with trapezoid holes of 1.5 mm and a distance sieve ring with trapezoid holes of 0.12 mm were used. The beads were first frozen by pouring liquid nitrogen on them and milled through the sieve 1.5 mm at a rate of 14,000 rpm. The milled particles were then frozen an additional time and milled again through the sieve 0.12 mm at a rate of 14,000 rpm. The resulting particles were then sieved using a sieve with 420 µm mesh aperture before mini-tableting.

5.2.2 Design of experiments (DoE)

Design of experiments was used as tool to analyze the influence of process parameters and formulations variables (factors) on the dissolution performances of the tablets. A full factorial DoE about the RetaLac[®]-containing tablets (see chapter 3.1) was carried out and involved three factors (compression pressure, compression speed and ethanol concentration in the media) on two factor levels, a lower and an upper level (-1; +1) (Table 33). Four formulations were produced.

Table 33: Description of the DoE performed with HPMC-containing matrix tablets

Factors	Unit	Level (-1)	Level (+1)
Compression pressure (P)	MPa	199	398
Rotation speed (Speed)	rpm	10	50
Ethanol concentration in media (EtOH)	% (v/v)	0	40

In this study, the evaluated responses were relative swelling, dissolution media uptake, mass loss and amount of released theophylline, expressed by the area under the curve (AUC_{120 min}) after 2 h dissolution test.

A 2³ full factorial design with three replications of the center point was performed with the XG-containing 8 mm tablets and 2 mm mini-tablets (see chapter 3.2). For both dosage forms, xanthan gum content, xanthan gum particle size and ethanol content in the dissolution medium were selected as factors. In Table 34 the levels for each factor are presented. As responses, the percentage of drug released after 1 h was evaluated for the mini-tablets, whereas the amount of drug released and the relative swelling, both after 2 h, were evaluated in regard to the 8 mm tablets. Since the amount of drug was varying within the monolithic formulations, the response “released drug” was expressed in mg.

Table 34: Description of the DoE performed with the XG-containing matrix tablets

Factors	Unit	Level (-1)	Level (0)*	Level (+1)
XG content (XGc)	% (w/w)	30	45	60
XG particle size (PS)	µm	75	127.5	180
Ethanol concentration in media (EtOH)	% (v/v)	0	20	40

* for the center point, a 1:1 mixture of Xantural[®] 75 and Xantural[®] 180 was prepared to get an arithmetic mean particle size of 127.5 µm.

The statistical analysis was performed using Modde 12.0 software (Umetrics, Umea, Sweden) and applying a linear regression model. In addition, the non-significant factors were deleted to enhance the model.

5.2.3 Analytical methods

5.2.3.1 Solubility

The solubility of theophylline was measured in 0.1 N HCl, 0.1 N HCl with ethanol concentrations of 5 % (v/v), 20 % (v/v) and 40 % (v/v). The solutions containing 5 % ethanol are most likely to simulate beer, those containing 20 % ethanol mixed drinks and those containing 40 % ethanol to most undiluted liquors [29]. The experiment was carried out by adding an excess of drug to 50 mL media-containing flasks. The obtained suspensions were then placed in a water bath at a temperature of 37 °C and shaken for 4 days. Samples of supernatant were then filtered through a 0.2 µm filter made of cellulose acetate (VWR International, Fontenay-sous-Bois, France), appropriately diluted and spectrophotometrically (Perkin Elmer Lambda 40, Germany) analyzed. The chosen wavelength was 271 nm and the drug concentration was measured in triplicate.

5.2.3.2 Laser diffraction

The particle size distribution of raw materials was investigated via laser diffraction (Mastersizer 3000, Malvern, UK). When needed, the material was sieved through a 355 µm sieve before starting the measurement. In addition, in order to disperse the agglomerated powders, a pressure of 3 bar was applied during the measurements. The data were then analyzed by the software Mastersizer 3000 (Malvern, UK) and the x_{10} , x_{50} and x_{90} were calculated. The measurement was performed in triplicate.

5.2.3.3 Scanning electron microscopy

To analyse the particle morphology, scanning electron microscopy (SEM) images were taken by microscope Phenom G2 pro (PhenomWorld, the Netherlands). The samples were first attached to aluminium stubs through a double-sided carbon tape and the microscope was used with a working voltage of 5 to 10 kV.

5.2.3.4 Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry measurements (DSC) were performed by using a DSC 1 (Mettler-Toledo, Gießen, Germany) and the data were analysed by the Software STARe (Version 9.20, Mettler-Toledo, Gießen, Germany). Samples of approximately 3 mg were sealed into pierced aluminium pans of 40 µl. An empty, pierced aluminium pan served as reference during the measurement. Measurements were conducted in duplicate at a heating rate of 10 K/min in the reported temperature ranges.

5.2.3.5 Viscosity

The viscosity of 0.1% (w/w) Xantural® 75 and Xantural® 180 solutions in 0.1 N HCl with 0 and 40 % (v/v) ethanol was measured with a rotational viscometer (Kinexus rheometer, Malvern Instruments, Herrenberg, Germany) equipped with a cone-plate system (cone: CP1/60 BS 007 SS, plate: PL65 S0520 SS) (angle of the cone: 1°). The temperature was set at 37 °C. For all solutions, a shear rate ramp was performed with shear rates from 0.1 s⁻¹ to 100 s⁻¹ (up curve) and from 100 s⁻¹ to 0.1 s⁻¹

(down curve) ($n = 3$). Apparent viscosity was determined in triplicate at a shear rate of 5 s^{-1} . The software rSpace (Malvern Instruments, Herrenberg, Germany) was used to analyze the data. To prepare the solutions, 0.1 g polymer were added to 100 g medium under stirring and the dispersions were left stirring until they resulted homogeneous. The solutions were let stand for 12 hours before performing the measurement.

5.2.3.6 Helium pycnometry

The true density (ρ_{true}) of raw materials and physical mixtures was measured with a helium pycnometer (AccuPyc 1330 V2.04N, Micromeritics, Norcross, USA). The sample chamber with an inner volume of 3.5 cm^3 was filled to two-thirds with the powder. The cleaning and the filling pressure amounted 134.45 kPa, whereas the equilibrium pressure amounted 0.0345 kPa. The measurements were conducted at $25.0 \pm 0.1 \text{ }^\circ\text{C}$ in triplicate, where for each measurement series, five runs were performed. The mean value and the standard deviation were calculated from the three measurement series.

5.2.3.7 Porosity

The porosity ϵ of the tablets and mini-tablets was calculated based on helium pycnometric density ρ_{true} (see 5.2.3.6) of the physical mixtures and the apparent density of the tablets $\rho_{apparent}$, as in accordance with the Equation 2:

$$\epsilon (\%) = \left(1 - \frac{\rho_{apparent}}{\rho_{true}} \right) \cdot 100$$

Equation 2: Porosity ϵ of the tablets and mini-tablets

where the apparent density was calculated based on the tablet mass and the tablet volume. Thickness, diameter and mass of the large flat-faced tablets were measured on a SmartTest 50 (Sotax, Switzerland) ($n = 10$). The dimensions of the XG-containing mini-tablets were determined using a stereomicroscope with the digital camera (MZ75, camera DFC 450, Leica, Wetzlar, Germany). Diameter and thickness of ten mini-tablets were determined for each batch by analyzing the acquired images with the software Image J. The mini-tablets in chapter 3.3 were measured by a caliper ($d = 0.01 \text{ mm}$) ($n = 10$). The volume could be calculated by knowing that the curvature radius of the punch, which amounted 2.4 mm. The mass was determined on an analytical balance (Sartorius MC 210 P, Sartorius, Göttingen, Germany).

The envelope density of the extrudates was measured with a powder pycnometer GeoPyc1360 Envelope Density Analyzer (Micromeritics Instrument, USA). The GeoPyc determines the sample envelope volume (V_{sample}) based on a displacement measurement technique and then, it calculates the envelope density ($\rho_{envelope}$) using the sample mass. The porosity was determined using the true density (ρ_{true}) of the starting material (see section 5.2.3.6). The calculations followed Equation 4 and Equation 3, where m is the mass of the extrudates (g), d_2 and d_1 are the displacement of the punch (mm) with and without the sample in the chamber and f is the conversion factor (cm^3/mm), which

depends on the chamber internal diameter. Approximately 0.75 g of the sample were weighed with an analytical balance (CP 224 S, Sartorius, Göttingen, Germany). The sample mass occupied between 14% and 17% of the chamber volume. Three blank cycles and three sample cycles were performed.

$$\rho_{envelope} = \frac{m}{V_{sample}} = \frac{m}{(d_2 - d_1) \cdot f}$$

Equation 3: Determination of the envelope density $\rho_{envelope}$

$$\varepsilon (\%) = \left(1 - \frac{\rho_{envelope}}{\rho_{true}} \right) \cdot 100$$

Equation 4 : Porosity ε of the extrudates

The measuring chamber had a diameter of 12.7 mm, the consolidation force was set at 28 N and the conversion factor (f) amounted 0.1284 cm³/mm. The measurement was conducted in triplicate and the obtained values were averaged.

5.2.3.8 Crushing and tensile strength

The tensile strength of the tablets was calculated [200] based on the radial crushing force (F), tablet diameter (d) and tablet thickness (t), which were determined by SmartTest 50 (Sotax, Switzerland) (Equation 5):

$$\sigma = \frac{2 \cdot F}{\pi \cdot d \cdot t}$$

Equation 5: Tensile strength σ

Due to the reduced dimensions and the low mechanical stability of mini-tablets, the radial crushing strength of each mini-tablet was evaluated with a texture analyser (TA-XTplus, Stable Micro Systems, Godalming, UK) instead of the common hardness tester [173]. This method has been already used for the investigation of pellets [201] and mini-tablets [76, 173, 202] and consists in the deformation of the tablets by a punch over a defined distance. A flat faced probe head with the diameter of 4 mm was used. The experimental parameters of the texture analyzer (TA) were the following: pretest speed 0.5 mm/s, test speed 0.1 mm/s, post test speed 1.0 mm/s, strain 50 % and trigger force 0.01 N. A force/displacement diagram was registered and the first maximum force was defined as crushing force. The tensile strength was finally calculated applying the same equation used for the flat-faced tablets [75, 200].

5.2.3.9 Dissolution testing

The dissolution testing was assessed using a USP-compliant dissolution bath (Erweka DT 700, Heusenstamm, Germany) with an Apparatus II (paddle method, Ph. Eur. 2.9.3. and USP <711>) controlled by the UV WinLab software (Perkin Elmer, Germany). The volume of the dissolution media was 900 mL, the paddle rotation speed was set at 50 rpm and the temperature of the dissolution bath at 37 ± 0.5 °C. Sink conditions were maintained in all tested media. The amount of released

theophylline was determined on-line spectrophotometrically (Lambda 25 and 40, Perkin Elmer, Germany) at a wavelength of 271 nm in flow-through cuvettes. The theophylline concentration was calculated based on calibration curves (Table 35).

Table 35: UV-calibration equations of theophylline in the used media (slope [l/mg]), Lambda 40, Perkin-Elmer, USA; wavelength of 271 nm; cuvette 1 cm

Drug	Medium	Regression equation and R^2
Theophylline anhydrate	0.1 N HCl	$y = 0.0551x + 0.0137, R^2 = 0.9996$
	0.1 N HCl 40 % ethanol (v/v)	$y = 0.0558x + 0.0095, R^2 = 0.9988$
Theophylline monohydrate	0.1 N HCl	$y = 0.0541x + 0.0099, R^2 = 0.9999$
	0.1 N HCl 5 % ethanol (v/v)	$y = 0.0552x + 0.0012, R^2 = 0.9999$
	0.1 N HCl 20 % ethanol (v/v)	$y = 0.0549x + 0.0086, R^2 = 0.9999$
	0.1 N HCl 40 % ethanol (v/v)	$y = 0.0552x + 0.0024, R^2 = 0.9999$
	0.05 M phosphate buffer pH 6.6	$y = 0.0571x + 0.0065, R^2 = 0.9999$

Samples were withdrawn automatically every 30 s regarding mini-tablets and extrudates, every 1 min regarding larger tablets. When necessary, the samples were then homogenized with an Ultra-Turrax® (IKA, Germany) and the amount of released drug was expressed in percentage or in mg with regard to the maximal achieved drug concentration.

To assess the risk of alcohol-induced dose dumping (ADD), the FDA recommends to evaluate the dissolution performance of modified release oral dosage forms in 0.1 N HCl (pH 1.2) with different concentration of ethanol, in order to simulate the gastric environment after ingestion of alcoholic beverages [29, 203]. Concentrations of ethanol ranges from 0 % (no addition of alcohol, used as control) to 40 % ethanol, concentration which is considered to be found in neat liquor. According to the FDA, intermediate alcohol concentrations of 5 and 20 % ethanol should be also evaluated, representative for the consumption of beer and mixed drinks respectively [29]. In this study, all formulations were tested in 0 and 40 % alcohol, whereas studies in 5 and 20 % alcohol were conducted only when not similar release profiles were previously seen in 0 and 40 % alcohol. The measurements were conducted in triplicate for each medium.

To perform the study regarding the drug release kinetics (chapter 3.4), 0.05 M phosphate buffer pH 6.6 was used as medium, based on USP 41 monograph *Theophylline Extended-Release Capsules Test 6*, however the medium volume amounted 900 mL instead of 1000 mL. The paddle rotation speed was set at 50 rpm and the test setup was the same as reported above. The measurements were conducted in triplicate.

To avoid the phenomenon of sticking of larger tablets on the vessel bottom and allow an uniform penetration of the medium in the tablets, sinkers made of stainless steel meshes (mesh aperture of 1 mm) (Figure 64) were in-house manufactured [74]. The sinkers were positioned centrally on the

bottom of the vessel and the distance from the vessel bottom to the lower edge of the paddle amounted 2.5 cm, as recommended by the USP.

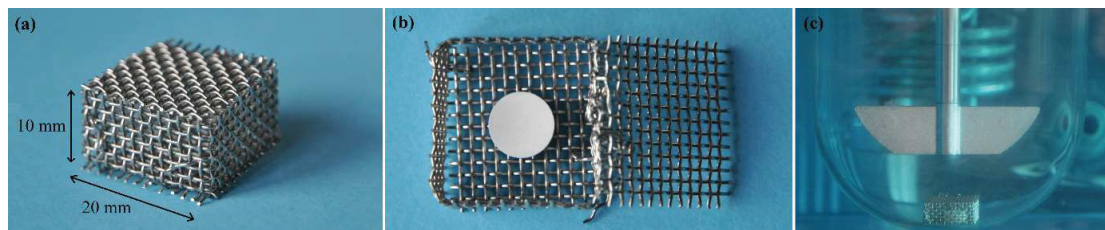


Figure 64: Designed stainless steel sinker: (a) dimensions, (b) position of the tablet (8 mm diameter) inside the sinker and (c) the inclusion of the sinker in the USP App. II (used by courtesy of the International Journal of Pharmaceutics, Elsevier [74])

5.2.3.10 Dissolution data analysis

To assess the similarity of the dissolution profiles in 0 and 40 % ethanol, the similarity factor (f_2 value) proposed by Moore and Flanner [204] was calculated (Equation 6).

$$f_2 = 50 \times \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

Equation 6: Similarity factor (f_2 value)

where n is the number of dissolution time points, R_t and T_t are the percentage of drug released from the reference (formulation in 0.1 N HCl) and from the test product (i.e. formulation in 40 % ethanol) respectively. The f_2 value ranges from 0 to 100 and dissolution profiles are declared to be similar when the f_2 value exceeds 50 [205]. Therefore, Schrank et al. [114] assumed that ADD does not occur and a formulation is alcohol-resistant or alcohol-robust if the determined f_2 value is above 50. To note, values lower than 50 might indicate two scenarios: (1) the formulation is vulnerable against ADD or (2) the formulation shows significantly lower drug release in alcohol than in hydrous media [24].

In addition, the area under the curve after 2 hours dissolution was calculated ($AUC_{120 \text{ min}}$).

To assess the diffusional release mechanism of the matrix formulations, the dissolution data were further analyzed using the Korsmeyer-Peppas equation (Equation 7):

$$\frac{M_t}{M_\infty} = kt^n$$

Equation 7

where M_t/M_∞ is the released amount of theophylline at time t in relation to the entire drug amount in the matrix, k represent structural and geometrical properties of the matrix and n indicates the diffusion mechanism [206]. Data between 10 % and 80 % drug release were fit by the Korsmeyer-Peppas model.

An application of the common logarithm on the Equation 7 leads to Equation 8:

$$\log_{10} \left(\frac{M_t}{M_\infty} \right) = \log_{10} k + n \log_{10} t$$

Equation 8

The drug release was furthermore described by the Higuchi equation (Equation 9), where Q represents the amount of drug released at time t per unit area (A), D the diffusivity of the drug in the polymeric matrix, C_0 the initial drug concentration and C_s the drug solubility in the matrix.

$$Q = \frac{M_t}{A} = \sqrt{D(2C_0 - C_s)C_s t}$$

Equation 9

Since the parameters D , C_0 and C_s were constant in all experiments in chapter 3.4 (dissolution testing in 0.05 M phosphate buffer pH 6.6), the Equation 9 was modified to Equation 10, as according to Korte et al. [207]:

$$\frac{M_t}{A} = D_k \sqrt{t}$$

Equation 10

with $\frac{Q}{\sqrt{t}} = D_k$, where D_k is the slope of the Higuchi plot (Q against \sqrt{t}). D_k was the value used to compare the tablets with different size.

5.2.3.11 Relative swelling, dissolution media uptake and mass loss

Swelling and erosion properties of the matrix tablets ($d \geq 8$ mm) in media of different composition were investigated using a modified version of the method described by Tahara et al. [208] and Kavanagh and Corrigan [209]. Testing was conducted in a USP-compliant dissolution bath, under the dissolution conditions described in section 5.2.3.9, in 900 mL 0.1 N HCl with 0 and 40 % ethanol. The tablets were exposed to the dissolution media for 2 hours, and then each unit was withdrawn and the excess of media was removed with a filter paper (Schleicher & Schuell GmbH, Germany). The wet tablets were weighted and afterwards dried to a constant weight in a vacuum drying oven (Heraeus VT6025 Vacutherm, Germany) at a temperature of 70° C and a pressure < 30 mbar.

Three parameters were calculated and chosen as an indication of the extent of the matrix swelling and erosion: relative swelling (RS) (Equation 11), dissolution media uptake (DMU) (Equation 12) and mass loss (ML) (Equation 13). The corresponding equations are the followings:

$$RS = \frac{W_w}{W_i}$$

Equation 11: Relative swelling

$$DMU (\%) = \frac{(W_w - W_d)}{W_d} \cdot 100$$

Equation 12: Dissolution media uptake

$$ML (\%) = \frac{(W_i - W_d)}{W_i} \cdot 100$$

Equation 13: Mass loss

where W_i refers to the initial, W_w to the wet and W_d to the dried mass. All experiments were conducted in triplicate for each medium.

The absolute tablet swelling (AS) values in 0 and 40 % ethanol (section 3.4.4) were calculated according to Equation 14:

$$AS = \frac{W_w - W_i}{SA}$$

Equation 14

where W_i refers to the initial, W_w to the wet tablet mass and SA refers to the tablet surface area ($n = 3$).

5.2.3.12 Image analysis

The dynamic of the media penetration into the formulations was evaluated by using a stereomicroscope (MZ75, camera DFC 450, Leica, Wetzlar, Germany) [74]. For this purpose, the samples were lightly glued onto small glass petri dishes by using a cyanoacrylate instant glue (Pattex[®], Henkel, Germany). This procedure was done to avoid the moving of the sample in the medium during the observation time. The tablets were positioned vertically, the extrudates longitudinally, in order to observe both axial and radial swelling [54]. The petri dishes were then filled with 10 mL (for tablets) and 3 mL (for mini-tablets and extrudates) of each medium (0 % and 40 % ethanol) by using a syringe. The observations were conducted at room temperature and the acquired images were finally analyzed by the software Leica V4.6 (Wetzlar, Germany). The scale was added by using a graduated ruler under the same conditions.

5.2.3.13 Gel layer strength

After dissolution in 0 and 40 % ethanolic media, the swollen tablets were patted lightly with a filter paper to remove extra moisture and subjected to analysis using a Texture Analyzer (TA-XTplus, Stable Micro Systems, Godalming, UK). The force-distance displacement associated with the penetration of a 2 mm round tipped stainless steel flat-faced probe into the swollen tablets were monitored, in order to analyze the effect of ethanol of the gel textural properties. The measurement settings were the same used by Missaghi et al. [46] and were the following: pre-test speed 1.00 mm/s, test speed 0.50 mm/s, post-test speed 10.00 mm/s, trigger force 0.005 N, target force 45 N. The work of penetration was determined for each textural profile and used to compare the formulations. All measurement were carried out in triplicates.

5.2.3.14 Mixer torque rheometer

The wet mass characterization was performed with a mixer torque rheometer (MTR) W 50 EHT (Brabender, Duisburg, Germany) (Figure 65). This method is described in the literature and has been used to determine the torque changes which occur during the wetting phase of powders [135, 177, 178, 210-212]. MRT was here used (i) to define the most appropriate liquid to solid ratio, which was subsequently applied in the wet extrusion processes, (ii) to study the interaction between the sole polymers and media containing 0, (eventually 20) and 40 % ethanol.

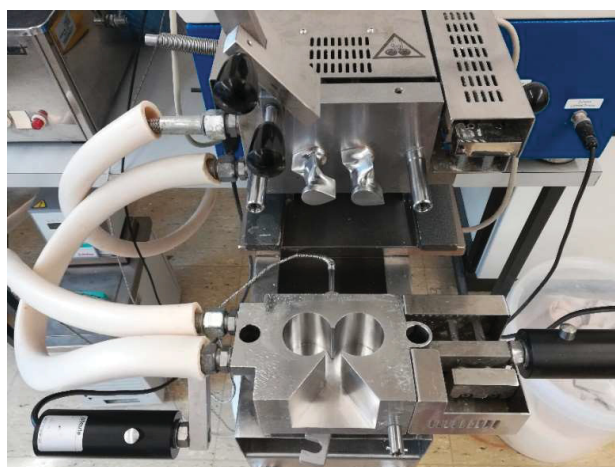


Figure 65: Mixer torque rheometer ((W 50 EHT, Brabender)

The mixing chamber of 55 cm³ volume was filled with an amount of powder which corresponded to a volume of 40 mL. A shaft speed of 30 rpm was used. If not differently indicated, the temperature of the mixing chamber was maintained at 25 °C through a circulation thermostat (F12, Julabo Labortechnik, Seelbach, Germany). 0.5 mL medium were then stepwise added with a 100 mL Eppendorf (Wesseling, Germany) pipette and after each liquid addition, the wet mass was mixed for 30 s. The torque values were collected every 2 s and analysed by the WINMIX software (Brabender, Duisburg, Germany). However, only the values registered in the mixing interval 15 s- 30 s were considered and averaged. If not differently indicated, the measurements were conducted in triplicate.

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Eigenständigkeitserklärung

Ich versichere an Eides Statt, dass die Dissertation „Development of alcohol-resistant single- and multiple-unit matrix formulations“ von mir selbständig und ohne unzulässige fremde Hilfe unter Beachtung der „Grundsätze zur Sicherung guter wissenschaftlicher Praxis an der Heinrich-Heine-Universität Düsseldorf“ erstellt worden ist. Außerdem versichere ich, dass die vorgelegte elektronische mit der schriftlichen Version der Dissertation übereinstimmt und die Abhandlung in dieser oder ähnlicher Form noch nicht anderweitig als Promotionsleistung vorgelegt und bewertet wurde.

Alessia Lazzari