Performance of various oral modified release dosage forms in hydroethanolic media

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1 Introduction

1.1 Modified release oral dosage forms

Oral modified release refers to the extension or delay of the release of a drug from a pharmaceutical formulation in the gastrointestinal tract (GIT) to improve the bioavailability, patient compliance, reduce side-effects or prolong the therapeutic effect [1]. The main approaches to achieve modified release are to disperse the drug homogeneously in the matrix of release-modifying agents, referred to as matrix systems, or to surround the drug and potential excipients with a layer of release-modifying agents, referred to as reservoir systems.

1.1.1 Release from matrix systems

Modified release matrix tablets have previously been the most widespread oral formulation type [2] and can include both soluble, or hydrophilic, and insoluble polymers [3]. The term matrix refers to a homogeneous distribution of the drug, the modified release agents, most often a polymer, and other included excipients.

The release from matrix tablets depends, among others, on the type and amount of polymer, its viscosity and particle size, the amount, solubility, and size of drug particles as well as the amount of excipients [4]. An increase in compression strength usually leads to a reduction in drug release [5]. The geometric shape of the tablet also has a profound effect on the release rate [6] as well as on the swelling, as tablets swell more in the axial direction compared to the radial direction [7].

Diffusion, swelling and, matrix erosion have been identified as possible mechanisms of drug release from systems based on hydrophilic matrix formers [8-11]. In contrast, the release from insoluble matrices is limited to diffusion and, potentially, swelling.

A lot of research regarding the release from hydrophilic matrix tablets has focused on hydroxypropyl methylcellulose (HPMC), likely being the most widespread hydrophilic matrix polymer in use [12]. Many of the models, also applied to other hydrophilic matrix polymers, derive from this research, rendering HPMC a model substance in this field.

Upon exposure to aqueous media, HPMC hydrates to form a swollen and viscous gel layer, depending on the concentration of the polymer, sustaining the further invasion of the medium (Fig. 1). Over time, the gel layer erodes as the HPMC dissolves in the medium. The diffusion front separates areas of dissolved drug from undissolved drug [2]. The interaction of the release medium with the HPMC reduces the glass transition temperature. This results in a glass-liquid transition, separating the more hydrated rubbery state from the lower hydrated glassy core. This is associated with a strong increase in the diffusion coefficient of the medium inside the polymer [13]. The position of these fronts can vary depending on the drug solubility [9]. Drug particles of low solubility can be transported with the gel layer and shift the diffusion front further outwards compared to drugs of high solubility. The presence of these undissolved particles also reduces the entanglement of the polymer, leading to less swelling and faster erosion. Drug release from these matrices is therefore by diffusion of the dissolved drug or by erosion of the polymer, resulting in the release of dissolved or undissolved drug.

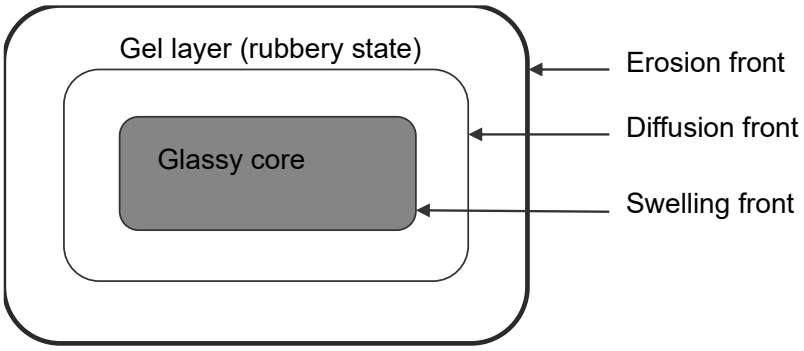

Fig. 1 Layers and fronts of a HPMC tablet in media, adapted from Pygall et al. [4]

The release-inhibiting properties of HPMC are highly dependent on its hydration rate and therefore on its hydrophilic properties. The most commonly used type for extended-release is the 2208 type (e.g. Methocel® K), which is cellulose substituted with 22% methoxy-groups and 8% hydroxypropyl groups [14] and available in different viscosity grades. Due to its high hydrophilicity, it swells faster than the 2906 (e.g., Methocel® F) and the 2910 (e.g., Methocel® E) grades and reduces media penetration into the inside of the tablet more. The viscosity of HPMC is determined in a 2% aqueous solution at 20°C and is an indirect measurement of the molecular weight. Lower viscosity grades of HPMC are recommended for low solubility drugs [14-16] to accelerate their release to allow complete drug release in the intestine.

Like HPMC, many other polymers used for formulating hydrophilic matrix systems contain a sugar structure and derive from starch or cellulose. Starch derivates can be applied in their natural form [4, 17] or chemically modified [18]. Corn starch has been used in the preparation of modified release matrix pellets [17]. However, a poor compactability and problems of enzymatic degradations often create a necessity to use modified starches. These include e.g. pregelatinized starch, carboxymethyl starch, or cross-linked starch [19].

Cellulose is water-insoluble and must be chemically modified to be used as a matrix polymer. Hydroxypropyl cellulose (HPC) is not substituted with methylene groups, but with a higher amount of hydroxypropyl groups of over 50% [20]. Due to the additional hydroxypropyl-part it is more hydrophobic than HPMC but can also be utilized for modified release and other applications like 3D printing [21, 22].

Other polymers successfully applied for extended-release matrices include natural oligosaccharides like xanthan gum [23, 24]. Polyethylenoxide (PEO) has recently attracted more attention for modified release [25] and releases drugs through a similar layer model in the release medium as HPMC [26]. While these polymers mainly release pH-independent, some matrix formers have a pH-dependent release behavior. Carbopol®, a brand of acrylic acid polymers with an acidic carboxyl group, swells more at neutral pH, which may result in a faster release of highly soluble drugs at low pH [27-29].

Different methods have been developed to calculate the release from matrix systems [30, 31]. Empirical approaches aim to give information about the mechanism, by which the drug is released. The most commonly used is the Peppas equation [8]:

$$\frac{\boldsymbol{M_t}}{\boldsymbol{M_\infty}} = \boldsymbol{k} * \boldsymbol{t^m} \qquad \text{equation 1}$$

Where $\frac{M_t}{M_\infty}$ is the drug amount released at time *t, k* is a kinetic constant and *m* is an exponent to resemble the release mechanism. A value of m of 0.5 would imply a diffusion-based release, a value of 1 would imply a Case-II release and higher values a super-Case-II release. Case-II refers to a special type of anomalous, diffusion mechanism characterized by linear kinetics and a sharp diffusion front, potentially occurring in systems with polymer swelling [32]. This equation is limited to the first 60% of release [31, 33]. There are a few expansions of this equation, introducing, e.g., a burst release [34] or a lag time [35]. The burst release is associated with the

presence of drug particles on the tablet surface, which are directly subjected to the dissolution medium. The lag time can be a result of slow drug dissolution or a reduction in medium penetration due to other excipients [35].

Another extension of this equation by Peppas and Sahlin separated the diffusional and the Case-II release to allow calculation of the %-release-via-diffusion [31]. These methods are not suited for quantitative predictions, but they can be useful to compare different release profiles due to their ease of application [30].

An analytical model considering medium diffusion, polymer swelling, and drug dissolution has been developed for soluble drugs. The model assumes an absence of volume contraction, perfect sink conditions and a time-invariance of the diffusivity of drug and water. Then, a quarter of the axial plane of the matrix is simulated with a uniform distribution of drug and polymer. Through a series of equations the diffusion of water into the tablet, the swelling of the polymer (and simultaneous increase in diffusivity), the diffusion of the drug and the dissolution of the polymer can be calculated simultaneously [11].

This sequential layer model can be applied to drugs of different solubility and different viscosity grades of HPMC [6]. Other approaches like the finite element method have later also been used to predict the release from HPMC tablets with high amounts of maltitol. They could, however, not predict the dissolution and release of the HPMC itself [36].

Insoluble polymers may swell, but do not dissolve in the release medium. They include, among others, the non-swelling ethylcellulose, which differs from the chemically similar hydrophilic cellulose ethers due to its higher degree of substitution. The mixture of polyvinylacetate with polyvinylpyrrolidone, marketed as Kollidon® SR combines an insoluble polymer with a soluble polymer, leading to a porous, but viscous matrix [3]. Polymethacrylates like Eudragit® RS are insoluble, but swell to various degree, depending on their substitution. All these polymers create a matrix system, where the drug is released via diffusion [37]. The release from these systems can be described using percolation theory [38]. In brief, the particles fill the sites of a volume with a specific probability *p*. Medium penetrating from the outside will fill the empty sites. Above the site percolation threshold, the medium cannot penetrate all empty sites as some of these will be completely surrounded by particles and thus inaccessible to medium. A similar approach can be taken for bonds between the individual particles. The percolation theory approach can be applied both to release [3] as well as to tablet compaction [39]. The percolation threshold can change in

the wet state if the glass transition temperature (T_g) is reduced and the polymer undergoes swelling [3]. A mechanistic mathematic model to predict the drug release from Kollidon® SR matrices, taking into account the tablet geometry, showed good agreement with experimental data [37].

Lipids can be used alternatively as an insoluble matrix former. They are usually pH-independent due to their insolubility in water and release drugs through fickian diffusion [40]. Calcium stearate has been employed as matrix former for modified release-matrix pellets of paracetamol and codeine phosphate [41]. The addition of xanthan gum accelerated the release rate in 0.1 N HCl and the addition of guar gum the release rate in phosphate buffer system (PBS) 6.8, whereas TiO_2 did not change the underlying release behavior [42].

1.1.2 Release from coated systems

Next to matrix systems, film coated pharmaceutical dosage forms are of utmost practical importance in formulation design [43]. They can be employed for pulsatile-release [44], colon-targeting [45], enteric protection [46] or extended-release [47]. Coated systems are often administered as multiparticulate system, e.g. as coated pellets, due to their higher bioavailability [48] and their better reproducibility [49]. These pellets can then be filled into a capsule or compressed into a tablet [50].

The release mechanism from coated pellets has been the subject of numerous investigations [51, 52]. Ozturk et al have identified three mayor release mechanism from ethylcellulose-coated pellets [52]: osmotic driven release, diffusion through aqueous pores and diffusion through the plasticized polymer phase (Fig. 2). However, an osmotically driven release itself can increase the number of aqueous pores by causing rupturing or cracking of the coating, as well as increase diffusion due to a higher medium uptake and a stretching, and thus thinning, of the coating.

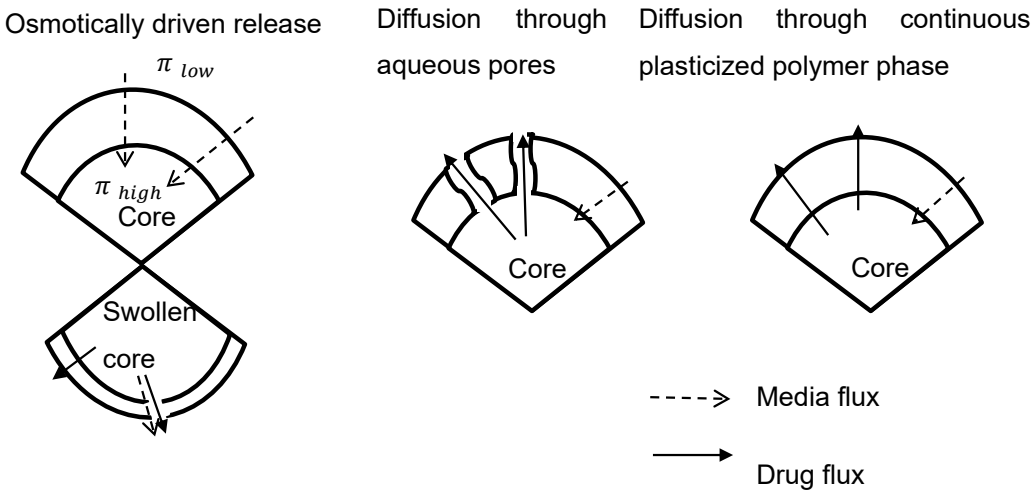

Fig. 2 Release mechanisms from pellets coated with an insoluble, non-swelling polymer. Adapted from Ozturk et al [52].

The drug is mainly released via diffusion, if the coating is permeable towards the drug, or via osmotic pumping, if the coating is semi-permeable towards the drug [51, 53].

If a drug cannot permeate through the coating, while the medium can, it can create an osmotic pressure. Medium penetrates into the core and dissolves the drug and other excipients, building up this osmotic pressure [52], if the medium volume exceeds the displaceable volume [54]. This creates a pressure on the coating, which may result in rupturing [55, 56]. The pressure is, strictly speaking, not created by the drug, but by the membrane [57]. As a complete semi-permeability is unlikely in practice, the reflection coefficient is used. It refers to the amount of drug, which cannot pass through the membrane in dissolved state. A high reflection coefficient is essential for the creation of the osmotic pressure [52].

The release mechanism, however, also depends on the preparation method. Coating from an aqueous dispersion will generally result in a less dense coating compared to an organic solution [58]. Coating from an aqueous-organic solution may result in phase separation of the polymer molecules during drying and the creation of a porous coating [59]. At low coating levels the coating may not completely cover the core. In this case, the wettability of the core is critical for release [60].

The distribution of the drug in the core affects the relative release rate [61], as drug-matrix cores have a comparatively higher drug loading at constant surface area compared to drug-layered cores. However, even for layered pellets the material of the core has an impact on release and to

factors such as medium osmolality [62]. Sugar cores will dissolve and may thus create an osmotic medium flow sustaining the release due to media convection, but also creating an osmotic pressure on the coating. The release from microcrystalline (MCC) cores does not show this strong media convection. However, the general release mechanism for MCC and sugar cores with ethylcellulose and small amounts of poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer has previously been stated to be similar [62]. Kállai et al investigated isomalt, sugar and MCC cores coated with Eudragit® RL and Eudragit® RS and found a strong difference between isomalt and sugar cores on one side and MCC cores on the other. They state the difference in release is due to less pressure created by the MCC core on the coating compared to the soluble compounds. They also showed a stronger effect of osmolarity on the release from MCC cores compared to isomalt and sugar cores [63].

The usage and type of plasticizer has a profound effect on the release [55, 64]. Plasticizers are small molecules, that can interact with the coating, either by acting as a lubricant between the polymer chains or by breaking up the intermolecular bonds [65]. Plasticizers can lower the T_g, allowing coalescence of coating polymers. They can be essential to ensure appropriate polymer properties like enteric-resistance [66]. However, the medium itself can also act as a plasticizer [55]. The elongation and the puncture strength may be increased by the addition of a plasticizer [55]. However, the tensile strength and the elongation to break may also be reduced, depending on the type and amount of plasticizer [67]. This results from the distribution of the plasticizer in the polymer matrix, which may be inhomogeneous [65, 68].

Ethylcellulose (EC) is a rather lipophilic and brittle polymer and thus it mainly releases through cracks created by osmotic pressure, but the inclusion of hydrophilic polymers [69] or the usage of lipophilic drugs [55] allows more release via diffusion through the coating.

Polymethacrylates, marketed as Eudragit®, are a versatile group of excipients derived from esterification of poly acrylic acid to achieve immediate release, extended-release with different swelling ability and even enteric-resistance.

Polymethacrylates often swell in release media. Swelling can increase the diffusivity [13] and allow the drug to diffuse through the swollen polymer [70]. Eudragit® RL and RS possess quaternary ammonium groups, which may interact with the drug or excipients to further facilitate the release [71].

For Kollicoat® SR a mixed effect involving both diffusion through the polymer and through pressure-induced cracks explains the release [72].

The combination of an insoluble coating polymer with a pH-dependent soluble polymer can be used to modify the release further. One approach is colon-targeting, where the introduction of a pH-dependent polymer will result in a lag time. This has been used for indomethacin pellets coated with Eudragit® RS as insoluble coating and Eudragit® L and S as pH-dependent soluble coatings [73]. Lecomte et al investigated the combination of ethylcellulose with Eudragit L in various ratios for the release of propranolol HCl [58, 64] and theophylline [61]. They identified an inverse correlation between ethylcellulose content and release rate in phosphate buffer 7.4, but a non-linear, plasticizer dependent order in 0.1 N HCl [64]. The release mechanism changed from diffusion through the intact coating for pure Eudragit® L at pH 1.2 to diffusion through water filled cracks with increasing ethylcellulose content [58].

Different models have been established to predict the release from pellets coated with extended-release polymers. Frenning et al developed a mathematical model employing liquid inflow, drug dissolution and liquid efflux for the release of salicylic acid from extruded-spheronized pellets of MCC coated with ethylcellulose. They additionally identified the core porosity and the solubility of the drug in the release medium as further factors affecting the drug release [74].
Rosiaux et al used a mathematical model to determine the release of theophylline from pellets coated with ethylcellulose and guar gum. They identified surface area, coating thickness, solubility of the drug in the medium, the partition coefficient between drug and polymer as well the diffusion coefficient of the drug inside the polymer as relevant factors [69]. Marucci et al developed a mechanistic model for the lag time prior to the release of remoxipride from ethylcellulose coated pellets of MCC. They simulated the medium uptake, the drug dissolution, the build-up of tensile stress and the deformation of the pellet before the onset of coating ruptures. They showed a nice fit to experimental data while only having to fit the tensile strength and the drug permeability of the coating.

Oral osmotic systems (OROS) are a special type of coated system, as they differ in their release behavior from both matrix- and other reservoir-systems. They take up medium through a semi-permeable coating, which dissolves an osmotically active excipient. The drug then gets transported out via convection through an orifice of a specified size (Fig. 3) [75]. A push layer consisting of hydrogels can be added to accelerate the release [76]. These systems can release drugs independent of pH and stirring rate [77]. The coating is often made of cellulose acetate,

which is semi-permeable, allowing the influx of medium but stopping any outward diffusion of the drug or the osmotic agent.

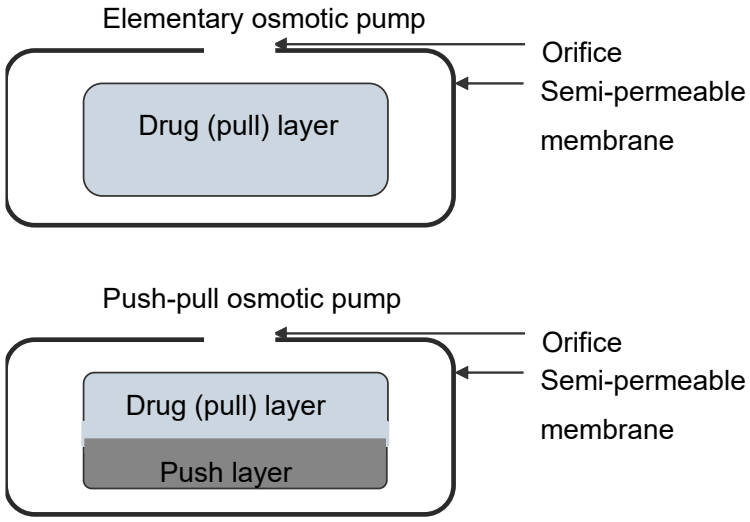

Fig. 3 Schematic description of different osmotic pumps, adapted from Chen et al [78]

Enteric coatings differ in their intended release mechanism, as they should only allow limited medium penetration or drug release in the stomach, but a rapid release in the intestine [46]. These polymers often possess a weakly acidic group, which is protonated in the acidic pH of the stomach and dissociates at the neutral pH in the intestine. The different enteric polymers differ in their permeability to water vapor and simulated gastric juice [79], their stability [80] as well as the pH, at which they dissolve [81]. The plasticizer used during the coating procedure can also have an effect on the water vapor transmission rate [82].

Thoma et al investigated the residual lipase activity of HPMCAS-coatings from an aqueous suspension or an organic solution and found a better enteric-resistance for the organic solution [80]. For aqueous dispersions of HPMCP they also concluded that a subcoating, a reduction in particle size or an increase in coating amount could improve the residual lipase activity.

Including a partially neutralized coating layer beneath the enteric layer can result in an acceleration of release in the intestine [83]. This is especially important, as there is some controversy regarding the buffering capacity inside the intestine and it has been suggested, that a reduced buffer capacity, compared to the standard USP phosphate buffer 6.8, is more representative of the in-vivo situation [84].
Enteric-resistance for one hour was achieved using ethylcellulose with carboxymethyl cellulose or sodium alginate [85]. An even better combination to achieve enteric-resistance of shellac with sodium alginate did not disintegrate or allow fast release at pH 6.8.

The dissolution of the enteric coating and thus the rate of drug release in the intestine have been successfully modelled for weakly acidic drugs [86]. However, only few publications have evaluated the release in 0.1 N HCl. Lecomte et al have proposed the release of propranolol HCl from pellets coated with an aqueous Eudragit® L formulation to be diffusion controlled [58].

1.2 Physiological considerations for release

In recent years different approaches have been employed to evaluate how the gastrointestinal milieu affects the release from peroral dosage forms [87]. Ideally, a formulation should release independent of food or ethanol effects, variations in gastrointestinal motility or gastrointestinal pH, the presence or absence of enzymes, gastrointestinal water volume and independent of pathophysiological changes in the gastrointestinal-physiology or -anatomy. If the absorption is affected by these factors, an ideal formulation may even equilibrate this effect.

The most common approach to mimic the GIT is the use of biorelevant media, hereby taking into consideration the fasted or postprandial state. These can be divided into 4 groups [88]: level 0 mimics the gastrointestinal pH, level 1 adjusts for the buffer capacity, level 2 adds bile salts, lipids and adjusts for osmolarity and level 3 adds dietary proteins, enzymes and adjusts for viscosity. The different stages of the GIT can be mimicked by a change of release medium [89]. Jantratid et al used in-vivo data summarized by Porter et al [90] to develop fed-state media mimicking different parts of the digestion process. They claimed this to be specifically relevant for monolithic extended-release dosage forms, which may experience changes in the intestinal medium composition due to their prolonged exposure and residence [91].

Other approaches have used grinded meals, milk or fat emulsions to simulate the release in fed-state [92]. In the case of HPMC, the fat content of the medium can reduce the release [93]. This was explained by a phase separation at the surface of the tablets, resulting in a coalescence of the fat and the creation of a lipid layer on the tablet surface. This effect is more pronounced for lower viscosity grades of HPMC, as the lipid layer can reduce the erosion rate of the tablet [94]. Such a film can also be caused by proteins and even reduce the disintegration rate of immediate release tablets [95]. Besides the creation of a separating layer, the media in the fed state may be more viscous, reducing the penetration of media into a tablet [96]. The food itself can also interact with the drug and reduce the absorption as shown e.g., for zolpidem [97].

The release is additionally affected by the hydrodynamic conditions and mechanical forces present in the GIT [87].

One of the first approaches to mimic the hydrodynamic conditions derive from Aoki et al, who included polystyrene beads into a paddle apparatus [98]. They found a relationship between their in-vitro results and the in-vivo release observed in dogs. A similar approach was later developed employing a beaker equipped with a magnetic stirrer, where the tablet is subjected to forces by both the glass beads as well as the stirrer [99]. They could replicate the effect of different stirring rates from paddle apparatus on two tablet formulations but did not extend to other applications. Abrahamson et al modelled the required amount of shear forces in-vitro to simulate the fed stomach [100]. They found a high correlation between the surface shear and the mass erosion rate of HPMC tablets using a fixed tablet in a rotating beaker.

The inclusion of random movements, generated by inflation of a balloon, was used to explain the drug release of Voltaren® Retard, a commercial product of diclofenac [101]. The new dissolution apparatus could explain the high variability observed in-vivo. In contrast, the use of osmotic tablets showed stable release characteristics, unaffected by mechanical forces [102]. This set-up was later extended to show a strong susceptibility of HPMC tablets to mechanical stress [103]. A similar conclusion was reached by Goldoozian et al, who tested tablets with different viscosity grades of HPMC. They showed that lower viscosity grades of HPMC more likely to show accelerated release in the case of a higher agitation rate [104]. In-vivo monitoring of different HPMC grades confirmed this behavior of a faster erosion rate of the lower viscosity grades. The erosion rates were significantly higher in the fed-state than in the fasted state [105].

Gastrointestinal motility and physiologically equivalent media were combined by Blanquet et al, who presented a multicompartmental in-vitro system (TIM-1) simulating the different parts (stomach, duodenum, jejunum, ileum) of the GIT using a series of glass jackets filled with heated water with a flexible wall, in which the simulated chyme is transported. They could show the difference in absorption of paracetamol from a modified release tablet vs. application as powder, the reduction of absorption by a reduction of transit time and the reduction in absorption in the presence of a meal [106].

Gastric emptying as a physiological process is likely the most relevant transition during drug release in-vivo. It often affects both the pH of the surrounding medium as well as the absorption of drugs, which are frequently absorbed mainly in the intestine [107].
Gastric emptying depends on the prandial status of the patients. The emptying of large dosage forms like tablets and capsules from the stomach is usually during phase III of the migrating motor complex, but can also be introduced by isolated antral contractions [108]. In fasted state, emptying times of both pellets and tablets vary over a wide range [109]. The emptying of mini-tablets is faster than for pellets, but the time of highest plasma concentration (t_{max}) is higher for mini-tablets than for pellets [110]. The data on gastric emptying of pellets in the fed state is non-conclusive and a long residence time in the fed state, at least for some patients, appears likely [111]. The caloric content of a meal can also have a negative effect on the gastric emptying of pellets [112]. Therefore, while both pellets and tablets are effective modified release formulations, neither can completely avoid the variability in gastric emptying associated with the intake of food [111].
A longer gastric residence time is especially relevant for the release from enteric coated dosage forms. Kenyon et al used gamma scintigraphy to follow the disintegration of enteric coated capsules. While nearly all remained intact in the stomach, the disintegration in the intestine was faster, if the gastric residence time was longer [113].

Knowledge of the physiological conditions in the stomach and the intestine are important, as they would both apply to a formulation taken without ethanol, as well as be altered in the presence of ethanol.

1.3 The effects of ethanol consumption

Ethanol is one of the most widespread legal drugs [114] with the highest intake recorded for Europe, America and the western Pacific region. Despite numerous programs to reduce the amount of ethanol intake, it still increases in some countries like Germany [115]. Frequent drinking is more often encountered in males than in females [115], in countries with higher income [115] as well as in lower income groups [116].

Ethanol consumption accounted for 5.3% of total deaths worldwide and for 5.1% of disability-adjusted life years (DALYs) in 2016 [115]. 21.3% of these deaths and 17.6% of these DALYs were attributed to digestive diseases, showing the long-term effect of ethanol intake on the gastrointestinal physiology, as explained in more depth by Patel et al. [117]. Briefly, different studies have shown an increase in the intestinal permeability due to acute intake of ethanol [118] as well as with chronic intake [119, 120] and up to two weeks after chronic intake [119]. Chronic intake of ethanol can alter the intestinal microbiota, especially increasing Proteobacteria and Firmicutes [121]. The type of ethanol intake also plays a significant role, as shown in a 20 day trial [122], where the increase in certain bacterial groups was attributed to the presence of polyphenols in red wine compared to gin. The chronic intake can also increase the bacterial growth in the small intestine, i.e., in the upper part of the GIT [123, 124]. Many of these bacteria are gram-negative, and possess lipopolysaccharides, which can cause inflammation and enhance the intestinal permeability [125]. This may not only affect drug uptake but has also been proposed to account for the alcohol-induced liver damage. The treatment with probiotics has shown to reduce this effect [126].

The results regarding the effect of ethanol on the gastric pH are contradictory, showing an increase at low (~5%) concentrations and no or inhibitory effects for high concentrations (40%). This may be caused by fermentation products present in low alcoholic beverages like beer or wine, but not present in distilled products [127]. A prolonged gastric residence time of meals is also described for ethanol [128], even though this may be mostly attributed to the higher caloric content of alcoholic beverages [129]. However, since the concomitant consumption of high concentrations of ethanol and food would lead to a dilution, the presence of highly concentrated ethanol at elevated pH in the stomach seems rather unlikely.

Ethanol can have different effects on the cardiovascular system. A few protective effects like a reduction in plasma glucose, endothelial protection or a reduction in platelet aggregation have been proposed. However, ethanol can also act as a direct toxin of the heart and the vascular system. By stimulating the renin-angiotensin-aldosterone-system, it can raise the blood pressure, further increasing the pressure on the cardiovascular system. An increase in cell apoptosis and a reduction in protein synthesis reduce the contractility of the heart and vascular system. This was believed to result in an overall J-shaped curve of the risk-drinking relationship [130]. However, the J-shape, sometimes also referred to as U-shape, was only visible in conventional observational studies. The use of genetic epidemiology showed no benefit of moderate ethanol consumption [131]. Ethanol dose not only affect the gastrointestinal and the cardiovascular system. Other effects include the fetal alcohol syndrome, an increased risk of cancer, diabetes and infectious diseases as well as unintentional and intentional injuries [115].

Another large problem associated with chronic intake of ethanol is addiction. There are different mechanisms underlying the addiction. In the beginning, patients encounter positive reinforcement, e.g., stimulation or pleasure due to the ethanol. This later turns to a negative reinforcement, where the patients aim to reduce any symptomatic of withdrawal. During this process termed allostasis, the neurotransmitters of the amygdala become dysregulated and cause changes in the reward and stress system [132]. Another mechanism is the incentive sensitization, where patients experience an increase in desire for ethanol, while the rewarding properties experienced during the consumption are either constant or decreasing [133]. However, distinguishing a high ethanol consume from an ethanol addiction is not simple, as different definitions of addiction exist, differentiating e.g., by different diagnostic criteria or special behavior [134].

1.3.1 Pharmacokinetics of ethanol

Ethanol is partially absorbed from the stomach following a zero order rate [135] with a constant value irrespective of ethanol concentration in the range of 1 to 6% of the consumed drink [135, 136], whereas the main absorption is via diffusion in the intestine [137]. However, this only holds for fasted absorption, as in the case of a meal ethanol is absorbed mainly from the stomach due to the longer gastric retention [138]. Without concomitant food intake, ethanol is emptied slower than water [135], but faster than an isocaloric glucose solution [139], indicating that the emptying

is more affected by the osmolarity than the caloric content. The absorption is reduced if the ethanol is cooled [140]. It remains unclear, to what extent and in what region ethanol is first-pass metabolized [141]. A multi-compartment model with a parallel Michaelis-Menten and first order elimination can be used to describe ethanol distribution [142]. Total-body-water-volume is considered to be the main physiological compartment [143] . Ethanol is eliminated mainly by metabolization [141] to acetaldehyde and later on to acetic acid [144]. There are however also other elimination routes like the lungs and the kidneys [145]. Ethanol also induces Cytochrome P450 2E1 (CYP2E1), which can affect both drug metabolism, as well as ethanol metabolization, increasing the risk for liver toxicity [146]. Feeding increases ethanolic metabolization compared to the fasted state [147]. Age affects the distribution of ethanol due to an altered body composition, but not the elimination [148].

1.3.2 Specific ethanol-drug interactions

There are different ways for ethanol to interact with drugs. In pharmacodynamic terms ethanol acts on gamma-amino-butyric acid (GABA) und glutamate dependent synapses [149], which are also the area of effect of many hypnotics like barbiturates, benzodiazepines or Z-drugs [150] leading to an (unwanted) synergistic effect. Alcohol can also increase the side effects of opioid therapy [150]. This is especially problematic, as patients having a methadone addiction also have a higher likelihood of alcohol addiction and a reduced efficacy in standard alcohol abstinence treatment [151]. One explanation may be a higher cerebral availability of unmetabolized methadone due to a modification of its metabolism by ethanol [152]. Pharmacokinetic interactions regarding the metabolism have also been described for paracetamol and ethanol [150]. This was attributed to the induction of CYP2E1, which can increase the creation of toxic metabolites of paracetamol and ultimately lead to liver failure [153].

The risk of concomitant ethanol and drug intake is especially high in elder people. In a 2005 study 77% of the study population aged above 65 used drugs, that have an interactive ethanol effect. Of these, 19% reported concomitant alcohol use, emphasizing the need for better patient information [154].

1.4 Effect of ethanol on release from oral dosage forms

The effects of ethanol on oral controlled release dosage forms have been investigated for nearly fifty years [155], but have gotten a lot more attention in the last two decades following reports of dose dumping from Palladone XL®. It was demonstrated, that upon administration of the 12-mg capsule of hydromorphone with 240 ml of 20% or 40% ethanol, the maximum plasma concentration (c_{max}) increased to values up to 6 or 16 times higher than without ethanol, respectively [156, 157]. Such an unintended, rapid release of the entire or a significant amount of the active substance in a modified release dosage form in-vivo is often referred to as Dose Dumping [158]. Palladone XL® was subsequently removed from the market [156], but this discovery brought about many more investigations on the effects of ethanol [129, 159-161]. Following up on this case, the Food and Drug Administration (FDA) as well as the European Medicines Agency (EMA) have issued guidelines to test for ethanol effects of controlled release dosage forms [158, 162]. For ethical reasons, this testing is mostly performed in-vitro, due to the risk of side effects [163]. However, if an in-vivo study is required, e.g., if the in-vitro experiments show an ethanol effect, the patients are given opioid antagonists at a carefully selected scheme to avoid any overdose complications [164].

The assessment of the effect of ethanol on pharmaceutical products has, in contrast to many other requirements, not been harmonized between the FDA and the EMA [162]. The FDA recommends in-vitro testing for the lowest and highest strength of a drug product employing the optimal apparatus and agitation rate in 0.1 N HCl and potentially an optimal dissolution medium. The dissolution media should contain 0, 5, 20 and 40% ethanol and the similarity factor (f_2) [165] should be employed for comparison of the release profile [166]. The EMA recommends testing at the same conditions as for routine testing, but with a justified range of alcohol added and gives 5%, 10% and 20% as an example [167].

There have been different approaches and goals in scientific testing in hydroethanolic media. The avoidance of drug extraction is often performed with highly concentrated ethanol over longer time period [22]. For the in-vitro release focus has been on prolonged exposure to ethanol [168] or a media exchange (i.e. a reduction in ethanol content), after 1 or 2 hours [169, 170]. The former concerns with prolonged drinking, whereas the later assumes a single drink. Some researchers claimed, that the regulatory requirements are too strict and not representative of the in-vivo

situation [1], while others propose that a two hour testing window may not be sufficient and a longer period should be considered [129].

The risk of accelerated release in ethanol may derive from the accidental intake of medicine with ethanol or the purposeful intake with larger amounts of ethanol. Wolf et al reported misunderstanding rates of five dosage instructions of marketed drug formulations in the range from 8 to 33% and these were patients, who were actively encouraged to read the prescription drug container labels [171]. Only about two third of patients report to read these kind of labels [172]. Even if ethanol consumption warnings are printed in colors onside the primary packaging material, there may still be questions left by the patient, e.g., if drinking at other times of the day is ok [173].

It is likely, that only a small subset of the population would consider the concomitant intake of drinks with high ethanol content and drugs. However, those at risk may suffer from addiction and are likely not dissuaded due to warning labels or contraindication, a point also mentioned by the FDA [158]. In such cases, to err on the side of caution may be preferable to the possibility of acute toxicity by dose dumping.

The mechanisms by which ethanol increases the drug release can be formulation dependent or formulation independent. Formulation independent are, e.g., the increase in drug solubility [169] or the increase in intestinal permeability [118]. Formulation dependent are the increase/decrease in excipient solubility as well as changes in swelling behavior [174]. In contrast, the use of multiparticulate systems is, supposedly, more susceptible to ethanol in the media [87], due to the reduced thickness of the coating.

Following the case of Palladone SR, many researchers investigated commercial products, where the focus was to determine the presence of dose dumping and not the underlying mechanism. A summary published by members of the FDA in 2010 showed that 9 of 10 capsules had accelerated release in 40% ethanol, while only 2 out of 17 tablets had accelerated release in 40% ethanol. No formulation had accelerated release in 5% ethanol. Of the investigated drug classes, opioid analgesics had the potentially highest accelerated release followed by antiarrhythmics and calcium channel blockers [175]. They did not further extend on excipients used in these formulations. Many companies published studies of their own product in hydroethanolic media like Alpharma Pharmaceuticals, who conducted an in-vivo study of Kadian®, a morphine sulphate extended-release capsule. They showed no accelerated release with concomitant ethanol intake

in-vivo [164]. Xanodyne pharmaceuticals was involved in an in-vitro release of their morphine sulphate tablets Oramorph® SR, which showed no sign of accelerated release [176].
Different modified release dosage forms have been evaluated for their susceptibility to ethanol in the release medium. These include matrix tablets [168, 169, 177], enteric dosage forms [178], extended-release coated systems [170], microcapsules [155, 179] and coated dosage forms for colonic targeting [180]. In most cases, ethanol effects seen in-vitro can also be observed in-vivo [181] but this effect can be more pronounced [157] or less pronounced [174].
There are also some issues of hydroethanolic media regarding immediate release dosage forms. Bisharat et al showed a reduced swelling of the super disintegrants sodium starch glycolate, croscarmellose sodium and crospovidone in the presence of 40% ethanol, but not in 10% ethanol. They showed an 8 times higher disintegration time for theophylline tablets in 40% ethanol [182].

1.4.1 Matrix systems in hydroethanolic media

Solubility, wettability, swellability, and mechanical properties have been identified as the key components of matrix tablets affected by hydroethanolic media. The addition of ethanol to water reduces the dielectric constant, leading to an increase in lipophilicity of the solvent mixture. This can lead to an increase in drug or polymer solubility, especially if the drug or polymer is lipophilic [29]. However, this reduction in the dielectric constant can also reduce the solubility of excipients. The solubility of sucrose decreases with increasing ethanol content [183]. Wettability, swellability and mechanical properties have only been investigated for specific excipients and will be discussed individually for the excipients where they were investigated.

The results on HPMC tablets in hydroethanolic media are non-conclusive. Tablets of acetylsalicylic acid and HPMC K4M showed an increase in release linked directly to the increase in solubility of acetylsalicylic acid and a possible higher amount released via diffusion [168], whereas another study found similar release behavior of tablets of various drugs and HPMC grades with different fillers [169]. The weight gain of pure HPMC tablets in 0 and 40% ethanol was similar [169]. However, in another study pure HPMC tablets swelled more in aqueous medium than in 40% ethanol [168]. The gel strength of HPMC tablets is increased in hydroethanolic media [184], as is the viscosity of HPMC in water-ethanol mixtures [185]. Interestingly HPMC solutions show a cloud

point in aqueous medium, but not in 40% ethanol, which was explained as a solvation effect due to a stronger interaction between ethanol and HPMC compared to water and HPMC [168].

Different fillers have been evaluated for their effect in hydroethanolic media. The inclusion of soluble lactose into HPMC tablets was supposedly associated with a faster release of different drugs in 40% ethanol compared to the insoluble MCC [177]. The authors explained this with a higher porosity due to the dissolution of lactose. In contrast, the inclusion of maltitol led to a slower release of theophylline in 40% ethanol due to a lower solubility of the maltitol in 40% ethanol [186].

Other hydrophilic polymers have been investigated with different drugs in different proportions. PEO, employed as a matrix polymer for gliclazide and metformin with MCC, showed no accelerated release in 5% or 40% ethanol [187]. Carbopol® was evaluated for the release of different model drugs in hydroethanolic media. The authors concluded that dose dumping from these tablets is unlikely, but the release mechanism and rate can be strongly affected, depending on the drug type. The ethanol affected both drug solubility and the swelling and erosion of the polymer. In buffered media, the addition of ethanol reduced polymer swelling and erosion of Carbopol® [28].

3D prints of tramadol with hydroxypropyl cellulose prepared by direct powder extrusion showed no accelerated release in hydroethanolic media [22]. Xanthan gum has been evaluated as a matrix former for theophylline at 30% and 60% polymer amount with different particle- and dosage form sizes. Large polymer particles and a low polymer amount were associated with more accelerated release in 40% ethanol. The accelerated release is more pronounced for mini tablets compared to normal tablets due to the shorter diffusion pathway [23]. All these factors may be influenced by wettability and swelling behavior. Less accelerated release in hydroethanolic media has been stated if the drug is presented in an extrudate instead of only being compressed [17, 188]. In these cases, the wettability is reduced, as the drug is mostly covered by the polymer.

Insoluble matrix formers are less frequently used for modified release matrix tablets. Different tablets of tramadol with Kollidon® SR did not show accelerated release, but a reduced release in 40% ethanol [189-191]. Kollidon® SR is also included in Locktab®, a mechanically strong formulation by Ethypharm, where the good compressibility of Kollidon® SR is used to produce tablets with a high crush resistance of up to 467 N [192].

Compritol® 888 ATO was used in tablets in comparison to and in combination with HPMC with tramadol and pentoxifylline by Lochař et al. [193]. Compritol® prevented accelerated release for tramadol, but not for pentoxifylline. Combinations of HPMC and Compritol® showed accelerated release in 40% ethanol for tramadol, but not for pentoxifylline. They attributed this difference to the ionizing behavior of tramadol and an increased wettability of Compritol® in the presence of ethanol. Keen et al evaluated the effect of twin screw and melt-mixing granulation of tramadol and Compritol® 888 on the release of tramadol. Neither formulation showed any accelerated release in 40% ethanol [194].
Jedinger et al showed pellets prepared from lipids showed a strong dependency on the solubility ratio, with ethanol independent release behavior for codeine phosphate and accelerated release for paracetamol. The wettability of Compritol® and Precirol® was, however, affected by the addition of ethanol [41]. The inclusion of titanium dioxide into extruded calcium stearate pellets resulted in less accelerated release in the presence of ethanol compared to the inclusion of xanthan gum or guar gum. This was due to the blocking of pores by the insoluble titanium dioxide [42].

The focus on resistance to accelerated release in hydroethanolic media is often combined with abuse-resistant dosage forms. Abuse-resistant dosage forms incorporate a physical barrier to reduce the release through physical or chemical interaction with the dosage form [195]. These are most often matrix system, as these are less susceptible to different forms of abuse like grinding or solvent extraction. For example DETERx® is an abuse-resistant technology based on microspheres containing fatty acids and waxes [196]. The Intac® technology employs hot melt extrusion of high molecular weight PEO to get a hard matrix that gels in contact with fluids. The SECUREL® technology combines HPMC with fumed silica and a thermo-softening material, e.g. fractionated coconut oil, to avoid drug extraction [192]. The Guardian® technology issued by Egalet utilizes injection molding of PEO with morphine sulphate at high temperature and pressure [197]. It was robust to vaporization, aqueous extraction and grinding and did not show accelerated release in the presence of ethanol [198]. However, many of these abuse-resistant formulations rely on similar technologies and most employ PEO as polymer, which can pose a problem, if methods of abuse are shared [197].

These systems are often employed for the use of opioid-drugs, but a risk of misuse is also given for other drugs, e.g., stimulants [199].

1.4.2 Coated systems in hydroethanolic media

The performance of film coated systems in hydroethanolic media depends among others on the amount of coating applied to the dosage form [200], the process conditions [200, 201], the type of pore-forming [24, 202] or the use of pore-blocking excipients [42].

Much research about the effect of hydroethanolic media on film coated systems has been performed with commercial products [180, 203]. Many film coatings show susceptibility to ethanol like ethylcellulose [157, 189, 200], some polyacrylates [178, 180], hydroxypropyl methylcellulose acetate succinate (HPMCAS) and hydroxypropyl methylcellulose phthalate (HPMCP) [178].

Aquacoat ARC® has been developed to avoid ethanol susceptibility and is an aqueous suspension of ethylcellulose and dissolved guar gum. The composition of 93% ethylcellulose and 7% guar gum proved to be the most useful, as the release is too fast at higher guar gum amounts and is accelerated in hydroethanolic media at lower guar gum amounts [200]. It has been tested with theophylline and shown to reduce ethanol-induced accelerated release even for highly soluble drugs like codeine phosphate [17, 69, 170, 200]. The guar gum, which is soluble in water, is insoluble in ethanol, compensating for the solubility of ethylcellulose in ethanol. Other modifications of ethylcellulose coatings to avoid ethanol susceptibility, like the addition of aliphatic alcohols, have also been patented [204].

Burger et al investigated the release of oxycodone from a compressed tablet of EC-coated sugar pellets and an Eudragit® RS matrix tablet in-vivo with concomitant ethanol intake. 240 ml of 20% ethanol had no effect, whereas 40% ethanol led to a slight increase in absorption, but not in c_{max}, for the pellets, and an increase in c_{max} and area-under-the-curve (AUC) for Eudragit® RS. However, no formulation showed dose dumping [205].

Not all coatings are designed for extended release. Immediate release coatings can be applied to a matrix system and still affect the drug release. ReadiLYCOAT® is a coating suspension containing hydroxypropyl starch extracted from peas as polymer. It showed more resistance to the influence of ethanol than Opadry® II, a polymer system comprising PVA and HPMC [206]. The authors of

the study concluded that higher amounts of matrix polymers were necessary when using Opadry® II to obtain similar release.

3D printed coatings of HPMC, derived from Affinisol®, and a commercial polyvinyl alcohol formulation were used to coat different matrix tablets consisting of Kollidon® SR, Compritol® and tramadol [191]. The Affinisol-derived coating could change the underlying release mechanism and even introduce a lag time before the begin of the dissolution. It was claimed to be beneficial to avoid alcohol-induced accelerated release.

Only very little work has been published on the performance of OROS and enteric dosage forms in hydroethanolic media.

The OROS system has only been evaluated in-vivo, where it was robust to concomitant alcohol intake [159]. The OROS system is also considered to be abuse-resistant due to its resistance to crushing or extraction [192].

Enteric polymers were evaluated both in products for colon-targeting and for release in the intestine. pH-dependent Eudragit® L coated pellets used in commercial products of mesalazine for colon-targeting showed accelerated release after 2 h in hydroethanolic media, whereas those employing Eudragit® S did not [180]. A more in-depth evaluation was performed on paracetamol tablets coated with HPMCP, HPMCAS, Eudragit® L and polyvinyl acetate phthalate. The polymers differed in their release rate and their media uptake, but all polymers failed enteric-resistance in the presence of ethanol and showed an increase in media uptake. SEM-pictures of the pellet surface showed pores, which were claimed responsible for the accelerated release. The effect of ethanol was even more pronounced, if a pH 4.5 buffer was used instead of the 0.1 N HCl [178].

Different patents have been issued on enteric dosage forms that resist the influence of ethanol. The use of cellulose acetate phthalate has been proposed to reduce ethanol susceptibility when used as a top coating [207]. A top coating of Eudragit® NE and Eudragit® E on an enteric layer showed less than 10% release after 120 minutes in 40% ethanol [208]. The drawback to these top coating methods is the slow release in phosphate buffer. The combination of an alginic acid salt and shellac coated onto tablets showed enteric-resistance at pH 1.2. However, release already started above a pH of 4.5 [209].

Some patents have combined enteric polymers like Eudragit® L or Eudragit® FS with extended-release polymers like Eudragit® NE [210]. These approaches, however, suffer the same drawbacks

as the top coating in that they are suitable for extended-release, but not for rapid release in the intestine.

1.5 Bioequivalence

One parameter to assess the similarity between two dosage forms and to decide, whether one may be exchanged for the other, is bioequivalence. Bioequivalence is defined by the FDA in that "*the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses*...." [1]. This concerns foremost the AUC of the drug concentration in the blood plasma vs. time and the c_{max}. However, for modified release products other parameters like partial-AUCs may be necessary to appropriately represent the originator product [1].

The requirement of bioequivalence can be encountered both in originator products, e.g. if a clinical trial has used a different formulation than is later going to be marketed [211], as well as in generic drug formulations as a prerequisite for approval. Bioequivalence has to be proven in comparison to the originator product, but may differ between two generic products deriving from the same originator product [212]. Different guidelines for the establishment of bioequivalence have been issued, focusing e.g. on the individual bioequivalence instead of the average of the population [213]. For drugs with a narrow therapeutic index the criteria of the bioequivalence, i.e. the range of the AUC and c_{max}, are stricter [214].

As the intention of bioequivalence is to ensure similar release profiles, bioequivalence studies with co-administration of food are generally required by regulatory authorities [215]. Similarly, the requirements for testing in hydroethanolic media also apply to generic products. While the absence of an ethanol effect is still the foremost desired outcome, an alcohol effect may be acceptable, if the originator product also has an alcohol effect [166]. In some cases, an in-vivo study on the effects of concomitant ethanol intake may be reasonable [1].

1.6 Statistical methods

1.6.1 Statistical comparison of release profiles

Release profiles of different dosage forms or in different media can be evaluated using model dependent approaches or using model independent approaches [33]. Model dependent approaches fit a perceived underlying release mechanism to the dissolution curve. In the beginning most of these models were analytical in nature, fixing a fitted value for the complete release, but further insight into release behavior has caused a need for numerical solutions to account for the change of coefficients, i.e. the permeability due to swelling, during the release [30, 216]. Examples to these models have been discussed (Chapter 1.1, P. 1). For a linear model, like the Peppas-Sahlin equation, described by the addition of individual terms, ordinary least squares (OLS) is often the preferred method of fitting. OLS, as described by the Gauss-Markov-theorem, is the best linear unbiased estimator, if the requirements are met [217]. These include absence of multicollinearity of the predictors, homoscedasticity, and independence of error from the model [218].

Model independent approaches like the similarity (f_2) and the difference factor (f_1) proposed by Moore et al. [165] are widely used and requested by the FDA for immediate release generic medicines [219] as well as in-vitro alcohol dose dumping studies [166]. Different research groups have also employed the f_2 due to its ease of interpretation for controlled release formulations [41, 190]. The f_2-factor, however, poses some drawbacks for statistical analysis, as the logarithmic calculus changes the underlying sample distribution, rendering it impossible to calculate the variance correctly [220]. Another issue may be the independence of direction, as an f_2-value only proves the presence of a difference, but not whether the test or reference formulation has an accelerated release.

The mean dissolution time (MDT) can be used to calculate a ratio between two or more dissolution curves. In contrast to using the AUC-ratio it does not change if additional data points at 100% are taken. The MDT is a standardized measure of the timepoint, at which 50% of the drug is released (D50). This may deviate from the experimental D50 value as the MDT is affected by the shape of the curve. The points at which specific amounts of drug are released, e.g. the D50 or the D80, can also be compared directly [33].

1.6.2 Handling of missing data

Missing data is frequently encountered in research [221]. It can be characterized as missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR). MCAR refers to data which are missing by chance, i.e., the reason that the datapoint is missing is not related to the inherent value of the data point nor to the variable it represents. E.g., if data is lost due to a power shortage, not deriving from the experimental set-up itself, it can be considered MCAR. MAR refers to data points that are missing due to the variable they represent, but not due to their inherent value, after correcting for other factors in the model [222]. This can happen e.g., if some researchers do not report a specific measurement, e.g., a tablet size, while other researchers do. MNAR refers to data points missing due to their inherent value. This means e.g., that a researcher will not report the hardness of a tablet, because it is outside of the measurement range of his equipment. Both MCAR and MAR data can be used for analysis, whereas MNAR data will falsify the results and should be treated with care [223].

The different approaches to address missing data in regression analysis include line- or pairwise deletion, mean substitution, multiple imputation (MI) and full-information maximum likelihood estimation (FIML) [222]. Line- and pairwise deletion remove data, which decreases the power and can lead to biased estimates, especially for MAR-data. They should only be applied to MCAR data. Mean substitution will not reduce data but reduce the variability and thus falsely increase the significance of the data calculation. It is generally not recommended [223]. MI and FIML are therefore the preferable approaches to handle missing data [224]. MI refers to creating multiple datasets, where the missing data is filled (imputed) by different methods, e.g. by a chain of mathematical equations [225]. Each dataset is then analyzed and the results combined according to Rubin's rules [226]. MI may pose problems if the analysis model and the imputation model differ, i.e. if variables are included in the analysis model, that are not included in the imputation model [227]. Recently, MIDAS, a MI-model based on deep learning, has been developed for programming languages [228]. MIDAS uses denoising autoencoders, a type of unsupervised neural network to corrupt datasets and reconstruct them using nested non-linear transformations. The advantages of MIDAS are an increased accuracy over other approaches to MI as well as a higher computation rate.

Multiple imputation is a common procedure in clinical trials [229] and medicine [230]. It is seldomly found in in-vitro analysis. To et al. used multiple imputation for chemical prioritization applications with up to 80% of data missing for certain chemicals. They concluded that MI, is preferable to ignoring missing data. They, however, referred to mean substitution also as a method of multiple imputation [231].

FIML is built upon maximum likelihood estimation, which estimates parameters of a distribution of predictor and outcome variables so that these maximize the likelihood of the values observed [232]. FIML extends this principle to the missing data. FIML is easier to implement and does not require additional steps to interpret the results, but it has drawbacks regarding its accessibility and potential assumption of multivariate normality [227]. FIML has proven to be more powerful than deletion methods regardless of the type and amount of missing data [233].

Both of these methods, MI and FIML, can produce similar results if the underlying model is correctly specified, but differ in their results if misspecification is present [234]. No method is generally superior to the other.

1.6.3 Multiple linear regression

Multiple linear regression (MLR) is a method to establish a relationship between a set of independent predictor variables and a dependent outcome variable [235]. A linear regression model with p independent variables and n observation in this sense refers an equation of the type:

$$\mathbf{y} = \boldsymbol{XB} + \boldsymbol{\varepsilon} \qquad \text{equation 2}$$

where *y* is a n*1 vector of the dependent variable, *X* is a n * (p + 1) matrix of values of the independent variable, which comprises an n*1 vector of ones to include the regression constant, the intercept in simple linear regression. B is a 1* p vector of the partial regression coefficients and ε is a n*1 vector of errors [236].

The multiple linear regression is an extension of the simple linear model and thus also requires homoscedasticity of the residual errors and the absence of correlation of errors [237]. It does not require a linear relationship between y and x but a linearity in the parameters b_n [238], meaning, that the parameters are added in a linear fashion opposed to e.g. an exponential way.

Homoscedasticity is necessary to ensure the accuracy of standard errors, even though the estimated parameters themselves remain unbiased [239]. It can be assessed using e.g. the Breusch-Pagan test [240] for normally distributed errors or the white test [241], if the errors are distributed non-normal.

MLR does not require normality in the residual errors to produce the best linear unbiased results, but to calculate unbiased standard errors and therefore p-values and confidence intervals [242, 243]. The residual errors should not indicate a clear trend, as this would imply a non-linear relationship between the predictors and the outcome.

An appropriate choice of predictors should ideally be performed a priori to the regression analyses. The commonly used method of forward, backward, or stepwise regression uses latent degrees of freedom and introduces overfitting. This will create a regression that fits very well to the observed data, but cannot be extrapolated to other applications [244]. To avoid overfitting, some authors have introduced guidelines on the subject-per-variable ratio. Austin and Steyerberg used Monte-Carlo simulation to propose a two-subject-per-variable-ratio in linear regression analyses [245]. However, their work was later criticized as being too general and a more specific approach, depending on the type of study was suggested [246].

Care also must be taken when performing sub-group analysis in methods like MLR, as there is a risk of both under- as well as overestimating the significance of subgroups. Instead, sub-group analysis should only be performed if proposed in advance and carefully justified [247].

The goodness of fit of an MLR model can be quantified using e.g., the coefficient of determination, R^2. The R^2 describes how much of the variability of the data can be explained by the predictor variables. An R^2 of 1 would imply that all variability can be explained by the model [248].

MLR has been performed in the field of pharmaceutical technology on very specific research questions. Lambert & Janjic used MLR to estimate the droplet size of perfluorocarbon nano emulsions. They identified oil, oil blend type and amount as the key components to calculate droplet size ($R^2 > 0.91$) [249]. Mercuri et al analyzed the in-vitro release from nifedipine capsules using MLR to establish an in-vitro-in-vivo correlation (IVIVC). Volume, stirring rate and ethanol content were relevant to establishing an IVIVC and the use of water or orange juice without additional ethanol did not reflect the in-vivo conditions ($R^2 > 0.95$) [250]. Pund et al. used MLR in

the preparation of site-specific release of isoniazid from pellets coated with Aquacoat® ECD. They assessed the effect of amount of granulating fluid, amount of binder and spheronization rate as well as their interactions on multiple outcome variables like the usable yield, the porosity or the moisture content ($R^2 > 0.99$) [251].

1.7 Objectives

- Identification of parameters in the composition and formulation of pharmaceutical products that affect their behavior in hydroethanolic media in comparison to aqueous media according to previous publications using multiple linear regression
- Assessment of the effect of aqueous and hydroethanolic media on commercially available generic oral modified release products
- Investigation of the effect of formulation parameters on the release in aqueous and hydroethanolic media of different drugs from matrix tablets and identification of approaches to avoid accelerated release
- Investigation of the effect of formulation parameters on the release in aqueous and hydroethanolic media of different drugs from pellets coated with enteric polymers and identification of approaches to avoid accelerated release
- Investigation of the effect of formulation parameters on the release in aqueous and hydroethanolic media of different drugs from pellets coated with extended-release polymers and identification of approaches to avoid accelerated release

2 Materials and Methods

2.1 Materials

2.1.1. Drugs

Carbamazepine, metoprolol tartrate, paracetamol, theophylline (BASF SE, Ludwigshafen, Germany), propranolol-HCl (IPCA Laboratories Limited, Mumbai, India)

2.1.2. Polymers

Ethylcellulose (Ethocel® 10 FP, Ethocel® 10), hydroxypropyl methylcellulose (HPMC, Methocel® E5, K100LV CR, K4M CR, K100M CR, Colorcon Ltd., Dartford, UK), guar gum (polygal ag, Märstetten, Switzerland), hydroxypropyl methylcellulose-phthalate (HPMCP, HP-55®, Shin-Etsu chemical, Tokyo, Japan), hydroxypropyl cellulose (HPC, Klucel® MXF, Ashland Inc, Wilmington, USA), polyethylenoxide (PEO, Sentry Polyox® WSR 303 LEO NF Grade, Dow, Inc., Connecticut, USA), poly(ethylacrylate-methyl-methacrylate-trimethylammoniuoethylmethacrylate chloride) [1:2:0.1] (Eudragit® RS), methacrylic acid-methyl-methacrylate-copolymer [1:1] (Eudragit® L, Röhm GmbH, Darmstadt, Germany), polyvinyl pyrrolidone (PVP, Kollidon® 30), polyvinyl acetate (PVAc) with PVP (Kollidon® SR), aqueous dispersion of polyvinyl acetate with polyvinyl pyrrolidone (Kollicoat® SR 30D, BASF SE, Ludwigshafen, Germany), polyvinylacetate phthalate (PVAP, Sureteric®, Colorcon Ltd., Dartford, UK),

2.1.3. Pellet cores

Microcrystalline cellulose cores 600-800 µm (MCC, Celphere® 507, Asahi Kasai Chemical, Tokyo, Japan), 1000-1400 µm (Cellets®, Harke Pharma GmbH, Mülheim an der Ruhr, Germany), sugar spheres (Suglets® 710–850 µm, NP Pharma, Bazainville, France), theophylline matrix cores (Fujisawa Deutschland GmbH, München, Germany).

2.1.4. Other excipients

Lactose (Flowlac 100, Meggle GmbH & Co. KG, Wasserburg am Inn, Germany), magnesium-stearate (Baerlocher GmbH, Unterschleissheim, Germany), microcrystalline cellulose (MCC

(Avicel PH 102, FMC Corp., Philadelphia, PA, USA), silicium dioxide (Aerosil® 200, Evonik Industries AG, Hanau, Germany), talc (Imerys Talc, Luzenac France, Luzenac, France), triethyl citrate (Citrofol A, Jungbunzlauer Ladenburg GmbH, Ladenburg, Germany), HCl, ethanol (99.8%)(Carl Roth GmbH + Co. KG, Karlsruhe, Germany), isopropanol (IPA, VWR International LLC, Radnor, PA, USA).

2.1.5. Commercial products

All commercial products used in this thesis were marketed in Germany (Table 1).

Table 1 Overview of commercial products

Commercial product	Dose [mg]	Batch-Nr.	Drug	Supplier
Cymbalta®	30	D185967	Duloxetine HCl	Eli Lilly and Company
Duloxetine 1A Pharma®	30	KX1329	Duloxetine HCl	1 A Pharma GmbH
Duloxetine Beta	30	210549	Duloxetine HCl	Betapharm GmbH
Duloxetine Aurobindo	30	QJ3020007-B	Duloxetine HCl	Aurobindo Pharma Limited
Cardular® PP	4	CY4687	Doxazosin mesylate	Viatris Pharma GmbH
Doxazosin AL	4	93401	Doxazosin mesylate	Aliud Pharma GmbH

2.2 Methods

2.2.1 Solubility

An excess of drug was added to 0.1 N HCl containing 0, 20 or 40% (v/v) of ethanol and exposed to a horizontal shaker (80 rpm, 37 °C, n=3, innova 4230 Refrigerated Incubator Shaker, New Brunswick Scientific, New Jersey, USA). After 48 hours samples were withdrawn, centrifugated (VWR Mega Star 1.6 / 1.6R, VWR International bvba, Leuven, Belgium) and, were measured via UV-spectrophotometer (UV HP 8453, Agilent Technologies Deutschland GmbH, Waldbronn, Germany) at 222, 319, 244, 235 and 255 nm for metoprolol tartrate, propranolol HCl, paracetamol, theophylline, and carbamazepine, respectively.

The solubility of lactose was determined at room temperature by addition of 1 g lactose to 3.5 ml of the agitated medium (n=3). After 30 min intervals, additional medium was added, until the lactose had dissolved completely.

In cases, where the solubility was not measured, it was calculated either with own data (for 20% ethanol, if the solubility in 40% ethanol was measured), or using literature data (if indicated) according to equation 3 [252]:

$$S_{mix} = S_{Aqua}\, 10^{(1.32+0.933\, logD)f + [\frac{(-2.28+0.287\, logD)f}{(1+10^{3.6(f-1)})}} \qquad \text{equation 3}$$

Where S_{mix} is the solubility of the drug in an ethanol-water mixture with an ethanol fraction of f, in range 0 to 1. S_{Aqua} is the solubility in aqueous medium and log D the partition coefficient between octanol and water.

2.2.2 Partition coefficient

Ethylcellulose films were casted from isopropanol-water mixtures (88:12 w/w, polymer content = 6%) onto a Teflon plate. After drying at 60 °C for 12 h, square films samples of 3 cm were carefully cut and weighed into a screw cap glass. After addition of 10 ml of drug solution (1 mg/ml) of the different media, the films were exposed to a horizontal shaker (n=3, 80 rpm, 37°C). At predetermined time points, samples of the aqueous content were withdrawn and measured UV-spectrophotometrically. When the concentration plateaued, film samples were taken out, dried, weighed (to determine the medium uptake), and dissolved in pure ethanol for UV-analysis.

2.2.3 Preparation of tablets

Tablets consisting of 49.5% drug, 49.5% polymer and 1% Mg-Stearate were blended in a Turbula mixer (Willy A. Bachofen AG, Basel, Switzerland) for 10 minutes and then manually compressed on a Korsch EK-0 (Korsch AG, Berlin, Germany, 7 mm round stamp) at a compression force of 25±2 kN (MGCplus, catman, HBM, Darmstadt, Germany).

Deviating, tablets with fillers consisted of either

- 30% drug, 35% polymer, 33% lactose, 1% Mg-stearate and 1% Aerosil®
- 49.5% drug, 24.5% HPMC, 24.5% filler and 1% Mg-stearate or
- 24.5% paracetamol, 49.5% HPMC, 24.5% filler and 1% Mg-stearate or
- 10% carbamazepine, 35% Kollidon® SR, 53% lactose, 1% Mg-stearate and 1% Aerosil®

Colored tablets consisted of 48.5% drug, 48.5% polymer, 2% Patent Blue V and 1% Mg-stearate or 24.5% drug, 24.5% lactose, 48.5% polymer, 2% Patent Blue V and 1% Mg-stearate and drug-free matrix compacts for swelling consisted of 99% polymer and 1% Mg-stearate or 49.5% HPMC K4M, 49.5% lactose and 1% Mg-stearate and were compressed with a 10 mm round stamp.

2.2.4 Preparation of pellets

2.2.4.1 Layering

Theophylline, propranolol-HCl and metoprolol tartrate were layered onto different cores employing HPMC (Methocel E5, 20% based on drug) as a binder. Theophylline (as milled suspension, Dyno-Mill Typ KDL A, Willy A. Bachofen AG, Basel, Switzerland) and metoprolol tartrate (as solution) were sprayed from an aqueous mixture, propranolol-HCl from an isopropanol/water (80:20 w/w%) solution. Layering was performed either in a Glatt GPCG-1 (Glatt GmbH, Binzen, Germany) or in a MiniGlatt (Glatt GmbH, Binzen, Germany) fluidized bed coater. The layering conditions are given in Table 2:

Table 2 Layering conditions

Drug	Propranolol	Propranolol	Theophylline	Theophylline	Metoprolol
Core	Celphere® 507	Cellet®	Celphere® 507	Suglet®	Celphere® 507
Coater	GPCG 1.1	MiniGlatt	GPCG 1.1	GPCG 1.1	MiniGlatt
Batch size [g]	900	60	900	900	60
Inlet temperature [°C]	51	34	48	48	54
product temperature [°C]	39±1	27±1	30±2	30±2	33±2
Nozzle diameter [mm]	1.2	0.8	1.2	1.2	0.8
Spray rate [g/min]	8.9	0.7	9	9	0.8
Spray pressure [bar]	1.2	0.8	1.2	1.2	1

2.2.4.2 Coating

The coating of the pellets was performed in a fluidized bed coater (MiniGlatt, Glatt GmbH, Binzen, Germany). The coating conditions varied depending on the polymer (Table 3):

Table 3 Coating conditions

Polymer	Eudragit® L	HP-55	Ethyl-cellulose 10 Std.	Sureteric®	Methocel® E5	Eudragit® RS	Kollicoat® SR
Dispersion medium [w/w%]	IPA/ Water 90:10	IPA/ Water 80:20	IPA/ Water 88:12	Water	Water	IPA/ Water 90:10	Water
Plasticizer [w/w% of polymer]	10	6.66	-	-	-	10	10
Talc [w/w% of polymer]	50	43	-	-	-	50	50
Solid contents [w/w %]	12.59	9.1	6.22	10	5	12.6	8
Inlet temperature [°C]	38	34	42	41	50	34	40
Product temperature [°C]	31±3	27±2	31±1	33±1	37±1	29.5	27
Nozzle diameter [mm]	1.2	1.2	1.2	1.2	1.2	0.8	0.8
Spray rate [g/min]	0.7	0.8	0.7	1	0.8	0.8	0.7
Spray pressure [bar]	1	0.8	1	1	0.8	0.75	0.9

2.2.5 Size of tablets

Tablets were characterized with regards to their size using a hardness tester (n=5, Manual Tablet Hardness Tester, MT50, Sotax, Lörrach, Germany) and a caliper.

2.2.6 Release testing

Release testing for tablets and pellets was conducted in 0.1 N HCl containing 0, 20 or 40% (v/v) of ethanol or in phosphate buffer (PBS) 6.8 using a USP II paddle apparatus (500 or 900 ml, 75 rpm, or, if specified, at 10 or 150 rpm. 37°C, n=2-3, VK 7010, Vankel Industries, Edison, NJ, USA) For release testing employing a media change method, pellets were placed in 750 ml of 0.1 N HCl in a USP I basket apparatus at 37°C. After 120 minutes, 250 ml of prewarmed 0.2 M Na_3PO_4 were added to to the release medium to mimic the transition into the intestinal pH. For hyperosmolar medium, NaCl was dissolved in the release medium prior to release testing. Samples were measured on-line via UV-spectroscopy (Cary 50 Tablet, Varian Optical Spectroscopy Instruments, Mulgrave, Victoria, Australia) at 222, 319(270), 244, 235(270), 255, 246 and 290 nm for metoprolol tartrate, propranolol HCl, paracetamol, theophylline, carbamazepine, doxazosin mesylate and duloxetine HCl, respectively. Additional release set-ups were used to assess specific aspects of the release (Fig. 4). Release of paracetamol was evaluated from matrix tablets in a diffusion cell, with a specified surface area. Diffusion through tablet was employed to measure the diffusion rate of dissolved paracetamol through drug free tablets of HPMC K4M or HPMC K4M/lactose. Diffusion through film was measured with theophylline in 0.1 N HCl containing 0, 20 or 40% (v/v) of ethanol.

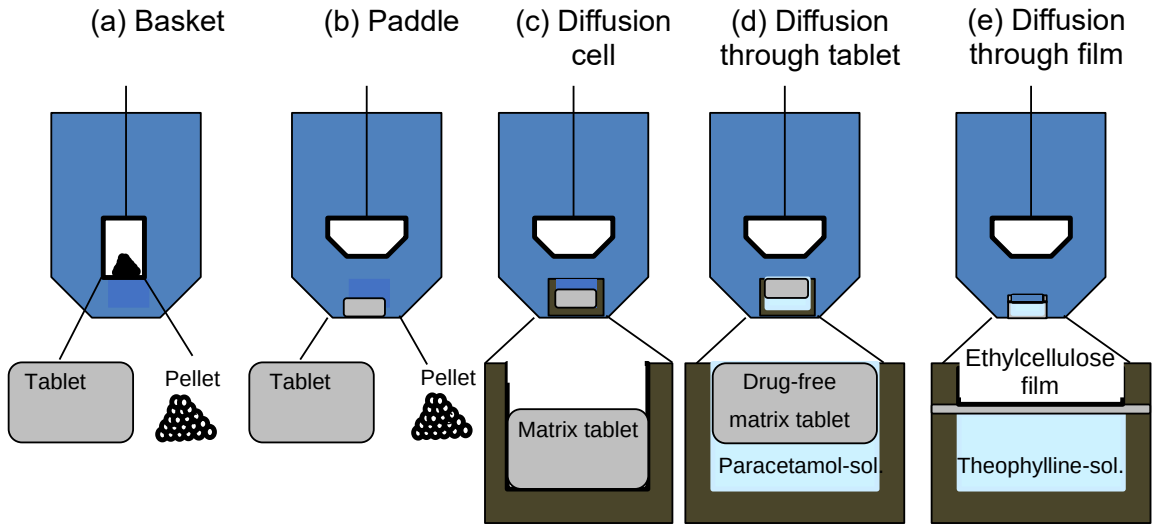

Fig. 4 Schematic overview of different dissolution set-ups

2.2.7 Medium uptake & dry weight loss

Medium uptake studies were conducted in a USP-I-basket method (VK 7010, Vankel Industries, Edison, NJ, USA) in 0.1 N HCl containing 0, 20 or 40% (v/v) of ethanol (75 rpm, 37°C, 900 ml, n=2). Samples were taken at predetermined time points, weighed (m_{wet}), dried overnight in a drying oven (105°C) and weighed again (m_{dry}). Medium uptake was determined as $\frac{m_{wet} - m_{dry}}{m_{dry}}$, dry weight loss as $\frac{m_{initial} - m_{dry}}{m_{initial}}$.

2.2.8 Solvent content

Ethanol and isopropanol content was determined like the media uptake studies on HPMCP- and EC-coated pellets of Propranolol-HCl. Samples were taken at predetermined time points and analyzed using headspace gas chromatography (GC-2014, Shimadzu Corporation, Kyoto, Japan) comprising a flame-ionization detector (FID-2014), a split injector and a moderately polar fused silica capillary column (3 µm x 30 m Rtx-1301 w/Integra-Guard, Restek, Bellefonte, USA). Nitrogen was chosen as carrier gas at a flow rate of 32.3 ml/min. Samples were dissolved in 5 ml of DMSO

and heated for 45 min at 110 °C prior to injection. 1 ml of the gas phase was injected with a split of 1:10. Ethanol was detected at 40 °C at a retention time of 3.9 min, isopropanol at 4.8 min.

2.2.9 Mechanical properties

2.2.9.1 Puncture strength and elongation of polymeric films

Ethylcellulose films were casted onto a Teflon plate (IPA: H_2O: 88:12 w/w, polymer content = 6%). After drying at 60°C for 12 h, square film samples of 3 cm were carefully cut. Thickness was measured via a Minitest 600 (Erichsen GmbH & Co. KG, Hemer, Germany). Film samples were measured dry or after 2 hours of immersion into 0.1 N HCl containing 0, 20 or 40% ethanol (v/v) (Incubation shaker, 37°C, 80 rpm, n=3). After dabbing the fluid with a paper cloth, the films were punctured using a texture analyzer (TA.XTplus, Stable Micro Systems Ltd., UK) (5 mm probe, 5 kg loading weight) in a set-up similarly to those previously described [253]. In brief, the films were fixed on a holder with an orifice (r = 0.4 cm), and the probe penetrated through the film in the middle of the orifice at a rate of 6 mm/min. The puncture strength was calculated according to equation 4:

$$\boldsymbol{puncture\ strength} = \frac{\boldsymbol{F}}{\boldsymbol{A_c s}} \qquad \text{equation 4}$$

Where F is the force at puncture and $A_c s$ is the cross-sectional area located inside the hole of the film holder. The elongation was calculated according to equation 5:

$$\boldsymbol{elongation}\ \% = \frac{\sqrt{(\boldsymbol{r^2} + \boldsymbol{D^2})} - \boldsymbol{r}}{\boldsymbol{r}} * \boldsymbol{100} \qquad \text{equation 5}$$

Where r is the radius of the exposed film in the hole of the film holder and D is the displacement of the probe at the point of film puncture.

2.2.9.2 Gel strength of polymer tablets

HPMC matrix compacts were immersed inside a diffusion cell into 0.1 N HCl containing 0 or 40% (v/v) of ethanol inside a glass-bowl equipped with a propeller stirrer (100 rpm, 1 cm above

diffusion cell). The set-up deviated from the USP-paddle method to increase the hydrodynamic stress applied to the tablet and as the diffusion cell was necessary to allow complete tablet transfer and avoid tablet movement during the measurement. Gel strength was measured using a texture analyzer (TA.XTplus, Stable Micro Systems Ltd., UK, equipped with a 2 mm flat, cylindrical probe).

The gel strength was calculated according to equation 6 [104, 254]:

$$\boldsymbol{G = \frac{F}{x} * \frac{F1}{r_p} * 0.0098} \qquad \text{equation 6}$$

Where *G* is the gel strength (MPa), *F* is the force (g) registered at the penetration depth *x* (mm) and r_p is the radius of the probe. Measurement began at a trigger force of 0.1 g with a movement rate of 0.1 mm/s.

2.2.9.3 Viscosity

The kinematic viscosity v of a 5% (w/w) solution of Kollidon® 30 was measured using a capillary viscosimeter (k = 0.03 mm²/s², n=3, SCHOTT AG, Mainz, Germany) at 19°C using equation 7

$$\mathbf{v = k * t} \qquad \text{equation 7}$$

Where k is the viscosimeter dependent correction factor and t is the flow time of the liquid.

2.2.10 Visual observations and swelling

Video monitoring of tablets and pellets was performed using a light macroscope supplied with an image analyzing software (ICCapture, The Imaging Source Europe GmbH, Bremen, Germany). Tablets were clamped between two transparent inert discs and placed in the medium (37°C of 0.1 N HCl with 0% or 40% (v/v) ethanol) and pictures were taken against a white background with either top-lighting or back-lighting. The brightness, if necessary, was adjusted using the auto-function of FIJI [255]. The dry area of tablets was calculated via the color-threshold function of

FIJI [255] by using the Hue-Saturation-Brightness (HSB)-system (Hue: 80/120 – 220/255; saturation: 0/125 – 255, brightness: 50 – 255).

Pellets were monitored in a petri dish or on a sieve on top of a magnetic stirrer (0.1 N HCl containing 0, 20 or 40% (w/w) ethanol or with addition 2M Na_3PO_4 solution, 37°C, 80 rpm). MCC cores were evaluated with or without 3% (w/w) additional NaCl. The size of pellets and tablets was calculated using FIJI [255]. The feret diameter was used for pellets.

2.2.11 Statistical evaluation of release behavior

Release curves were compared via the similarity factor (f_2) [165], given by equation 8

$$\boldsymbol{f_2 = 50 * \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{j=1}^{n} w_j \left|R_j - T_j\right|^2\right]^{0.5} * 100\right\}} \qquad \text{equation 8}$$

with n being the sample number, w_j being an optional weigt factor, R_j being the amount of drug released at timepoint j of the reference product and T_j being the amount of drug released at timepoint j of the test product. The similarity factor can take on values between 0 and 100 (completely identical). A value above 50 is considered as similar [33].

Release curves were analyzed by a methodology proposed by Peppas and Sahlin [31]:

$$\boldsymbol{\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m}} \qquad \text{equation 9}$$

Where the exponent *m* is chosen based on the geometric properties of the tablet and the kinetic constants k_1(diffusional release) and k_2(Case-II transport) are fitted to equation 1 using an ordinary least squares regression programmed via Python[256] v.3.6. The program code is included in Appendix A (Chapter 7.1, P. 164)

The quotient between these constants was used for the estimation of the average % of drug release-via-diffusion until 60% ($\bar{F}$, equation 10*)*.

$$\bar{F} = \frac{\sum_{t=0}^{T_{60\%}} \frac{1}{1 + \left(\frac{k_2}{k_1}\right) t^m}}{T_{60\%}}$$ equation 10

For the analysis of literature data, a lag-time was introduced to account for other dosage forms (equation 11):

$$\frac{M_t}{M_\infty} = k_1(t-l)^m + k_2(t-l)^{2m}$$ equation 11

Where l is the lag time. The term $t - l$ was limited to $t - l \geq 0$. The calculation of the average %-release-via-diffusion was adjusted accordingly for the lag time (equation 12):

$$\bar{F} = \frac{\sum_{t=t-l \geq 0}^{T_{60\%}} \frac{1}{1 + \left(\frac{k_2}{k_1}\right) t^m}}{T_{60\%}}$$ equation 12

The comparison between the values was performed using a Welch-Test or a paired T-test [257]. The requirements of these tests were confirmed using the Levene's test for equality of variances [258] and the Shapiro-Wilk test for normality [259].

The mean dissolution time (MDT) was calculated [33] according to equation 13

$$MDT = \frac{\sum_{i=1}^{n} \hat{t}_i \Delta M_i}{\sum_{i=1}^{n} \Delta M_i}$$ equation 13

Where i is the sample number, n is the number of sample time points, $\hat{t}_i$ is the time at the midpoint between t_i and t_{i-1} and ΔM the additional amount of drug released between t_i and t_{i-1}. The MDT included an additional 100%-value in the numerator with $t_n(\Delta 100\% - M_n)$, if the release was stopped prior to 100% release.

2.2.12 Evaluation of literature data

2.2.12.1 Literature search

Literature was found by usage of different search terms ([in-vitro] + [dissolution] + [ethanol/hydroalcoholic]; [Alcohol] + [Dose dumping]) in PubMed as well as through the reference section or different reviews [29, 87] published between 2007 and August 2022. Literature articles were included if in-vitro release data for aqueous release media as well as with 20% or 40% ethanol were provided. Not included were release data for drug powders without additional excipients as well as for immediate release dosage forms (e.g. [260]).

2.2.12.2 Data preparation

Release data was extracted from the publications using WebPlotDigitizer [261]. Available data were analyzed with the Peppas-Sahlin equations (equation 11 & equation **12**). n was fixed to 0.4501 for calculation purposes and as there were only very little studies with data on width and height of formulations. If available literature data only included data points larger than 60% release, an additional point at $\frac{t_1}{2}$ with $\frac{R_1}{2}$ was added, where t_1 is the first measured time point and R_1 is the amount of drug released at this time point.

The f_2-value (equation 8) and the MDT-ratio ($\frac{MDT_{Ethanol}}{MDT_{No\ ethanol}}$, equation 13) was calculated for 20% and 40% ethanol in comparison to aqueous medium.

The included data extracted from the papers include the type of release system (coated or matrix), the preparation method (melted/granulated or compressed), the desired release profile (sustained or extended), the size of the system, the type of drug and excipients in their respective amounts, the compression strength and hardness as well as the coating level if mentioned. The complete list is given in APPENDIX C (Chapter 7.3, P. 180). The solubility of the drug in the aqueous

release medium (adjusted to the pH), if not given in the publication, was calculated using the ADMET Predictor® module in GastroPlus® (Version 9.0, Simulation Plus, Inc., Lancaster, USA), along with the according log D value. The solubility of the drug in the 20 or 40% ethanol-containing medium, if not mentioned in the publication or given by another publication employing the same drug, was calculated using equation 3.

2.2.12.3 Multiple imputation and linear regression

A subset of the data excluding the data on sustained release [178, 180] was used to perform an exploratory data analysis. Excipients were included in the Multiple Imputation (MI) and in the regression model, if exact information on the (non-zero) amount of at least 2 tested formulations was available. Multicollinearity was assessed by calculating the Variance Inflation Factor (VIF) [262, 263]. Variables with a value above 10 were evaluated and excluded from the analysis if justified.

Data was multiply imputed using MIDAS [228], using Python (layer structure: 256, 256; vae_layer=False, seed= 89, input drop = 0.5).

The estimates from the multiply imputed estimates were combined by MIDAS using Rubin's rules [226]. The estimate of a quantity $\hat{\theta}$ is calculated as the mean, or as sum of the individual estimations $\hat{\theta}_j$ with the variance W_j from the j^{th} imputed dataset from m_i imputed datasets (equation 14).

$$\widehat{\boldsymbol{\theta}} = \frac{\mathbf{1}}{\boldsymbol{m_i}} \sum_{\boldsymbol{j=1}}^{\boldsymbol{m_i}} \widehat{\boldsymbol{\theta}}_{\boldsymbol{j}} \qquad \text{equation 14}$$

The variance of $\hat{\theta}$ (equation 15) includes both the within-imputation variability W (equation 16) as well as the between-imputation variability B (equation 17).

$$\boldsymbol{var}(\widehat{\boldsymbol{\theta}}) = \mathbf{W} + \left(\mathbf{1} + \frac{\mathbf{1}}{\boldsymbol{m_i}}\right) \boldsymbol{B} \qquad \text{equation 15}$$

$$W = \left(\frac{1}{m_i}\right)\sum_{j=1}^{m_i} W_j \qquad \text{equation 16}$$

$$B = \frac{1}{m_i - 1}\sum_{j=1}^{m_i}(\hat{\theta}_j - \hat{\theta})^2 \qquad \text{equation 17}$$

Heteroscedasticity was calculated for each imputed file separately according to the White-test [241] and reported. The f-test statistic and p-value are reported as median of the imputed datasets [264].

The linear regression was performed both via MIDAS [228] and via Scikit-Learn [265]. The latter was used to calculate the determination coefficient R^2 as well as present the residual errors, which the first one does not supply.

3 Results and Discussion

3.1 Multiple linear regression of published studies on the in-vitro results of oral modified release formulations in hydroethanolic media

This chapter is focused on identifying patterns in published studies of the release profiles of modified release formulations in 0 vs. 20 or 40% ethanol. The effect of different formulation and preparation parameters on the difference in release between hydro- and aqueous media was assessed in an exploratory multiple linear regression (MLR). Furthermore, the effect of formulation and preparation parameters on the change in release mechanism, assessed using the empiric Peppas-Sahlin equation [31], in 40% ethanol was studied using MLR.

The literature search yielded a total of 197 release test combinations published in 39 articles comprising 177 unique formulations. Of these, 4 enteric formulations of paracetamol [178], 4 commercial products of metoprolol [203], 2 matrix tablets of theophylline with hydroxypropyl methylcellulose (HPMC) and maltitol [186], 2 commercial formulations of morphine [198], 2 matrix tablets of theophylline with HPC and sesamum polysaccharide gums [266] and 6 pH-dependent matrix tablets of Carbopol® with different drugs [28] were tested at different pH. 189 tests were conducted in 0 and 40% ethanol, whereas only 101 tests were conducted in 0 and 20% ethanol.

The most tested drug was tramadol HCl [22, 157, 177, 189-191, 193, 267]. It was evaluated in 42 experiments and showed accelerated release in 40% ethanol in 4 formulations, two coated tablets [189] and two HPMC tablets [177]. Accelerated release in 20% ethanol was only reported for the coated system of Eudragit NE. In contrast, it showed slower release in 40% ethanol compared to 0% ethanol in 17 formulations, including 2 HPMC tablets. Tramadol HCl is an opioid which has less restrictions in its usage compared e.g., to oxycodone or morphine. The original guidelines of the Food and Drug Administration (FDA) mainly focused on dose dumping of opioid medication, thus tramadol HCl has been chosen by many formulators as model drug. However, the statistical likelihood of tramadol, 10%, to show accelerated release is far lower than that of the other opioids combined with a likelihood of 29% (6 formulations showing accelerated release, 11 being similar and 4 formulations being decelerated in 40% ethanol).

3.1.1 Mean-dissolution time and similarity factor

The MLR was performed in an exploratory style to identify risk- or protective factors for accelerated release in ethanol-containing media. Due to the limited number of studies on ethanol effects and the numerous possibilities in drug formulation, a confirmatory approach is not feasible.

The variables excluded due to a high variance inflation factor (VIF), and therefore risk of multicollinearity, were (in this order) Aerosil, dibutylsebacate, magnesium stearate, coating level, solubility in 20% ethanol, stearic acid, copovidone, weight and height (see also Appendix D, 7.4, P. 182). The determination coefficient R^2 (calculated for the mean dissolution time (MDT) 40/ratio) reduced from 0.71 to 0.69 after the deletion of these 9 variables, implying that the eliminated variables indeed explained only a very small amount of the outcome variable. Aerosil and magnesium stearate were commonly only used in very small amounts to improve compression and showed multicollinearity with the matrix formers they are combined with. Dibutylsebacate was combined exclusively with ethylcellulose [69, 170, 200], as was copovidone with Eudragit® RS [206]. The solubility in 20% ethanol correlated with the aqueous solubility and the solubility in 40% ethanol. Coating level correlated both with tablet type (coated), as well as with ethylcellulose. Both height and weight are correlated to the size but have less available data points (see also Appendix C, 7.3, P. 180).

The distribution of the missing data showed a strong concentration on a few parameters of size and mechanical forces (Fig. 5).

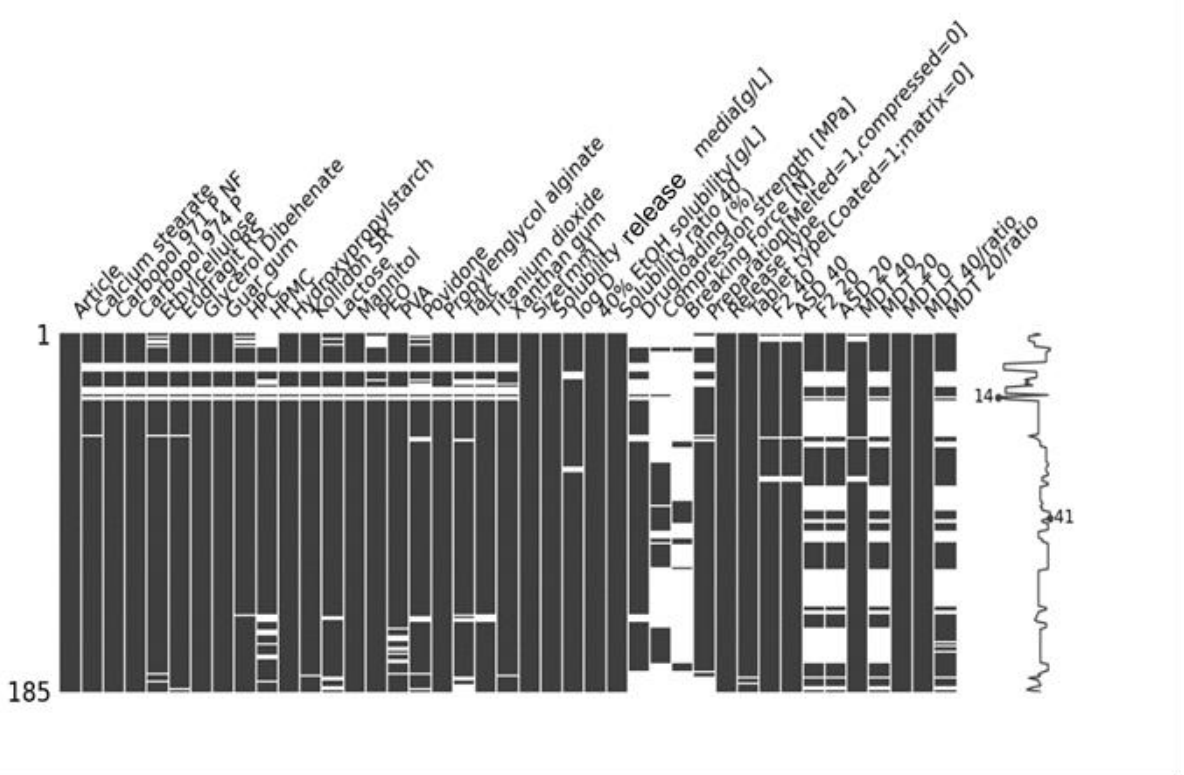

Fig. 5 Matrix distribution of missing data, white spaces resemble missing data.

The high number of missing values also implies, that the multiple imputation (MI) and linear regression of this data should only be used for the establishment of hypothesis [227]. For the breaking force, a maximum of 87% data points were missing. According to the rule of thumb proposed by White et al. [225] this required approximately 90 imputations.

There was no trend in the residual errors (Fig. 6, all $R^2 < 0.00001$). Heteroscedasticity was rejected according to White's test for 40% ethanol ($f_{2\ 40}$%: p = 0.26, t = 183.3) (MDT 40%: p = 0.25, t = 183.9) and was failed to reject for 20% ethanol (f_2 20%: p =0.04, t = 184.0) (MDT 20%: p = 0.04, t = 185.14). Thus, the standard errors in 20% ethanol are unreliable and while the direction of the effect is correct, they may not be statistically significant despite a $p < 0.05$.

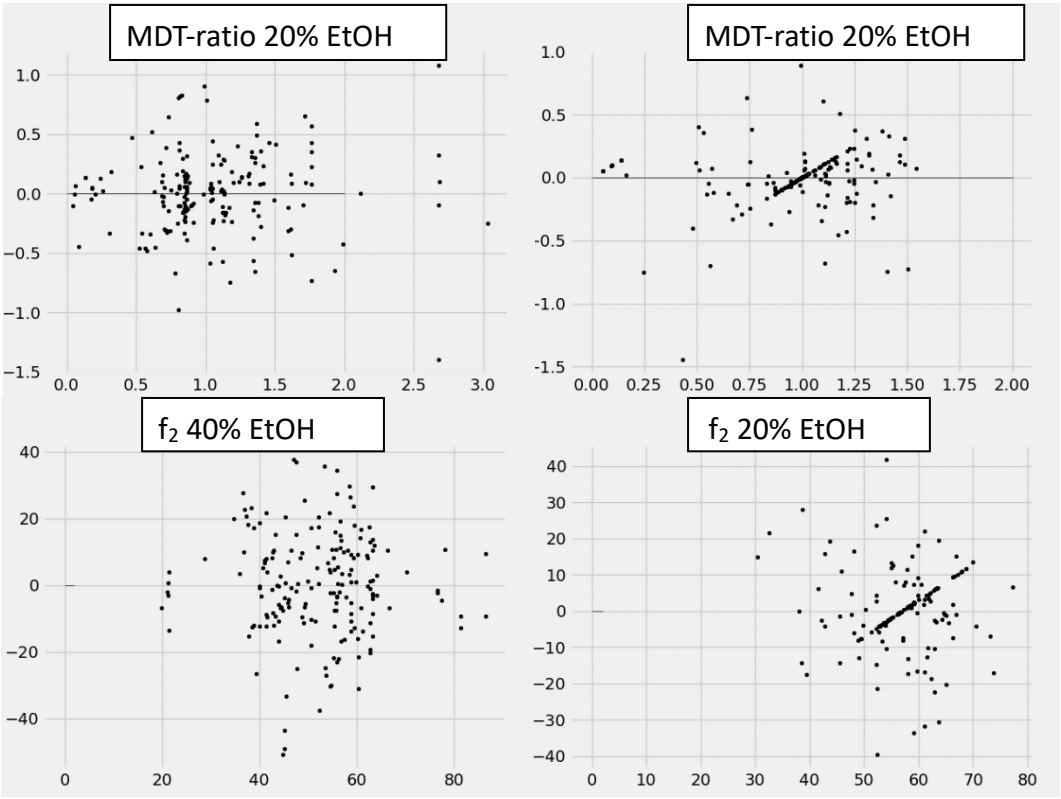

Fig. 6 Residual errors of the multiple linear regression

3.1.1.1 MDT-ratio

According to the calculation of the MDT-ratio $\frac{MDT_{Ethanol}}{MDT_{No\ ethanol}}$, a value below 1 would indicate accelerated release in the presence of ethanol. Accordingly, a positive relationship between β_j and MDT-ratio would imply a protective action.

An increase in dosage form size as well as preparing the core via melting or granulation was associated with a significant reduction in accelerated release in 40% ethanol (Table 4, $R^2 = 0.70$, $f = 11.58$, $p < 0.0001$). An increase in the log D or the use of a coating was associated with an increase in accelerated release ($b = -0.19$, $p < 0.01$ and $b = -0.34$, $p = 0.01$, respectively). The solubility ratio had a small but significant positive effect ($b = 0.001$, $p = 0.01$). However, this effect was only present if log D was included in the model as the bi-variate correlation between solubility ratio and MDT ratio was negative. As the log D and the solubility ratio were partially correlated ($R = 0.6$), the solubility ratio may account for error terms not explained by the log D.

Table 4 Results of regression for MDT-ratio in 40% ethanol
$R^2 = 0.70$, $f = 11.58$, $p < 0.0001$

term	estimate	std. error	statistic	df	p value
Const*	**0.37**	**0.13**	**2.79**	**139**	**0.01**
Calcium stearate*	**-0.01**	**0.00**	**-2.69**	**142**	**0.01**
Carbopol 971 P NF	0.02	0.01	1.74	151	0.08
Carbopol 974 P	0.02	0.01	1.71	149	0.09
Ethylcellulose	0.01	0.01	0.98	128	0.33
Eudragit RS	0.00	0.01	-0.30	151	0.77
Glycerol Dibehenate	0.00	0.00	-0.56	146	0.57
Guar gum	0.00	0.01	0.35	152	0.73
HPC (Hydroxypropyl cellulose)	-0.01	0.01	-1.07	150	0.29
HPMC	0.00	0.00	-0.86	149	0.39
Hydroxypropyl starch	0.00	0.04	-0.02	151	0.99
Kollidon SR**	**0.03**	**0.00**	**8.06**	**145**	**0.00**
Lactose	0.00	0.00	0.83	149	0.41
Mannitol	0.00	0.01	0.06	152	0.95
MCC* (Microcrystalline cellulose)	**0.01**	**0.00**	**2.07**	**146**	**0.04**
PEO (Polyethylenoxide)	0.00	0.00	1.26	147	0.21
PVA (Polyvinyl alcohol)	-0.01	0.02	-0.50	149	0.62
Povidone	0.14	0.14	0.96	141	0.34
Propylenglycol alginate	0.00	0.01	0.07	151	0.94
Talc	0.03	0.15	0.23	139	0.82
Titanium dioxide	0.01	0.02	0.25	152	0.80
Xanthan gum	0.00	0.00	0.28	148	0.78
Size[mm]**	**0.05**	**0.01**	**4.47**	**147**	**0.00**
Solubility release media[g/L]	0.00	0.00	0.41	150	0.68
log D (partition coefficient)**	**-0.19**	**0.03**	**-5.43**	**150**	**0.00**
40% EtOH solubility[g/L]	0.00	0.00	-0.15	149	0.88
Solubility ratio 40*	**0.001**	**0.00**	**2.49**	**151**	**0.01**
Drug loading (%)	0.00	0.00	0.06	148	0.95
Compression strength [MPa]	0.00	0.00	0.89	150	0.38
Breaking Force [N]	0.00	0.00	-1.40	148	0.16
Preparation [Melted=1,compressed=0]**	**0.38**	**0.12**	**3.23**	**93**	**0.00**
Tablet type [Coated=1;matrix=0]*	**-0.34**	**0.12**	**-2.78**	**115**	**0.01**

* $p < 0.05$

** $p < 0.01$

Std. error refers to standard error and df to degrees of freedom.

Three excipients included in the analysis showed significant associations. Kollidon® SR ($b = 0.03$, $p < 0.01$) as a matrix polymer as well as MCC ($b = 0.01$, $p = 0.04$) showed a positive relationship with MDT – ratio, while calcium stearate ($b = -0.01$, $p = 0.01$) showed a negative relationship.

As there was less data available for testing in 20% ethanol, some excipients present in the model for 40% ethanol were not actually tested in 20% ethanol. To avoid a purely computer-driven prediction, these variables were excluded from the analysis of 20%. These included Eudragit® RS, HPC, Hydroxypropyl starch, Kollidon® SR, Mannitol, PEO, PVA, Povidone, Propylene glycol alginate and Xanthan gum.

The size of the dosage form ($b = -0.01$, $p = 0.03$) and the use of a coating ($b = 0.59$, $p < 0.01$) was associated with a reduction in MDT-ratio, while the breaking force ($b = 0.001$, $p < 0.01$) was associated with a small increase (Table 5, $R^2 = 0.60$, $f = 12.38$, $p < 0.0001$). Increasing the amount of calcium stearate ($b = -0.01$, $p < 0.01$), glycerol dibehenate ($b = -0.005$, $p = 0.03$) or MCC ($b = -0.01$, $p = 0.03$) were associated with a small reduction in MDT-ratio, while increasing the ethylcellulose amount ($b = 0.03$, $p = 0.01$) resulted in an increase in MDT-ratio.

Table 5 Results of regression for MDT-ratio in 20% ethanol
$R^2 = 0.60$, f = 12.38, $p < 0.0001$

term	estimate	std. error	statistic	df	p value
Const**	**1.15**	**0.09**	**13.52**	**151**	**0.00**
Calcium stearate**	**-0.01**	**0.00**	**-3.28**	**155**	**0.00**
Carbopol 971 P NF	0.01	0.01	1.05	160	0.30
Carbopol 974 P	0.01	0.01	1.87	161	0.06
Ethylcellulose*	**0.03**	**0.01**	**2.67**	**124**	**0.01**
Glycerol Dibehenate*	**-0.005**	**0.00**	**-2.21**	**157**	**0.03**
Guar gum	0.00	0.01	-0.54	160	0.59
HPMC	-0.01	0.00	-1.84	150	0.07
Lactose	0.00	0.00	0.19	156	0.85
MCC	-0.01	0.00	-2.82	155	0.01
Talc	0.09	0.11	0.78	118	0.44
Titanium dioxide	0.02	0.02	0.88	158	0.38
Size[mm]*	**-0.01**	**0.01**	**-2.25**	**160**	**0.03**
Solubility release media[g/L]	0.00	0.00	-1.11	156	0.27
log D	-0.04	0.02	-1.79	159	0.08
40% EtOH solubility[g/L]	0.00	0.00	1.17	155	0.24
Solubility ratio 40	0.00	0.00	-0.52	158	0.61
Drug loading (%)	0.00	0.00	-0.39	152	0.70
Compression strength [MPa]	0.00	0.00	1.92	159	0.06
Breaking Force [N]**	**0.001**	**0.00**	**4.01**	**150**	**0.00**
Preparation [Melted=1,compressed=0]	0.071	0.07	0.96	105	0.34
Tablet type [Coated=1;matrix=0]**	**-0.59**	**0.08**	**-7.14**	**101**	**0.00**

3.1.1.2 f_2-value

While the MDT is a useful tool, it is not defined by regulatory agencies like the f_2-value. However, the f_2-value is bi-directional, meaning it does not indicate whether the release with or without ethanol is higher. For 40% ethanol size, log D, solubility ratio, preparation type or coating were all non-significant, but the direction of the effect complied to the MDT-ratio, meaning that an increase of these parameters for the MDT-ratio was associated with an increase in f_2-value (Table 6, $R^2 = 0.35$, f = 2.68, $p < 0.001$). Interestingly, ethylcellulose (b = 1.93, $p < 0.01$), xanthan gum (b = 0.61, $p < 0.01$) and HPC (b = 0.61, p = 0.03) were associated with a significant increase in f_2-value, whereas Kollidon® SR (b = -0.59, $p < 0.01$) resulted in a decrease. As the amount of Kollidon® SR increased the MDT-ratio (Table 4), this reduction in f_2-value resulted from a slower release in 40% ethanol.

Table 6 Results of regression for f_2-value in 40% ethanol.
$R^2 = 0.35$, $f = 2.68$, $p < 0.001$

term	estimate	std. error	statistic	df	p value
Const**	**41.95**	**6.26**	**6.70**	**144**	**0.00**
Calcium stearate	-0.12	0.13	-0.94	143	0.35
Carbopol 971 P NF	0.78	0.50	1.56	151	0.12
Carbopol 974 P	0.08	0.53	0.16	149	0.88
Ethylcellulose**	**1.93**	**0.67**	**2.87**	**131**	**0.00**
Eudragit RS	-0.50	0.45	-1.11	151	0.27
Glycerol Dibehenate	0.16	0.16	1.00	144	0.32
Guar gum	0.79	0.62	1.27	152	0.20
HPC*	**0.61**	**0.28**	**2.23**	**151**	**0.03**
HPMC	0.31	0.22	1.44	141	0.15
Hydroxypropyl starch	0.04	1.97	0.02	149	0.98
Kollidon SR**	**-0.59**	**0.20**	**-3.00**	**145**	**0.00**
Lactose	0.25	0.24	1.03	145	0.30
Mannitol	-0.54	0.50	-1.07	152	0.29
MCC	0.24	0.21	1.15	134	0.25
PEO	-0.03	0.17	-0.19	146	0.85
PVA	0.85	1.05	0.81	140	0.42
Povidone	-4.25	7.82	-0.54	98	0.59
Propylenglycol alginate	0.53	0.50	1.06	150	0.29
Talc	-13.48	7.92	-1.70	101	0.09
Titanium dioxide	0.81	1.17	0.70	149	0.49
Xanthan gum**	**0.61**	**0.16**	**3.81**	**148**	**0.00**
Size[mm]	0.80	0.48	1.66	151	0.10
Solubility release media[g/L]	0.00	0.02	-0.15	148	0.88
log D	-1.40	1.67	-0.84	145	0.40
40% EtOH solubility[g/L]	0.01	0.02	0.32	146	0.75
Solubility ratio 40	0.00	0.02	-0.21	150	0.83
Drug loading (%)	-0.11	0.10	-1.06	150	0.29
Compression strength [MPa]	0.00	0.01	-0.45	147	0.66
Breaking Force [N]	-0.03	0.03	-1.15	135	0.25
Preparation [Melted=1, compressed=0]	4.40	5.62	0.78	91	0.44
Tablet type [Coated=1;matrix=0]	-6.69	5.66	-1.18	122	0.24

For 20% ethanol, solubility in the release medium ($b = -0.05$, $p < 0.01$), log D ($b = -3.85$, $p < 0.01$), breaking force ($b = -0.03$, $p < 0.05$) and the use of a coating ($b = -13.27$, $p < 0.01$) were associated with a significant reduction in f_2-value (Table 7, $R^2 = 0.30$, $f = 3.43$, $p < 0.001$). The solubility in 40% ethanol ($b = 0.06$, $p < 0.01$) and the amount of calcium stearate ($b = 0.21$, $p = 0.01$) and ethylcellulose ($b = 1.27$, $p < 0.01$) were associated with an increase in f_2-value.

Table 7 Results of regression for f_2-value in 20% ethanol.
$R^2 = 0.30$, $f = 3.43$, $p < 0.001$

term	estimate	std. error	statistic	df	p value
Const**	**51.07**	**3.62**	**14.09**	**148**	**0.00**
Calcium stearate*	0.21	0.08	2.71	153	0.01
Carbopol 971 P NF	-0.08	0.28	-0.29	160	0.77
Carbopol 974 P	-0.57	0.30	-1.91	161	0.06
Ethylcellulose**	**1.27**	**0.43**	**2.95**	**118**	**0.00**
Glycerol Dibehenate	0.03	0.09	0.36	156	0.72
Guar gum	0.04	0.38	0.10	159	0.92
HPMC	0.05	0.14	0.37	144	0.71
Lactose	0.20	0.15	1.36	155	0.18
MCC	0.20	0.10	1.90	152	0.06
Talc	-8.99	5.02	-1.79	100	0.08
Titanium dioxide	0.53	0.76	0.69	157	0.49
Size[mm]	0.28	0.27	1.02	161	0.31
Solubility release media[g/L]**	**-0.05**	**0.01**	**-4.36**	**156**	**0.00**
log D**	**-3.85**	**1.06**	**-3.65**	**151**	**0.00**
40% EtOH solubility[g/L]**	**0.06**	**0.01**	**4.66**	**156**	**0.00**
Solubility ratio 40	0.01	0.01	0.62	156	0.54
Drug loading (%)	-0.03	0.05	-0.64	153	0.52
Compression strength [MPa]	0.00	0.01	-0.64	157	0.53
Breaking Force [N]*	**-0.03**	**0.02**	**-2.01**	**145**	**0.05**
Preparation[Melted=1,compressed=0]	0.54	3.24	0.17	91	0.87
Tablet type[Coated=1;matrix=0]**	**-13.27**	**3.57**	**-3.71**	**93**	**0.00**

3.1.2 Empiric comparison of release mechanism

The Peppas-Sahlin equation (equation 11) was chosen due to its simple implementation and its applicability to different systems. The %-release-via-diffusion ratio ($\frac{\%-diffusion_{40\%}}{\%-diffusion_{0\%}}$), calculated from the %-release-via-diffusion according to equation 12, was used to emphasize the difference in %-release-via-diffusion between 40% and 0% ethanol. Neither MDT-ratio nor f_2-value were included in the model, as these are not appropriate predictors and, a causality, if given at all, would be inverse. Also, none of these variables correlated with %-release-via-diffusion ratio more than 0.22, implying that these variables do not show a meaningful correlation.

In the MLR-model, the White test rejected heteroscedasticity ($p = 0.46$, $t = 173.41$), implying that the standard errors are unbiased. The solubility-ratio showed a significant correlation ($b = 0.02$, $p < 0.01$) with the %-release-via-diffusion ratio (Table 8, $R^2 = 0.46$, $f = 4.17$, $p < 0.0001$). This appears plausible, as a higher solubility would result in more dissolved drug and thus a higher concentration gradient between the formulation and the medium. The significant increase ($b = 3.11$, $p < 0.01$) associated with the presence of a coating may be a result of an increased permeability of the coating polymer to the drug. This is in accordance to own experimental data (Chapter 3.4, P. 97). The log D has a negative correlation ($b = -0.72$, $p = 0.02$) with the %-release-via-diffusion ratio. This may be the residual part, after correcting for the increased solubility and the diffusion through a coating.

Both Carbopol 971 P NF and glycerol dibehenate showed a significant correlation, which may imply a change of release behavior for systems with polymers to a more diffusion-based release. For Carbopol 971 P NF, the authors observed such an effect and ascribed it to the reduced polymer erosion [28]. For glycerol dibehenate, the drug is mainly released via diffusion through pores [194], however, Jedinger et al mentioned the possibility of erosion in aqueous media [41] and Lochař et al proposed a better wettability of glycerol dibehenate in 40% ethanol [193]. The effect of HPMC was nonsignificant ($b = 0.07$, $p = 0.06$), which may be a result of the variability of the included studies.

Table 8 Results of regression for %-release-via-diffusion ratio in 40% ethanol
$R^2 = 0.46$, $f = 4.17$, $p < 0.0001$

term	estimate	std. error	statistic	df	p value
Const	0.79	1.10	0.71	151	0.48
Calcium stearate	0.01	0.02	0.64	149	0.52
Carbopol 971 P NF*	**0.19**	**0.09**	**2.17**	**152**	**0.03**
Carbopol 974 P	0.01	0.09	0.14	151	0.89
Ethylcellulose	-0.17	0.11	-1.45	148	0.15
Eudragit RS	0.00	0.08	-0.02	152	0.99
Glycerol Dibehenate**	**0.08**	**0.03**	**2.90**	**151**	**0.00**
Guar gum	0.01	0.11	0.08	152	0.94
HPC	0.01	0.05	0.17	152	0.86
HPMC	0.07	0.04	1.86	150	0.06
Hydroxypropyl starch	0.03	0.35	0.08	151	0.93
Kollidon SR	-0.05	0.04	-1.49	151	0.14
Lactose	-0.02	0.04	-0.43	150	0.67
Mannitol	0.00	0.09	0.04	152	0.97
MCC	-0.01	0.04	-0.23	147	0.82
PEO	0.03	0.03	1.01	150	0.31
PVA	-0.01	0.18	-0.03	148	0.98
Povidone	0.41	1.27	0.32	130	0.75
Propylenglycol alginate	0.02	0.09	0.26	151	0.80
Talc	-0.25	1.27	-0.19	139	0.85
Titanium dioxide	0.01	0.21	0.06	152	0.95
Xanthan gum	0.00	0.03	-0.04	151	0.97
Size[mm]	0.01	0.09	0.09	151	0.93
Solubility release media[g/L]	0.00	0.00	-0.54	151	0.59
log D*	**-0.72**	**0.29**	**-2.45**	**151**	**0.02**
40% EtOH solubility[g/L]	0.00	0.00	-0.15	150	0.88
Solubility ratio 40**	**0.02**	**0.00**	**6.24**	**152**	**0.00**
Drug loading (%)	-0.01	0.02	-0.72	151	0.47
Compression strength [MPa]	0.00	0.00	0.10	151	0.92
Breaking Force [N]	-0.01	0.00	-1.09	147	0.28
Preparation [Melted=1,compressed=0]	-1.17	0.89	-1.31	133	0.19
Tablet type [Coated=1;matrix=0]*	**3.11**	**0.94**	**3.30**	**147**	**0.00**

3.1.3 Conclusion

For both the MDT-ratio and the f_2-value the same predictor variables were used, but differences were made between 20% and 40% ethanol. The different R_2-values for the MDT-ratio and the f_2-value indicate, that the MDT-ratio is a better outcome variable to predict than the f_2-value.

The use of a coating and a high log D can universally cause accelerated release in ethanol. This may result from the increased permeability of many coating polymers in the presence of ethanol [174] and for drugs with a higher log D [268] as well as an increased drug solubility in the presence of ethanol [168]. Apparently, log D reflected this behavior better than the solubility ratio. Melting or granulating a product and increasing the size of a product reduces accelerated release in ethanol except for the MDT-ratio in 20% ethanol. However, this effect was small (b = -0.01, p = 0.03) and, due to the heteroscedasticity of the errors, may not be unbiased. Drug loading and compression strength had no significant effect.

Only the amount of ethylcellulose had a protective effect against accelerated release in hydroethanolic media for all outcome variables. However Kollidon® SR, being only tested in 40% ethanol, showed a reduction in release in the presence of ethanol when used as a matrix polymer. Calcium stearate had a risk of accelerated release for all but the f_2-value in 20% ethanol. Other excipients had either differing effects or were not significant for any outcome variable.

Combining these results allows some general guidelines for formulation scientists: A formulation robust to the influence of ethanol should, ideally, consist of Kollidon® SR as a matrix former, be granulated or molten and preferably of a larger size. A coating is not advised, but if a coating is required, ethylcellulose is the polymer of choice.

The %-release-via-diffusion ratio can be a useful tool to observe a change in the underlying release mechanism. The presence of ethanol can increase the release via diffusion for specific systems. However, this change in release behavior does not necessarily result in a difference in MDT-ratio or f_2-value.

3.2 The behavior of commercial products in aqueous and hydroethanolic media

3.2.1 Commercial products of duloxetine HCl

Duloxetine is a selective serotonin-noradrenaline reuptake inhibitor and as such indicated as a treatment against major depressive disorder, generalized anxiety disorder and polyneuropathic pain as well as stress urinary incontinence [150]. It is used as hydrochloric salt and has been patented in 1994 [269]. It was introduced to the European Union (EU) in 2004 and generic products have been marketed since 2015 [270]. Cymbalta, the originator product, is applied as pellets coated with the enteric polymer hydroxypropyl methylcellulose-acetate-succinate (HPMCAS, because, in acidic media, duloxetine is prone to degradation, resulting in the elimination of 1-naphthol [271]. For duloxetine, the Food and Drug Administration (FDA) has issued the recommendation for Cymbalta and generic products to include in-vitro alcohol dose dumping tests at different concentrations (5%, 20% and 40% (v/v)) in 0.1 N HCl [271]. In contrast, the European Medicines Agency (EMA) requests the testing at an elevated pH of 4.5 to simulate fed state, but does not ask for ethanol testing [272, 273].

The four tested commercial products are all marketed in the EU and would, therefore, be routinely tested up to 20% ethanol. The formulations were chosen to represent different enteric polymers and different dosage forms (Table 9). All formulations contain the same warning inside the package leaflet advising special caution when consuming alcohol, but not advising against the consumption.

Table 9 Composition of the evaluated commercial duloxetine HCl products

Formulation name	Enteric polymer	Core type	Additional excipients
Cymbalta®	HPMCAS	Sucrose / starch pellet	Hydroxypropyl methylcellulose (HPMC), talcum, titanium dioxide, triethyl citrate
Duloxetin Beta	Eudragit L (aqueous dispersion)	Sugar pellet	HPMC, talcum, titanium dioxide, triethyl citrate
Duloxetin Aurobindo	Hydroxypropyl-methylcellulose phthalate (HPMCP)	Sucrose/ corn starch pellet	HPMC, hyprolose, crospovidon, talcum, titanium dioxide, indigocarmin, sodium dodecylsulfate, triethyl citrate
Duloxetin 1A Pharma	HPMCAS	Minitablet	HPMC, pregelatinized starch, microcrystalline cellulose (MCC), povidone K30, talcum, magnesium stearate, sodium stearyl fumarate, titanium dioxide, lactose monohydrate, macrogol 4000

While being applied in capsules, the capsule shell was removed prior to release testing. Cymbalta pellets have a finishing layer consisting of talc, HPMC and titanium dioxide (Fig. 7), which is described in the patent [269]. All formulations showed enteric-resistance in 0.1 N HCl, and rapid disintegration in PBS 6.8, which represents the intestinal pH (Fig. 8). The release behavior in this buffer followed three distinct phases (Fig. 9). Initially, the top coating with the enteric polymer dissolved. Pigments or whiteners like titanium dioxide are often included in this top layer, which caused the white spreading. The second phase at about 6 to 8 min was likely the dissolution of HPMC, used as a separating layer to avoid interaction of duloxetine with the enteric polymer. Simultaneously the mixed bulk and surface erosion of the core and the drug layer began as can be observed by the size increase, which would not be visible for pure surface erosion.

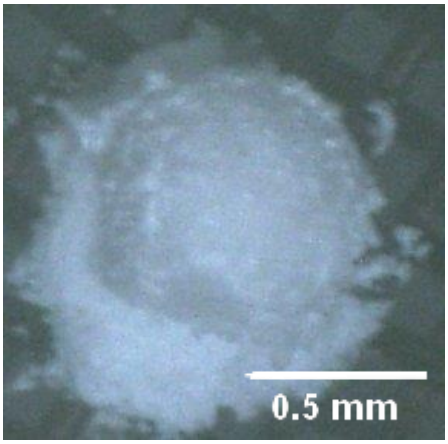

Fig. 7 Pellet of Cymbalta in 0.1 N HCl after 5 minutes. The white layer surrounding the grey core is a finishing layer consisting of talc, HPMC and TiO_2.

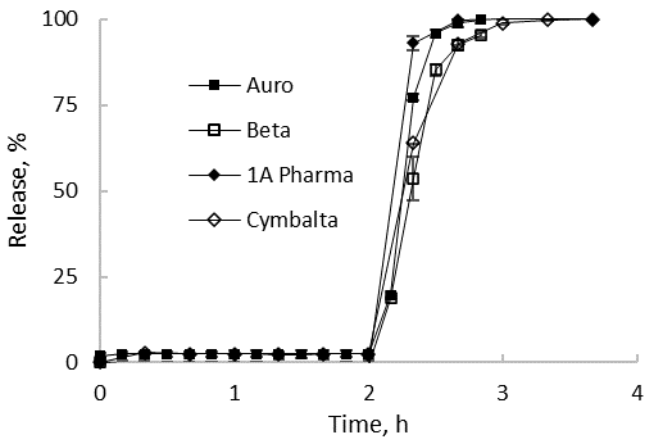

Fig. 8 Release of duloxetine HCl from different commercial products in 750 ml 0.1 N HCl. After 2 h, 250 ml of prewarmed $2M\ Na_3PO_4$ were added to the release media.

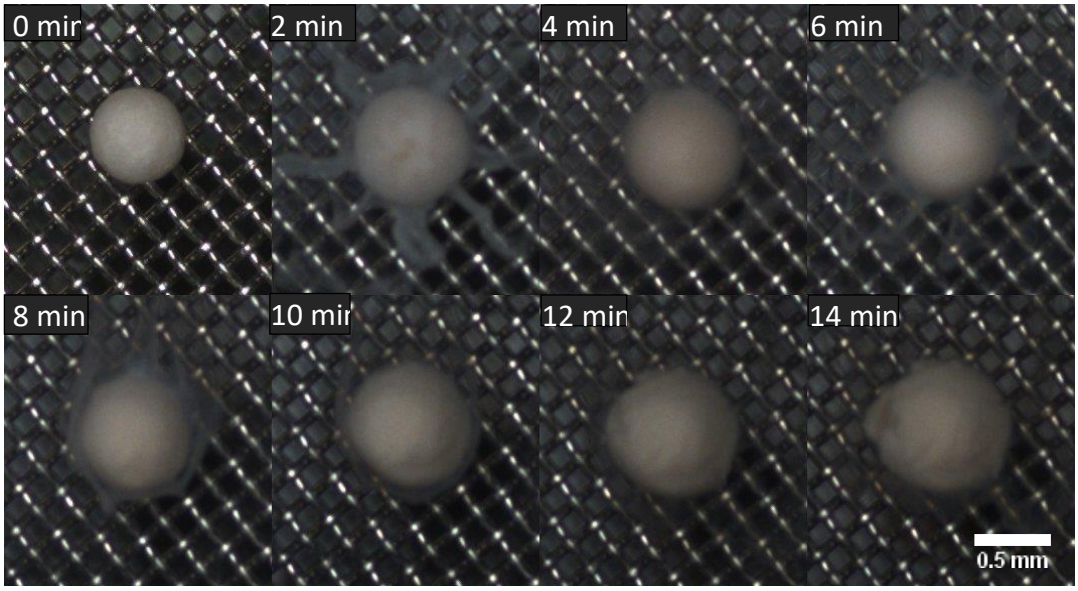

Fig. 9 Dissolution behavior of a Duloxetine Beta pellet in PBS-buffer 6.8.

The addition of ethanol at 20 and 40% to 0.1 N HCl led to premature release of duloxetine (Fig. 10). The only exception to this was the Duloxetine 1A Pharma, which is a mini-tablet formulation and accordingly larger in size (Table 10). This formulation showed no premature release in 20% ethanol and can thus be considered resistant to hydroethanolic media. HPMCAS is the polymer included in this formulation and is also the polymer used in Cymbalta. The resistance to hydroethanolic media is thus not a function of the polymer alone, but of the increased coating thickness, surface-volume ratio or due to different excipients included for tableting. Several of the excipients included in Duloxetine 1A Pharma are not soluble (e.g., MCC) in either water or

ethanol and, thus, would not execute an osmotic pressure, which may facilitate rupturing. Further, the drug is homogeneously dispersed inside the tablet instead of on the surface, prolonging the path of diffusion. The plateauing effect visible in 20% ethanol, resulting in less than 100% release may be due to interaction of duloxetine with the undissolved acidic groups of the polymer [274, 275]. Dissolution of the polymer in PBS 6.8 released additional drug. This effect did not affect the general observation or effect of hydroethanolic media.

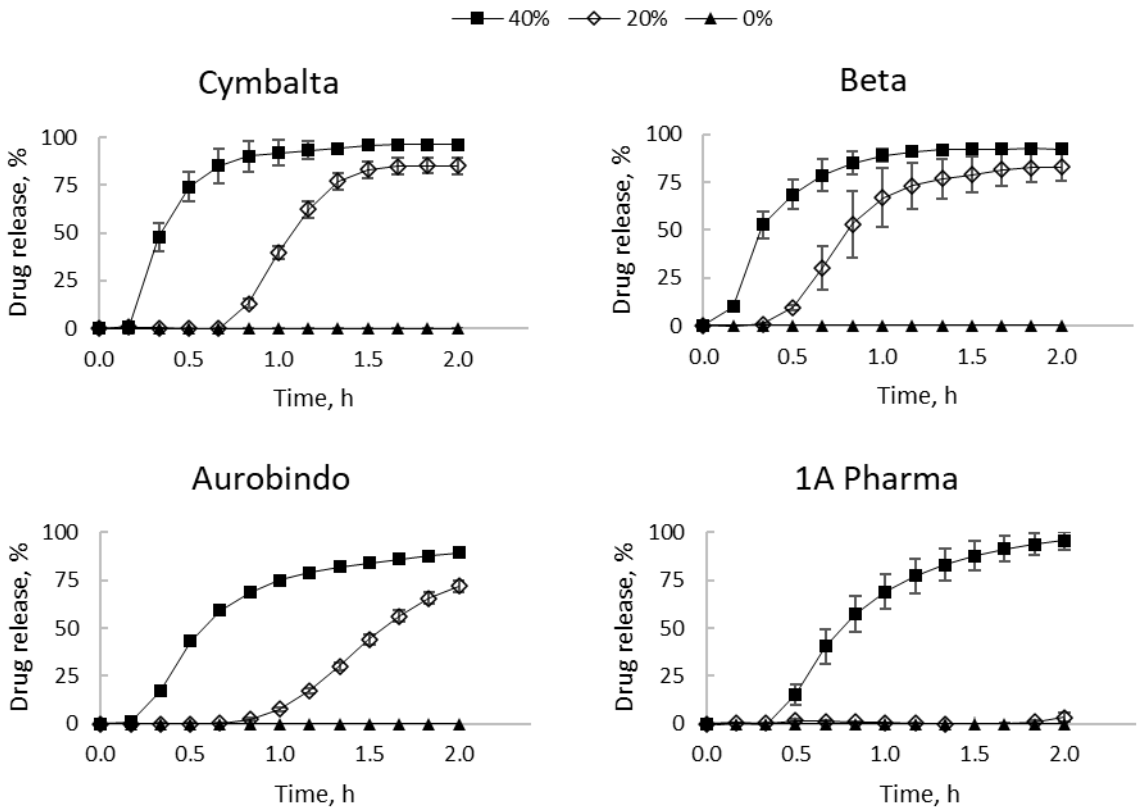

Fig. 10 Release of Duloxetine HCl from different commercial products in 0, 20 or 40% ethanol.

Table 10 Geometric and gravimetric data of evaluated commercial duloxetine products per capsule.

	Cymbalta	Beta	Aurobindo	1A Pharma
Total mass [mg]	130.94	165.85	173.66	179.04
Unit count	203	168	164	4
Unit mass [mg]	0.65	0.99	1.06	44.76
Unit size [mm]	1.13	1.30	1.41	3.45
Surface/volume – ratio	5.51	4.71	4.41	1.44
Density [mg/mm³]	1.45	1.45	1.42	3.22
Coating thickness [µm]	44	59	53	97

The premature release may be explained by the behavior of the pellets in the hydroethanolic media (Fig. 11, Fig. 12, Fig. 13). This differed from the polymer dissolution visible in PBS 6.8 (Fig. 9) and is thus a different mechanism.

Pellets of Cymbalta only showed minor swelling, but the build-up of osmotic pressure and the bulging of the coating could lead to small ruptures (Fig. 11). As this was only visible for one pellet, the other may have micro ruptures or rupturing on the non-visible side. Micro ruptures in hydroethanolic media have previously been reported for all tested polymers via SEM [178].

Pellets of Duloxetin Betapharm, coated with Eudragit® L showed a massive rupturing, splitting open the complete pellet side (Fig. 12). Upon opening, the (already) drastically eroded core could be seen. Thus, Eudragit® L has a high permeation of the medium, enabling rapid core dissolution. Eudragit® L is very flexible in the wet state [55], but apparently the presence of ethanol negatively affected the integrity of the polymer and its elongation properties.

Pellets of Duloxetine Aurobindo showed both rupturing and swelling (Fig. 13). While one pellet bulged and started rupturing after 20 min, the other swelled massively and showed indistinct rupturing only after 70 min. This implies a different coating integrity or -thickness between the two pellets.

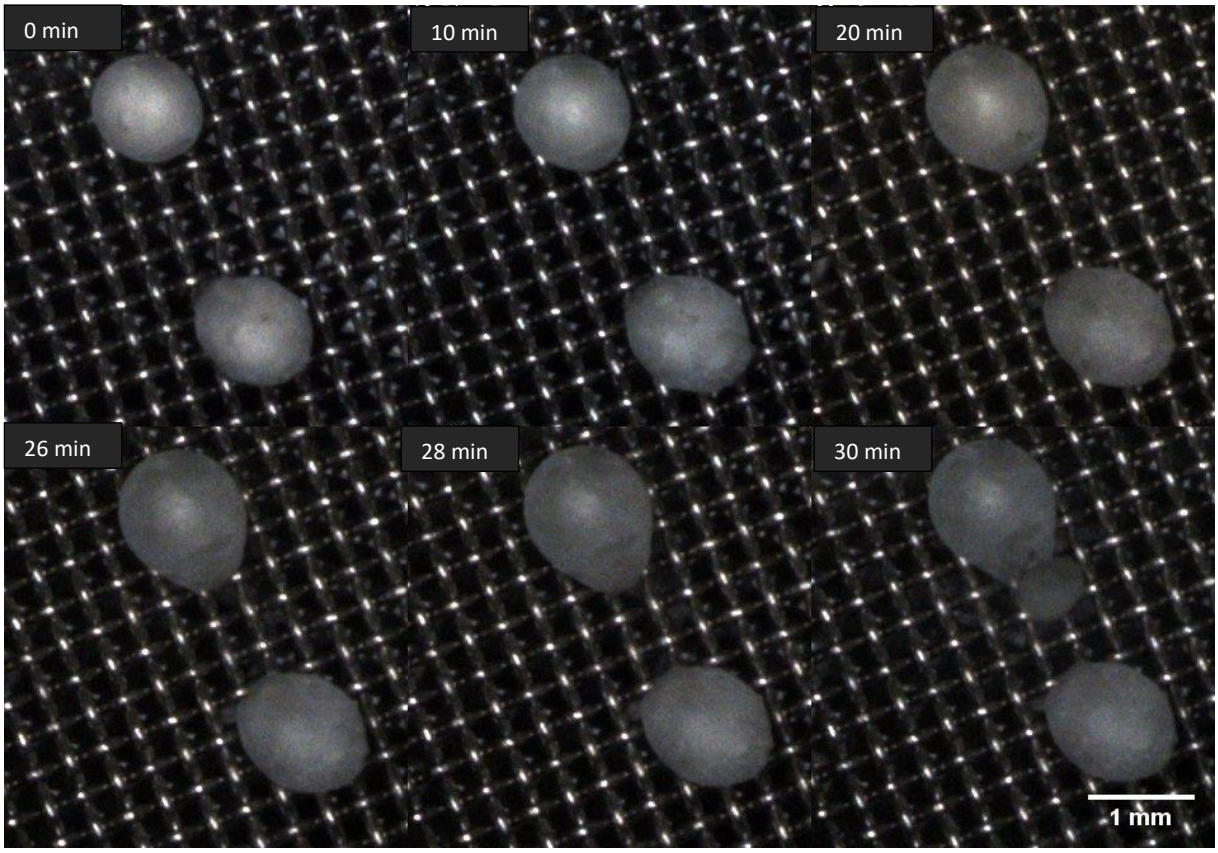

Fig. 11 Pellets of Cymbalta in 40% ethanol. Images were adjusted for brightness and contrast by the auto-function of FIJI. The upper pellet shows bulging and rupturing (opening) in the lower right side.

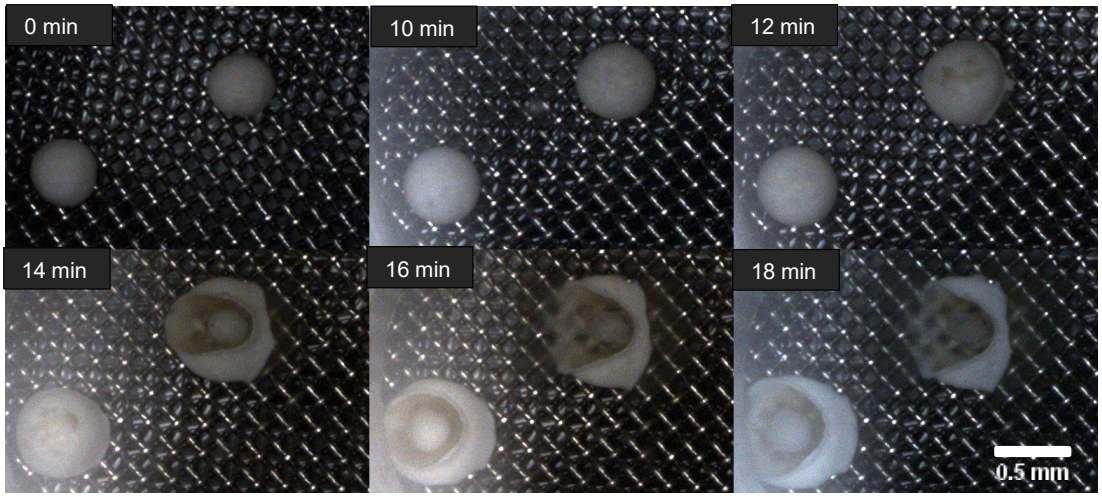

Fig. 12 Pellet of Duloxetine Beta in 40% ethanol. Images were adjusted for brightness and contrast by the auto-function of FIJI.

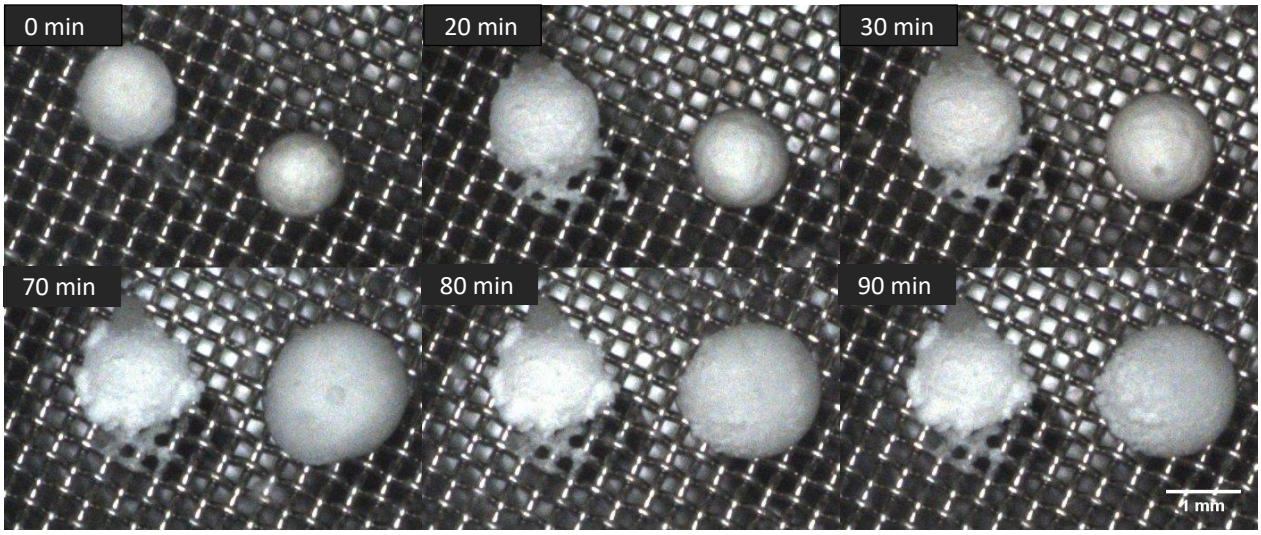

Fig. 13 Pellets of Duloxetin Aurobindo in 40% ethanol. The left pellet bulges and ruptures at the top after 20 min, the right pellet ruptures on the left side between 70 and 80 min, visible by the crizzeling of the film.

A direct comparison of the four formulations showed the same order of release for both 20 and 40% ethanol, but at different rates (Fig. 14). Betapharm had the earliest release, followed by Cymbalta and Aurobindo and the least affected 1A, which had a lag time of 25 min in 40% ethanol. While this is not robust according to FDA-requirements [158], the absence of release in 20% ethanol may be regarded as sufficient according to the requirements of the EMA.

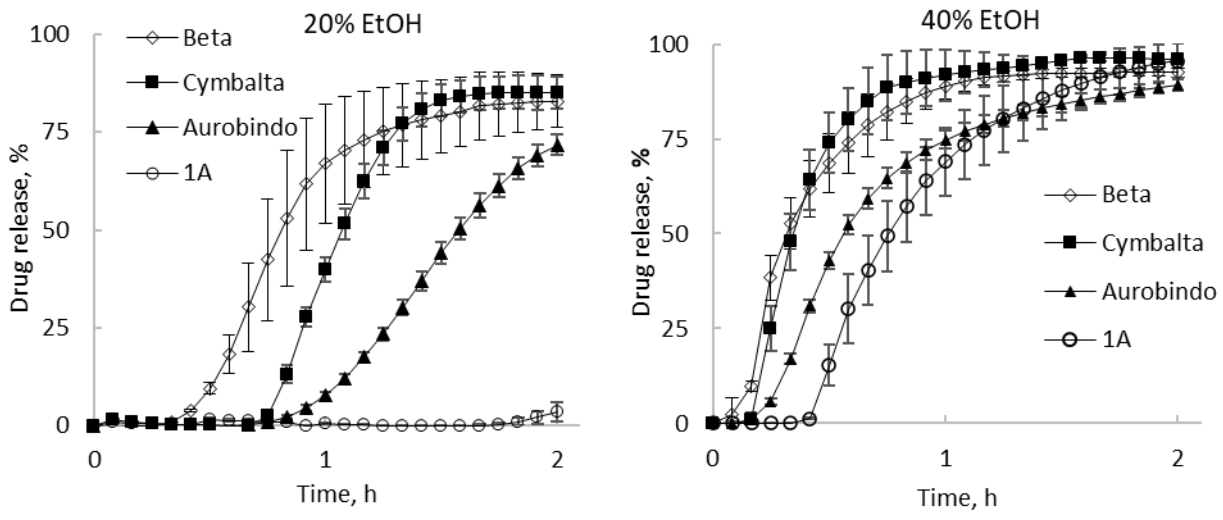

Fig. 14 Release of Duloxetine HCl from different commercial products in 20% or 40% ethanol

The different release of the pellets in 20% ethanol (Fig. 14) was reflected in the medium uptake (Fig. 15). Cymbalta, which showed very little visual swelling prior to rupturing, accordingly,

showed little wet weight gain. The dry weight loss was due to erosion and dissolution of the sugar core. Duloxetin Beta showed rapid medium uptake followed by a drastic decrease in wet and dry weight. The complete opening of the pellets (Fig. 12) accelerated the core dissolution and reduced the medium amount staying inside the pellets. The polymer did not dissolve and resulted in aggregation of the pellets; individual pellets could not be separated anymore. Due to the opening of the coating the medium and excipients are released from the pellet. This resulted in a wet-weight below 100%. In contrast, pellets of Cymbalta and Aurobindo constantly had a wet weight above 100%, indicating that the pellet shape is maintained. Pellets of Aurobindo showed the largest amount of swelling, as seen with the largest size increase (Fig. 13).

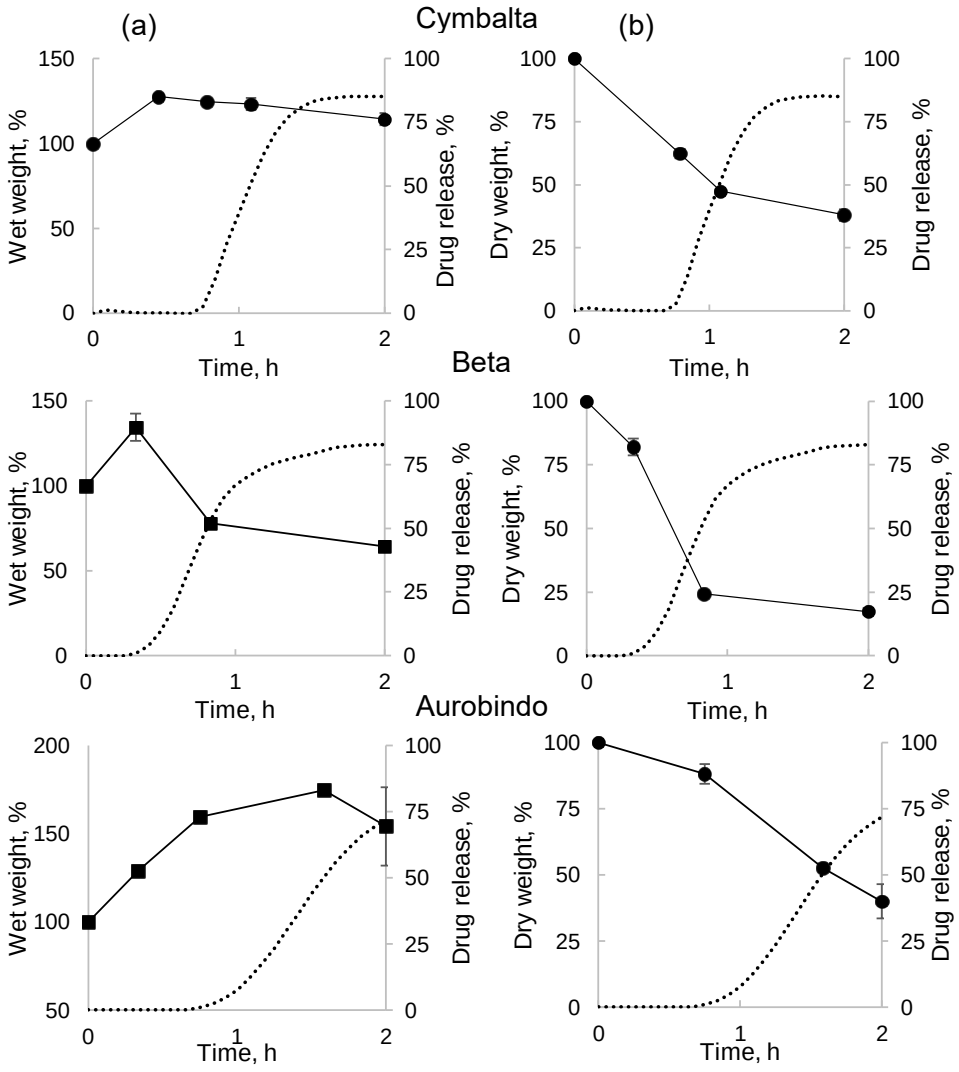

Fig. 15 (a) Wet and (b) dry weight of and release (dashed line) of commercial duloxetine products in 20% ethanol.

3.2.2 Commercial products of doxazosin mesylate

Doxazosin is an antagonist on adrenergic α-1 receptors and used in the therapy of hypertension [276]. Osmotic tablets of doxazosin mesylate have first been patented in 1989 [277], nearly ten years after the introduction of doxazosin [278].

Fig. 16 Pictures of a Cardular PP tablet, (a) top view, uncut, (b) lateral view, cut. The orifice for osmotic release is visible below the X in (a). The push (red) and the pull layer (white) are visible in (b).

Cardular PP is a push-pull osmotic system, consisting of a cellulose-acetate coating surrounding a pull layer of NaCl, drug, HPMC and polyethylenoxide (PEO) and a push layer of HPMC and PEO. Iron (II, III)-oxide is included as coloring agent in the push layer (Fig. 16). The generic product Doxazosin AL consists of a matrix core of PEO surrounded by an Eudragit® L coating. Neither formulation is accompanied by a warning label against the consumption of ethanol.

For both formulations, release was higher in 20% and 40% ethanol compared to 0% ethanol (Fig. 17). As expected, there were only slight differences between 0.1 N HCl (0% ethanol) and PBS for the osmotic system, despite the higher solubility of doxazosin mesylate in acidic media [279]. Doxazosin AL, however, released very differently, resulting from the dissolution of the enteric Eudragit® L coating.

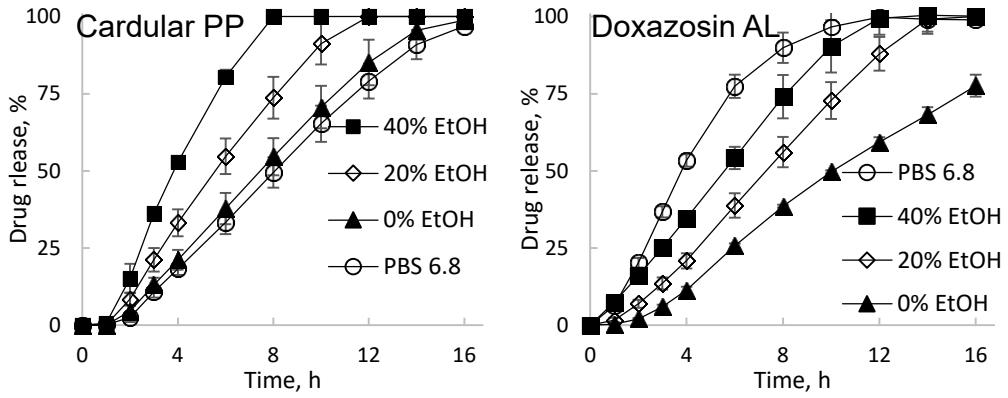

Fig. 17 Release of doxazosin mesylate from Cardular PP or Doxazosin AL in 0, 20 or 40% ethanol or PBS buffer 6.8.

The accelerated release of both formulations in hydroethanolic media resulted from the interaction of ethanol with the coating material. Eudragit® L does not dissolve like it does in PBS 6.8 but disintegrates substantially (Fig. 12). A similar behavior was seen for the cellulose acetate coating of Cardular PP (Fig. 18), where the coating seemed to disintegrate and pull together (white coloring on the tablet side). Interestingly, neither the disintegration of Eudragit® L nor that of cellulose acetate led to rapid release. This was due to the hydrophilic matrix formers, which are less affected by the presence of ethanol (Chapter 3.3.1, P. 68). This behavior will likely not extend to other osmotic tablets without hydrophilic matrix formers.

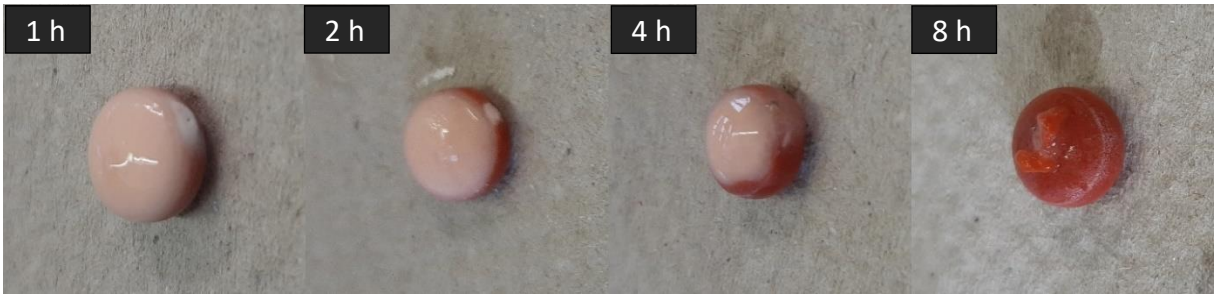

Fig. 18 Pictures of Cardular PP tablets after immersion in 40% ethanol. The white coloring seen e.g., in the red part in the 2 h picture are likely the remnants of the cellulose acetate coating.

As mentioned previously, osmotic tablets did not show accelerated release in-vivo [159], which contradicts these in-vitro results (Fig. 17). This can be attributed to the difference in study design. The patients of the study took the ethanol at the beginning and thus the ethanol will be diluted and absorbed over time. The lag time observed in-vitro may be sufficient to avoid dose dumping in-vivo and would comply with the FDA recommendation for 2 h testing [166]. The slight increase observed in-vivo may result from the disintegration of the coating, resulting in an exposure of the polymer former to the intestine, potential motility forces and accelerated release, as well as different tablet compositions and drug solubilities. Therefore, certain types of OROS do not result in in-vivo dose dumping despite accelerated release in-vitro.

A direct comparison between Cardular PP and Doxazosin AL showed the different release behaviors in 0% ethanol and PBS 6.8 resulting from the enteric coating (Fig. 19). In-vivo this difference may not be seen, due to the transition from acidic media in the stomach to the neutral medium in the intestine and thus the dissolution of the Eudragit® L. However, the variability of the stomach transit may cause problems that affect the difference in release. The release in 20%

ethanol was similar for both formulations, whereas in 40% ethanol Cardular PP releases faster. As both coatings disintegrate at this concentration, this may be explained by differences in the matrix part of the tablet.

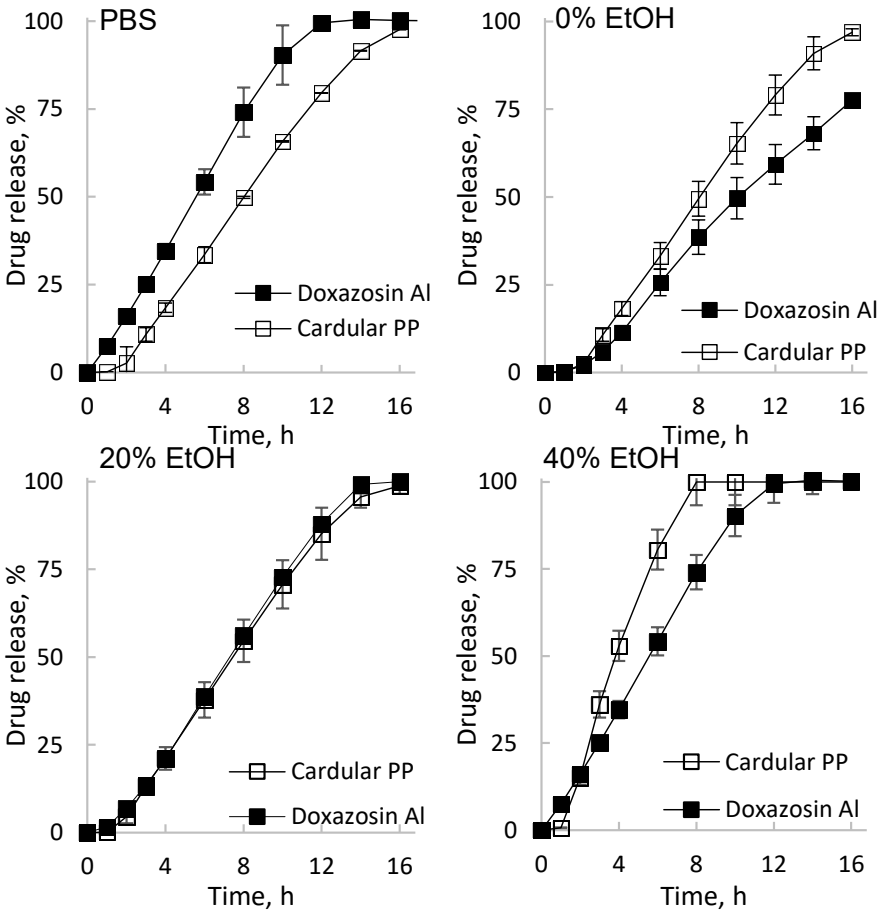

Fig. 19 Release of doxazosin mesylate from Cardular PP or Doxazosin AL in PBS buffer 6.8 or 0.1 N HCl containing 0, 20 or 40% ethanol.

The performance of commercial products in hydroethanolic media depended strongly on the type of system. The enteric products all showed different behaviors and the likelihood of observing an accelerated release in-vivo is, potentially except for Duloxetine 1A Pharma, very high. In contrast, the accelerated release of doxazosin tablets was less pronounced and would require extensive drinking over a longer period to have significant adverse effects.

3.3 The behavior of matrix tablets in hydroethanolic media

The main challenges associated with matrix tablets for release in hydroethanolic media are an increase in solubility of the drug and matrix-former and affected swellability of the matrix-former [29]. Matrix tablets show different release mechanisms depending on the type of polymer and the solubility of the drug [9, 280]. An increase in solubility of the drug can accelerate the release, an increase in solubility of the polymer may result in a near-immediate release. A higher medium uptake of the polymer can lead to faster dissolution of the drug and increase diffusion through the polymer [13], but may also close pores [174] or reduce medium penetration [2] due to swelling.

Different researchers have addressed the issue of matrix tablets in hydroethanolic media by varying e.g. the ethanol content [168], the drug type [169], the particle size [23] or the filler [186]. Some of these studies proclaimed accelerated release in 40% ethanol [23, 168], while others claimed robustness to hydroethanolic media [169, 187]. Thus, individual formulations can be stated as robust to hydroethanolic media but there is a lack of general guidelines or recommendations.

Thus, the object of this work was to identify the mechanisms with which ethanol accelerates release and how this can be mitigated by the choice of polymer or inclusion of excipients.

To assess the influence of solubility, different model drugs were chosen to account for different solubilities and ratios (Table 11). Hydroxypropyl methylcellulose (HPMC), polyethylenoxide (PEO) and hydroxypropyl cellulose (HPC) were chosen as hydrophilic polymers with different molecular structure and hydrophilicity. The influence of viscosity was evaluated by using three different grades of HPMC (K100LV, K4M, K100M). Ethylcellulose, Kollidon® SR and Eudragit® RS were chosen as insoluble polymers with different swelling behavior in aqueous media to reflect a broad spectra of possible release mechanisms.

Table 11 Solubility and solubility ratio of evaluated drugs [mg/ml] in 0.1 N HCl

Drug	0% EtOH	20% EtOH	40% EtOH	Ratio 40% / 0%
Metoprolol tartrate	> 1000		> 1000	-
Propranolol HCl	142.18	176.96	302.54	2.13
Paracetamol	7.63	34.65*	155.99	20.43
Theophylline	7.18	9.39	17.84	2.49
Carbamazepine	0.19	0.85*	3.76	19.97

* Value calculated according to equation 3

3.3.1 Hydrophilic polymers

The different drugs were tableted with the widely used HPMC K4M. Release of propranolol HCl and theophylline was independent of ethanol content (Fig. 20). Metoprolol tartrate showed slower release in 40% ethanol. Paracetamol and carbamazepine showed accelerated release in 40% ethanol.

The aqueous solubility influenced the release rate and -curve shape, but not the similarity. A high solubility ratio allows more drug to be dissolved inside the tablet and can thus increase the diffusion rate of the drug. A solubility ratio of 2.1 for theophylline or 2.5 for propranolol HCl was not sufficient to cause accelerated release and HPMC K4M is a suitable polymer for these types of drugs. Further experiments focused therefore on paracetamol and carbamazepine with a higher solubility ratio.

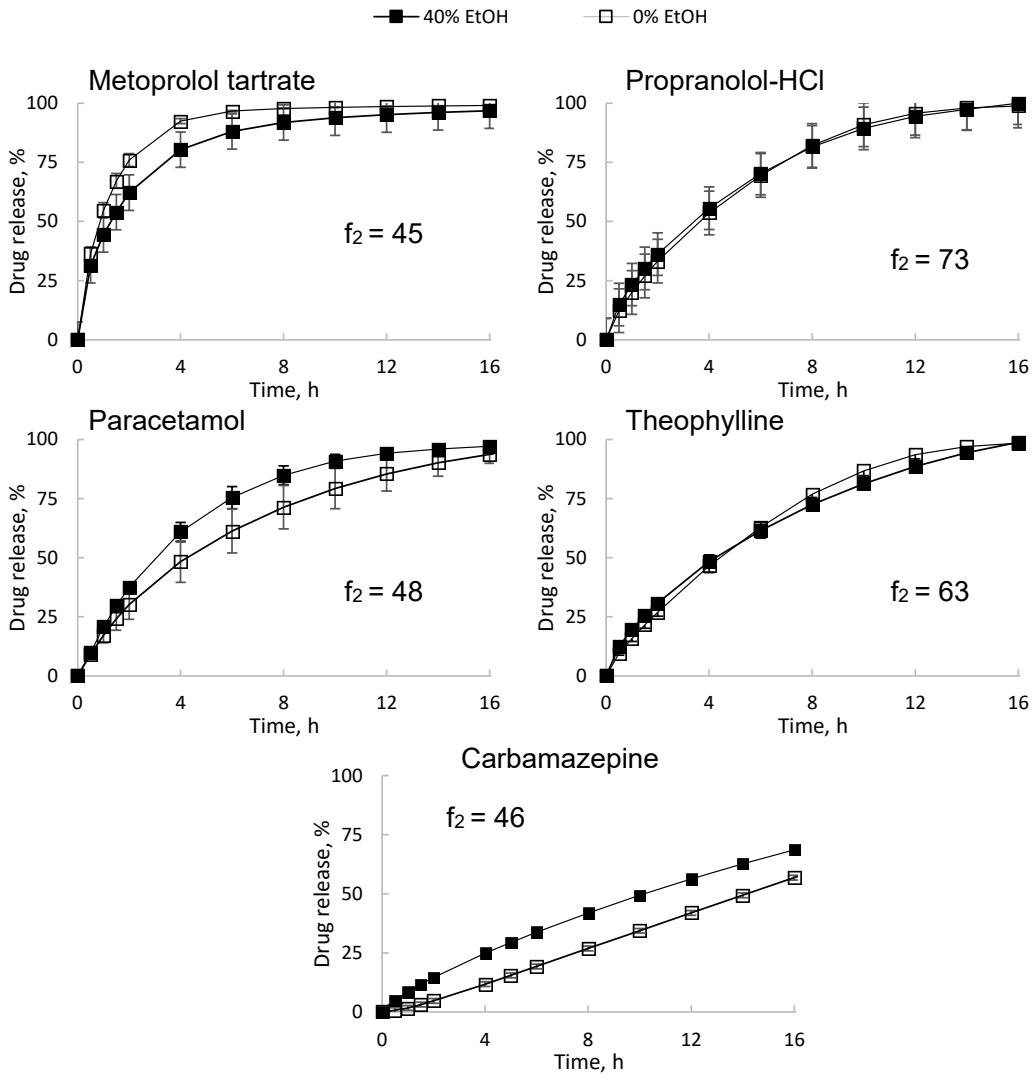

Fig. 20 Drug release from HPMC K4M tablets with different drugs in 0% or 40% ethanol.

3.3.1.1 Release of paracetamol

The release of paracetamol in 40% ethanol was accelerated from matrix tablets with all investigated viscosity grades of HPMC as well as PEO WSR 303. The release in aqueous media was fastest from HPMC K100LV and similar for the higher viscosity grades. For HPMC, an upper limit of viscosity has been identified, above which the diffusion coefficient is not reduced further [281]. The release from HPC MXF-containing matrix tablets was less affected and even slightly slower in 40% ethanol. Thus, it is a suitable polymer for avoiding accelerated release in ethanolic media for paracetamol. HPC is more hydrophobic than HPMC and may interact differently with ethanol, but it may also differ in its medium uptake behavior.

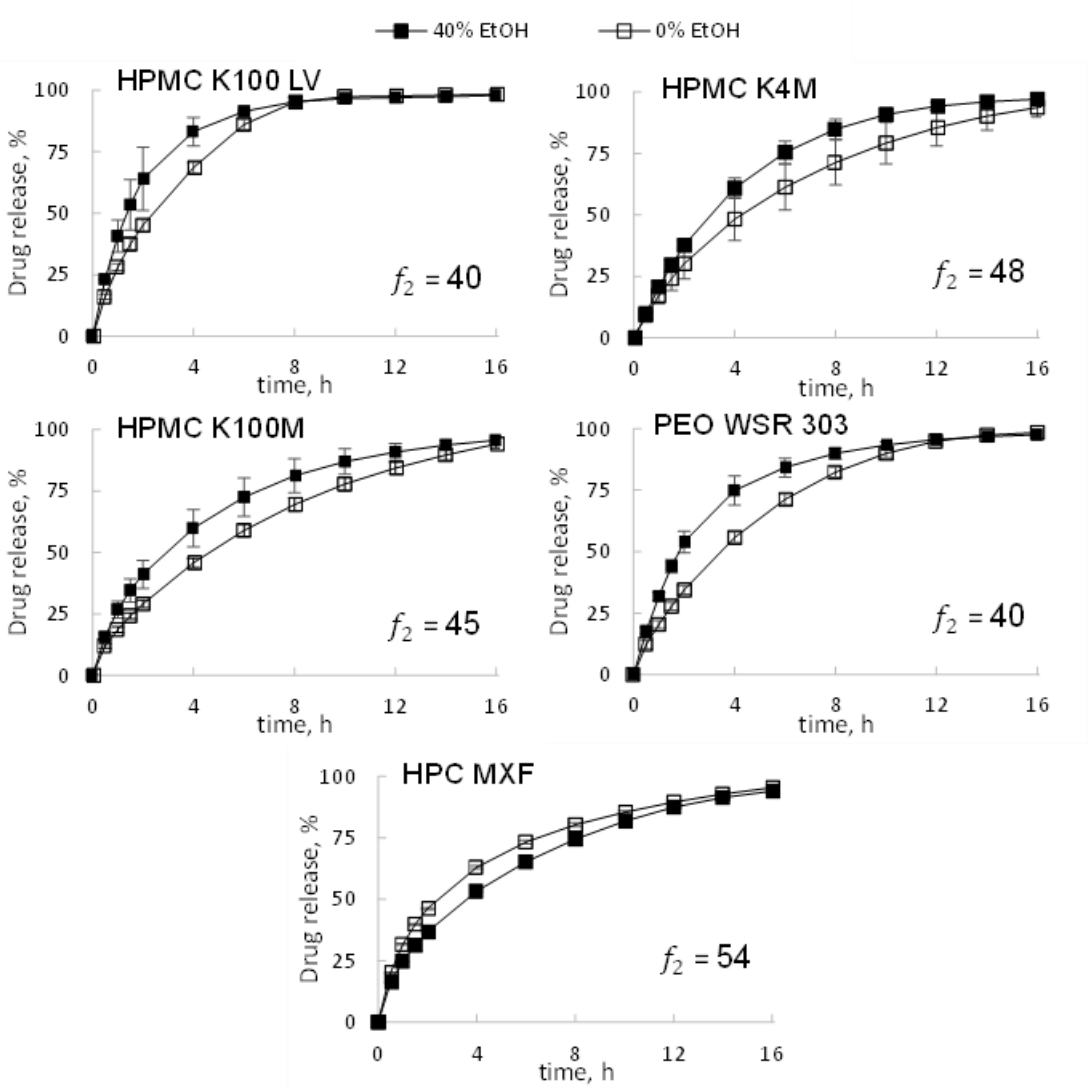

Fig. 21 Release of paracetamol from tablets containing hydrophilic matrix polymers in 0 or 40% ethanol.

3.3.1.2 Change of polymer properties in hydroethanolic media

The medium uptake is a part of the release mechanism and can depend on the release medium as well as the polymer(s) used for manufacturing of matrix tablets. The medium uptake of tablets consisting of pure polymers increased in the rank order: HPC MXF < HPMC K4M < PEO WSR 303 and was independent of the ethanol content in the medium (Fig. 22). The medium uptake of polymers depends on the molecular size, the hydrophilicity of the polymer as well as its three dimensional structure [282]. Larger molecules can bind more water before dissolving. The hydrophilicity and the three-dimensional structure affect the enthalpy upon mixing. HPC is less hydrophilic than HPMC due to the higher substitution grade [15, 20]. The substituted

hydroxypropyl groups, especially the multiple substituted, are more hydrophobic than the unsubstituted hydroxy groups present in the HPMC. PEO also erodes and dissolves in aqueous media [283]. Its molecular structure results in a hydrogen-bond acceptor, as the only hydroxy groups are at the ends of the chain [284]. With increasing molecule size, the ratio of hydrogen bond donor-to-acceptor decreases, resulting in a very low number of donors in the polymer. Accordingly, it has a higher affinity to water molecules, as there are very little intramolecular hydrogen-bonds which must be split prior to binding with water, especially in contrast to HPMC and HPC. The lower intramolecular bonding led to a larger heat of mixing when in contact with aqueous media [282], which resulted in a faster dissolution (Fig. 22b). A higher medium uptake was correlated with more accelerated release in 40% ethanol (Fig. 21). A higher medium content of the tablets allowed faster drug dissolution, and thus a higher diffusion gradient. As saturation effects are frequently found inside tablets [285], an increase in solubility will often increase the release.

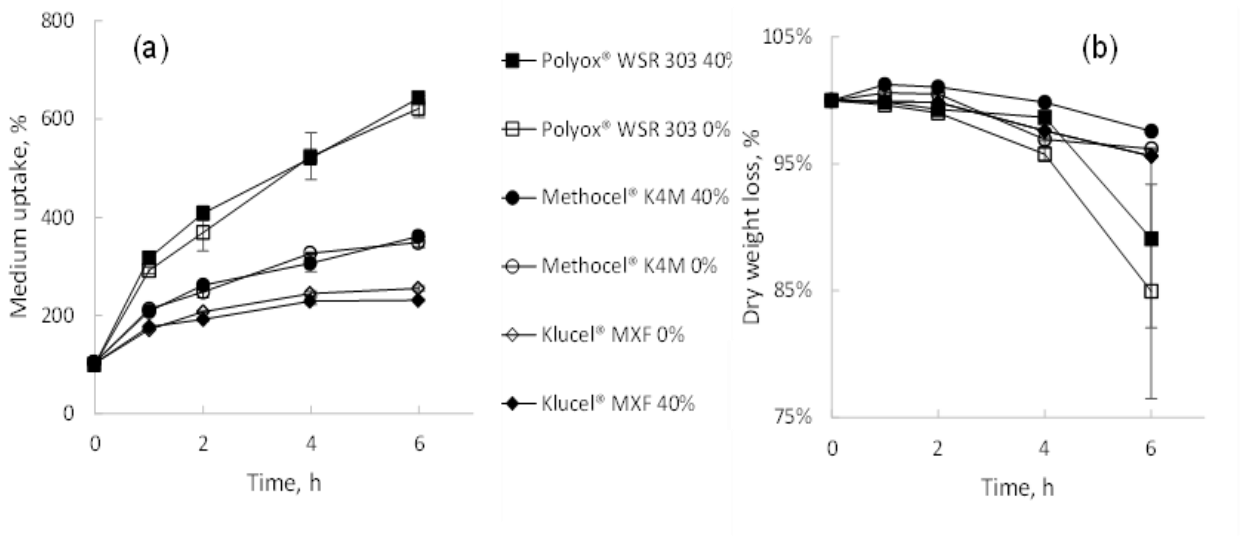

Fig. 22 (a) Medium content and (b) dry weight loss of drug-free polymer tablets after immersion in 0 or 40% ethanol. PEO WSR 303 tablets disintegrated after 4 hours, leading to high dry weight variability.

The dry weight loss was slightly faster in 0% ethanol but differed only little between the polymers. Dry weight loss often decreases when the viscosity is increased [286], as the polymer dissolution depends on the diffusion, which is lower for larger molecules and at higher viscosity. Ethanol can increase the viscosity of HPMC gels [168, 184], which may explain the slower dry weight loss in hydroethanolic media. The dry weight loss is also affected by the hydrodynamic conditions [104].

Thus, in a different experimental set-up, the extent of dry weight loss between these polymers may be increased.

Besides drug dissolution, polymer relaxation is necessary for accelerated release [13]. The size expansion of tablets of HPMC K4M was larger in 0% ethanol compared to 40% ethanol (Fig. 23). Therefore, the gel structure in 40% ethanol is denser, likely increasing the resistance to diffusion.

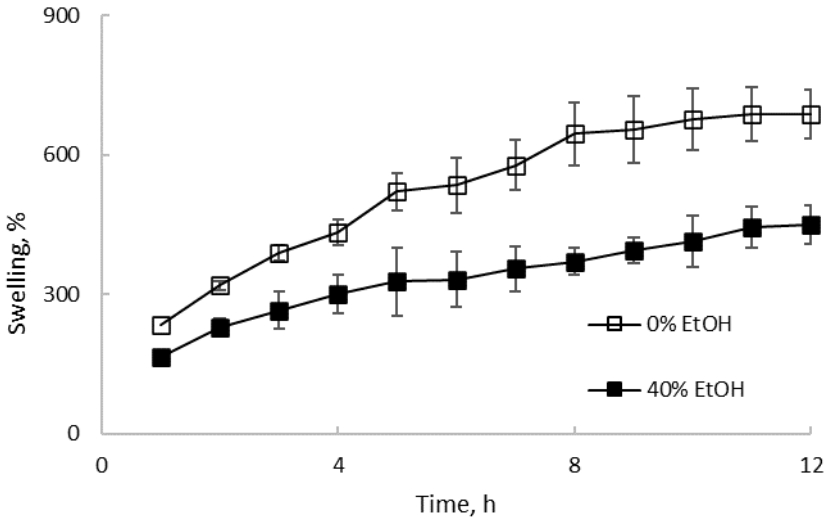

Fig. 23 Swelling of tablets of HPMC K4M after immersion in 0 or 40% ethanol.

This also resulted in a higher gel strength for hydroethanolic media compared to aqueous media (Fig. 24). Other researchers have also found a higher gel strength of HPMC tablets in hydroethanolic media [184] as well as an increase in viscosity for HPMC gels. A higher gel strength makes the tablet matrix more resistant to mechanical stress [104]. The shear viscosity of water-ethanol mixtures is larger than the viscosity of single components [287] and the self-diffusion of water is higher without ethanol. A “bell-shaped” curve of viscosity against ethanol content can be seen for most cellulose ethers [185]. This is attributed to a “dehydration” effect of ethanol. Increased ethanol-water interactions increase the inter- and intra- chain interactions of the HPMC. Thus, the mobility of the polymer molecules is lower in hydroethanolic media, resulting in the observed increased gel strength as well as in the reduced size-increase due to slower disentanglement. Interestingly, this did not negatively affect the medium uptake (Fig. 22).

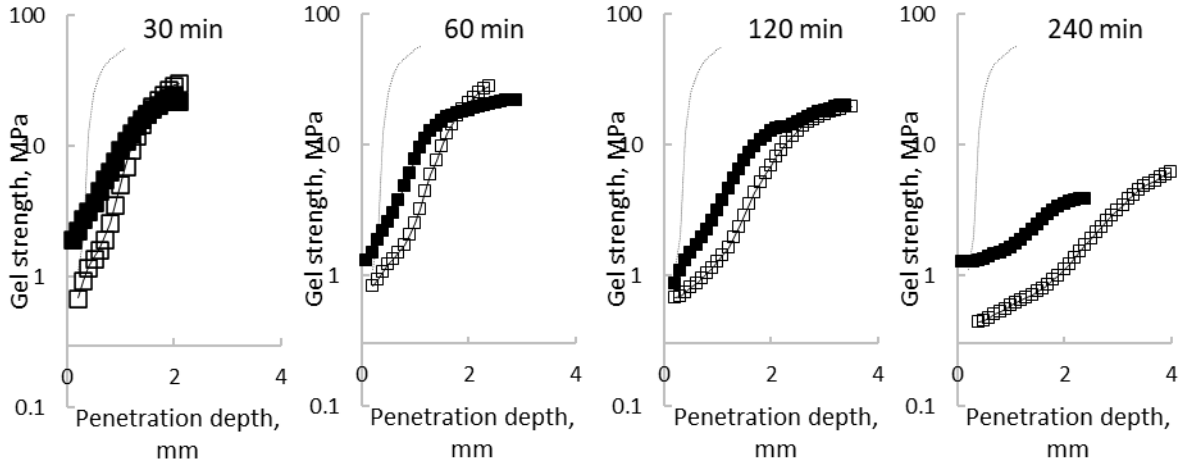

Fig. 24 Gel strength of HPMC K4M tablets after immersion in 0 or 40% ethanol. The dashed line shows the behavior of dry tablets.

A reduced mobility of the polymer will result in a slower diffusion. When omitting the dissolution step, the diffusion of paracetamol through a hydrated HPMC matrix was slower in hydroethanolic media (Fig. 25). However, the diffusion rate was similar for the first two hours before declining in 40% ethanol. This may be due to equilibration effects, where the water initially binds to the HPMC to a similar extent in both media, before reaching equilibrium and the faster disentanglement of the polymer chains takes place in 0% ethanol. This effect is likely to be dependent on tablet size. Thus, the accelerated dissolution of the drug is the critical aspect of HPMC matrix tablets in hydroethanolic media and drugs with a low solubility ratio will likely show similar or slower release for a sufficiently large tablet size.

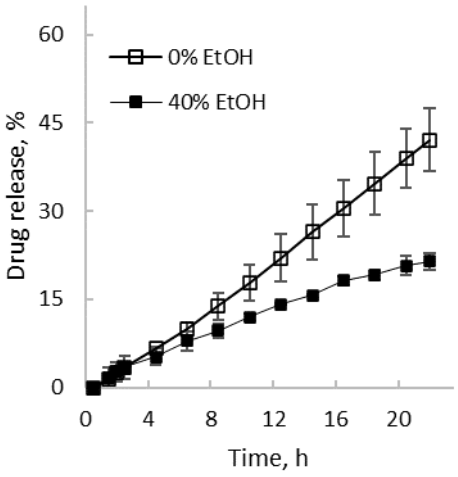

Fig. 25 Diffusion of paracetamol through a HPMC K4M-matrix tablet in a diffusion cell in 0 or 40% ethanol.

3.3.1.3 Influence of drug-polymer ratio on release of paracetamol in hydroethanolic media

Release from matrix tablets does not only depend on the type of polymer, but also on the amount of polymer. A lower amount of xanthan gum had a higher likelihood of burst release for theophylline in matrix tablets [23]. Thus, changing the amount of matrix polymer may lead to

different behaviors in hydroethanolic media. The release of paracetamol decreased when increasing the amount of matrix polymer from 30% to 50% for HPC, HPMC and PEO (Fig. 26). However, release only decreased further upon increasing the amount of matrix polymer from 50% to 70% for HPC, but not for HPMC and PEO. For some formulations, increasing the amount of matrix polymers did not change the release profile above a specific amount of matrix polymer [288]. It is likely, that this amount depends on the drug and differs with drug solubility, similar to the effect of coating level in extended-release pellets (Chapter 3.4.6, P. 110). Interestingly, the difference in release between 0% and 40% ethanol decreased for HPMC and PEO with an increase in polymer content. For HPC the difference was larger for 30% and 70% polymer compared to 50%. Thus, the “plateauing” effect of polymer content is different for the polymers. Tablets of HPMC and PEO reduced the release in 40% ethanol more at higher polymer contents than the release in 0% ethanol, whereas tablets of HPC showed the opposite behavior, leading to similar release at lower polymer amount. At low polymer amounts, matrix tablets are more affected by polymer disentanglement and erosion due to mechanical stress [104]. HPC showed a faster release in aqueous media if the mechanical stress is higher (Chapter 3.3.1.5, P. 78). At the higher polymer amount the resistance of the tablet to stress is higher, resulting in the faster release in hydroethanolic media. The opposite behavior was observed for HPMC tablets, which released slower in hydroethanolic medium at lower mechanical stress (Chapter 3.3.1.5, P. 78) and also for higher polymer amounts. This is supposedly a result of the different hydration speed. The faster release of HPC at 30% polymer content may be the result of a higher matrix porosity, due to the dissolution of the high amount of paracetamol.

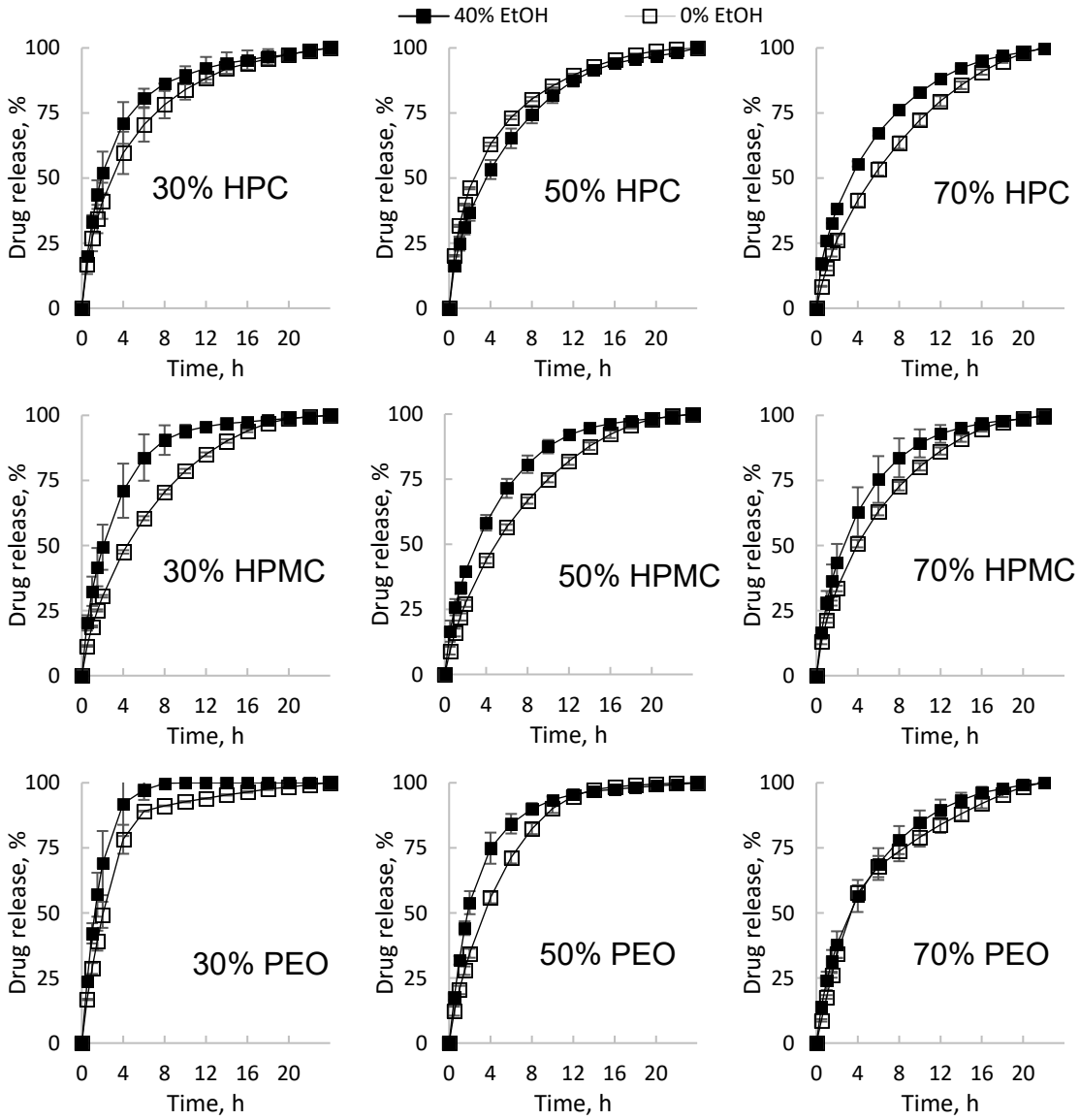

Fig. 26 Release of paracetamol from matrix tablets of different matrix polymers and matrix-polymer amounts in 0 or 40% ethanol.

3.3.1.4 Influence of fillers on the release of paracetamol from hydrophilic matrices

The addition of fillers is common in tablet manufacturing and can affect the release. Soluble fillers increase the diffusion rate by reducing the tortuosity and increasing the porosity of the polymer network. Insoluble fillers can disturb the polymer entanglement and accelerate erosion [9]. Lactose as a soluble and microcrystalline cellulose (MCC) as an insoluble filler were investigated with HPMC K4M tablets. The solubility of lactose decreases with increasing ethanol content

($S_{0\%}$=209.3 mg/ml, $S_{20\%}$=84.2 mg/ml, $S_{40\%}$=41.2 mg/ml). Some unspecific effects associated with dilution of either drug or matrix former by inclusion of fillers also needed to be considered.

Since the inclusion of a filler inevitably leads to a reduction of either drug or matrix polymer, both combinations were assessed. Substituting the polymer with filler increased the release rate in aqueous and hydroethanolic media (Fig. 27). Lactose increased the release rate more than MCC.

Both MCC and lactose reduced the difference in release by accelerating the release in aqueous media more than in hydroethanolic media. This acceleration was faster for lactose than for MCC due to the higher porosity resulting from the dissolution of lactose. This contrasts with a publication, which claimed better ethanol resistance for MCC compared to lactose [177]. Since, in this publication, the particle size of drug, polymer and filler are not specified, it is possible that the observed difference may be due to a rapid initial release.

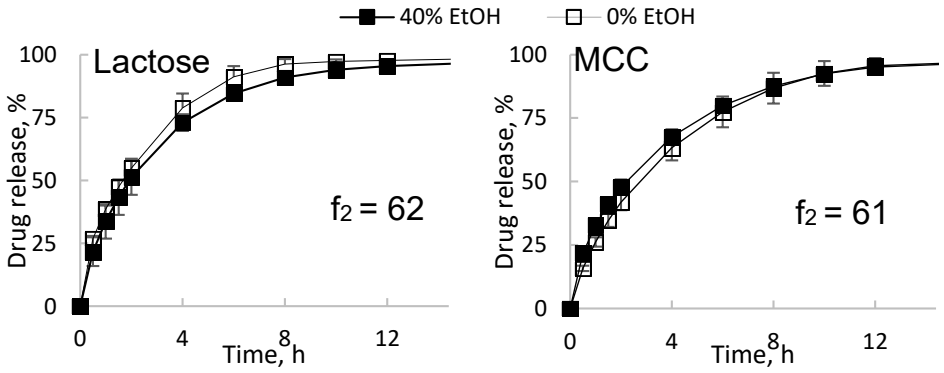

Fig. 27 Release of paracetamol from a tablet consisting of 49.5% drug, 24.25 % HPMC K4M and 24.25% of lactose or MCC in 0 or 40% ethanol.

When substituting the drug with filler, the release rate was also increased (Fig. 28). Interestingly, the release was similar, irrespective of the filler. Thus, the matrix polymer determines the release at these concentrations. This conforms to previous reports, which claimed that the type of diluent does not change the release profile above a certain polymer amount [288].

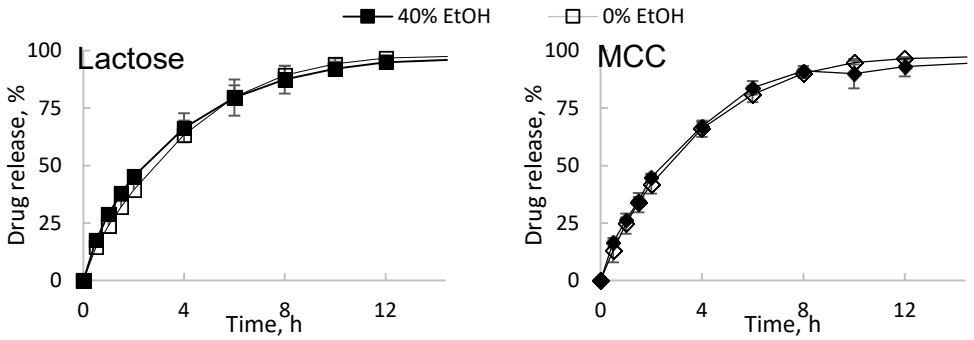

Fig. 28 Release of paracetamol from a tablet consisting of 24.25% drug, 49.5 % HPMC K4M and 24.25% of lactose or MCC in 0% or 40% ethanol.

To confirm the effect of lactose against accelerated release in ethanol, the diffusion of dissolved paracetamol through matrix tablets of HPMC K4M and lactose was investigated. The release rate was faster in 0% ethanol and slower in 40% ethanol compared to the pure HPMC tablet (Fig. 29). This may result from the different solubilities, i.e., more medium is needed to dissolve the lactose in 40% ethanol.

Thus, the inclusion of lactose is a suitable approach against a different, faster release in hydroethanolic media.

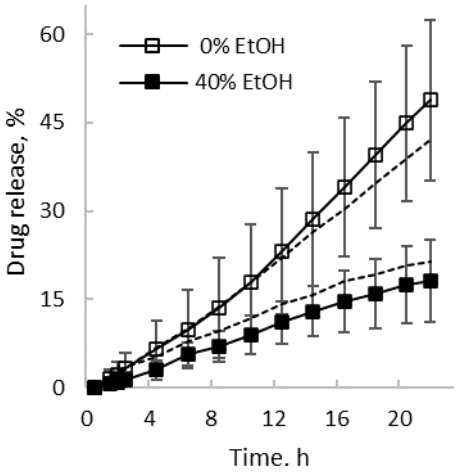

Fig. 29 Diffusion of paracetamol through a HPMC-lactose-matrix tablet in a diffusion cell in 0% or 40% ethanol. The dashed line indicates the release in a pure HPMC tablet without lactose.

The applicability of fillers for other polymers was assessed using a more realistic tablet composition with 30% drug, 35% matrix polymer and 33% filler.

Tablets of PEO WSR 303 and HPMC K4M with lactose showed similar release behavior at 0, 20 and 40% EtOH. The release from HPC MXF was inversely proportional to the ethanol content and no longer similar (20% EtOH: f_2=45, 40% EtOH: f_2=36). Thus, the addition of lactose increases release in aqueous media more than in hydroethanolic media and may even lead to a more rapid release in aqueous media compared to hydroethanolic media.

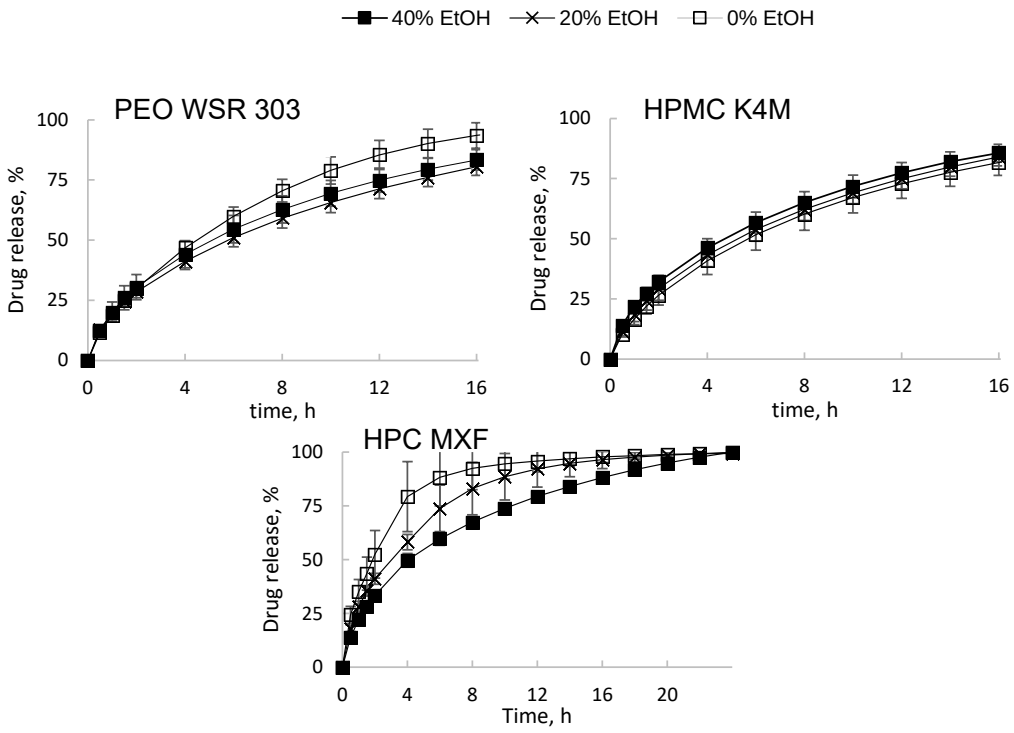

Fig. 30 Release of Paracetamol from a tablet consisting of 35% matrix polymer, 30% paracetamol and 33% lactose in 0, 20 or 40% ethanol.

3.3.1.5 Influence of agitation on the release in hydroethanolic media

There is evidence suggesting that ethanol intake can reduce gastrointestinal movement, especially for chronic alcohol abuse [289]. This would lead to a reduction in mechanical stress on the dosage form and may affect the release rate [290].

Tablets of HPC MXF showed accelerated release in 0% ethanol when immersed in a paddle apparatus (Fig. 31). The density of the medium with 0% ethanol is higher than with 40% ethanol, resulting in a higher likelihood of tablet swimming, which was seen during the release testing. The tablet was therefore subjected to increased hydrodynamic motility in the release vessel and a faster removal of dissolved drug, lactose, or polymer in the diffusion layer around the tablet. Switching to a basket method decreases this hydrodynamic mobility in 0% ethanol and also the release. It is, however, still larger than that of 40% ethanol. Placing the tablet in a diffusion cell results in a change of release behavior with a slightly faster release in 40% ethanol. The poor

hydrodynamic conditions inside the diffusion cell led to a near zero-order release in 0% ethanol, whereas the higher solubility in 40% resulted in an initially faster release.

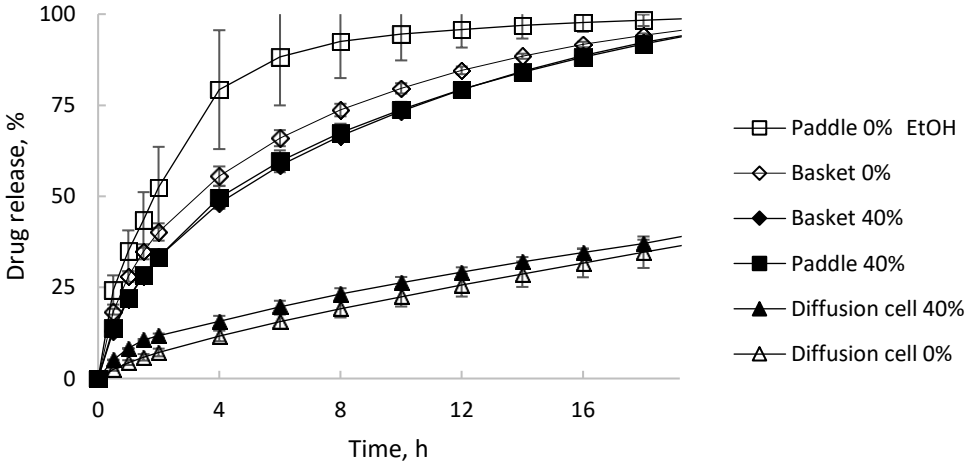

Fig. 31 Release of paracetamol from matrix tablets of HPC MXF and lactose from different release-testing set-ups in 0 or 40% ethanol.

Interestingly, the same behavior was not observed for HPMC K4M tablets (Fig. 32), where the release was slightly faster from a paddle apparatus in 40% ethanol and slightly slower in a diffusion cell. The difference to HPC MXF in the paddle apparatus has been explained earlier (Chapter: 3.3.1.2, P. 70). The difference in the diffusion cell is a result of the different gel layer formation of the two polymers. A fast gelling of the polymer, as in the case of HPMC K4M, will reduce the medium penetration. HPC gels slower compared to HPMC [2] and as a result more medium may penetrate into the matrix and dissolve the drug. This difference was only visible in the diffusion cell set-up due to less hydrodynamic movement, which gives the polymer more time to hydrate before the drug or other excipients can diffuse away.

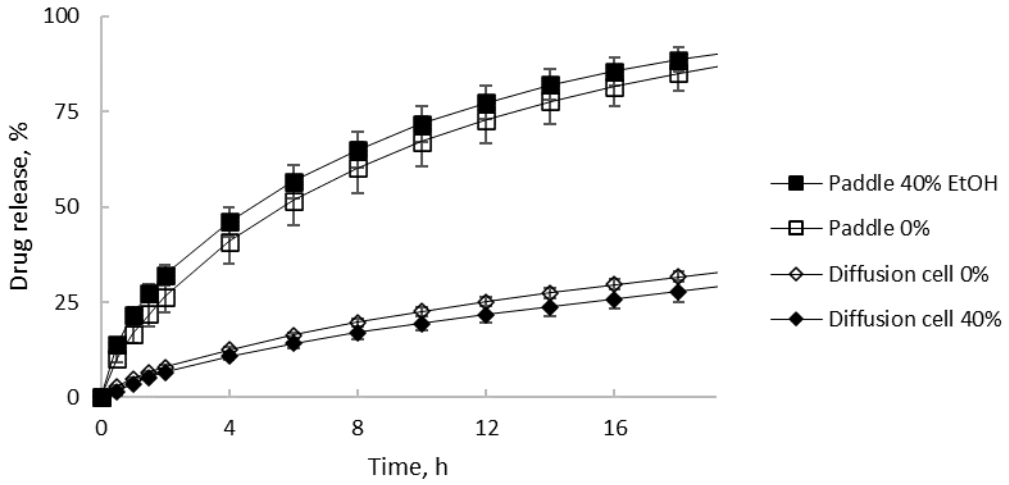

Fig. 32 Release of paracetamol from matrix tablets of HPMC K4M and lactose from different release-testing set-ups in 0 or 40% ethanol.

The influence of fillers may also change depending on the hydrodynamic conditions. A low agitation rate in a paddle apparatus led to an accelerated release in 40% ethanol, whereas the release was similar at higher agitation rates (Fig. 33). The difference was bigger if MCC was used as a filler compared to lactose. As pointed out earlier (Chapter: 3.3.1.4, P. 75), MCC acts by disturbing the gel formation. This effect is likely to be more pronounced at higher agitation rates, as polymer erosion increases with agitation rate [104]. At 10 rpm, the release in 40% ethanol is similar for MCC and lactose, but the release in 0% ethanol is lower for MCC compared to lactose. At 75 rpm, the release is similar for both MCC and lactose as well for 0% and 40% ethanol. Thus, MCC appears to be more affected by the agitation rate than lactose.

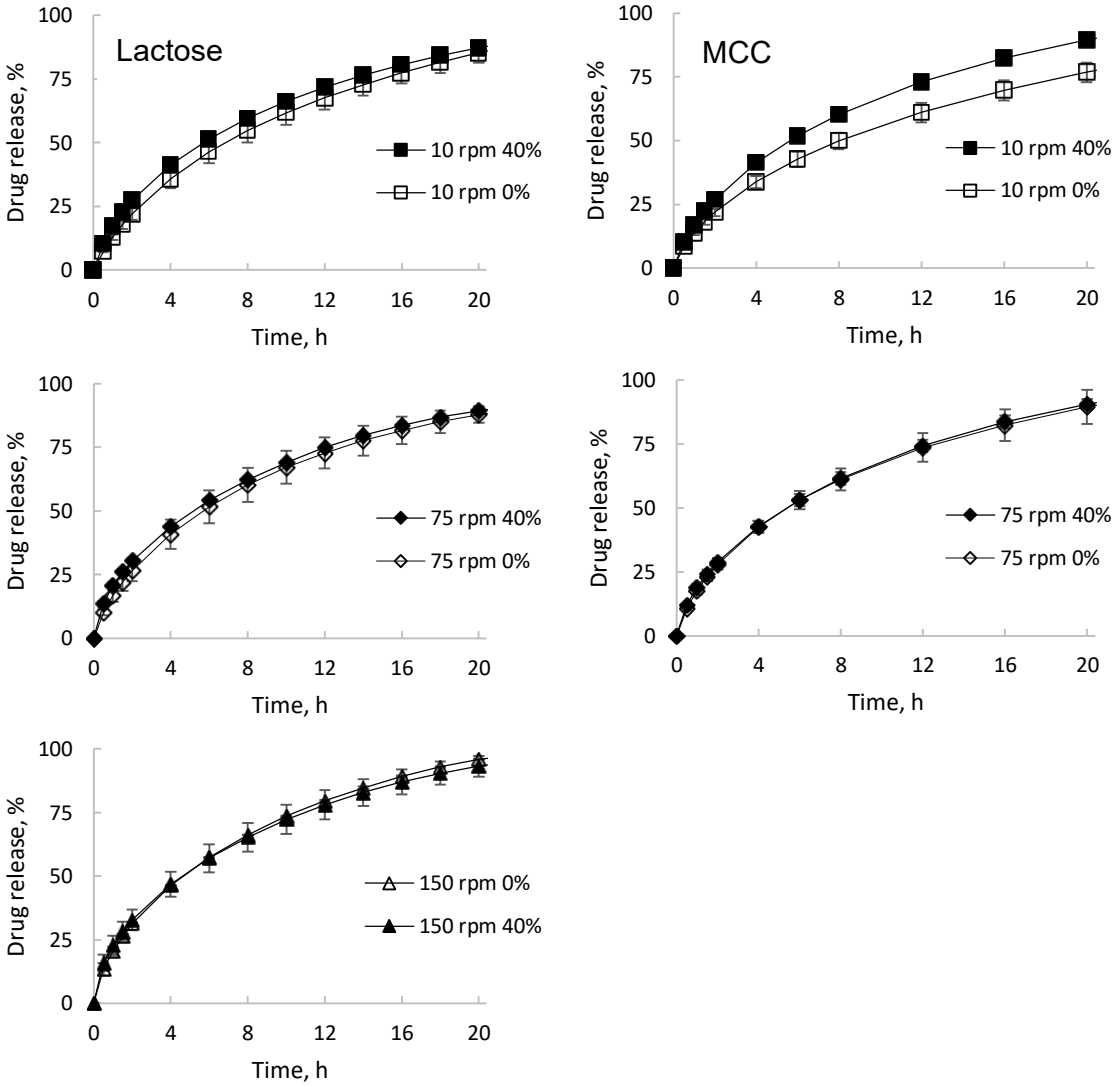

Fig. 33 Release of paracetamol from matrix tablets of HPMC K4M and filler in a paddle apparatus at different rpm in 0 or 40% ethanol.

3.3.1.6 Release of carbamazepine from hydrophilic polymers

The release of poorly soluble drugs from erodible tablets in aqueous media occurs predominantly via erosion [280]. Nevertheless, the release from erodible matrix tablets with HPMC K4M or K100M, PEO WSR 303 and HPC MXF was accelerated in hydroethanolic media also for carbamazepine (Fig. 34), which has a similar high solubility ratio.

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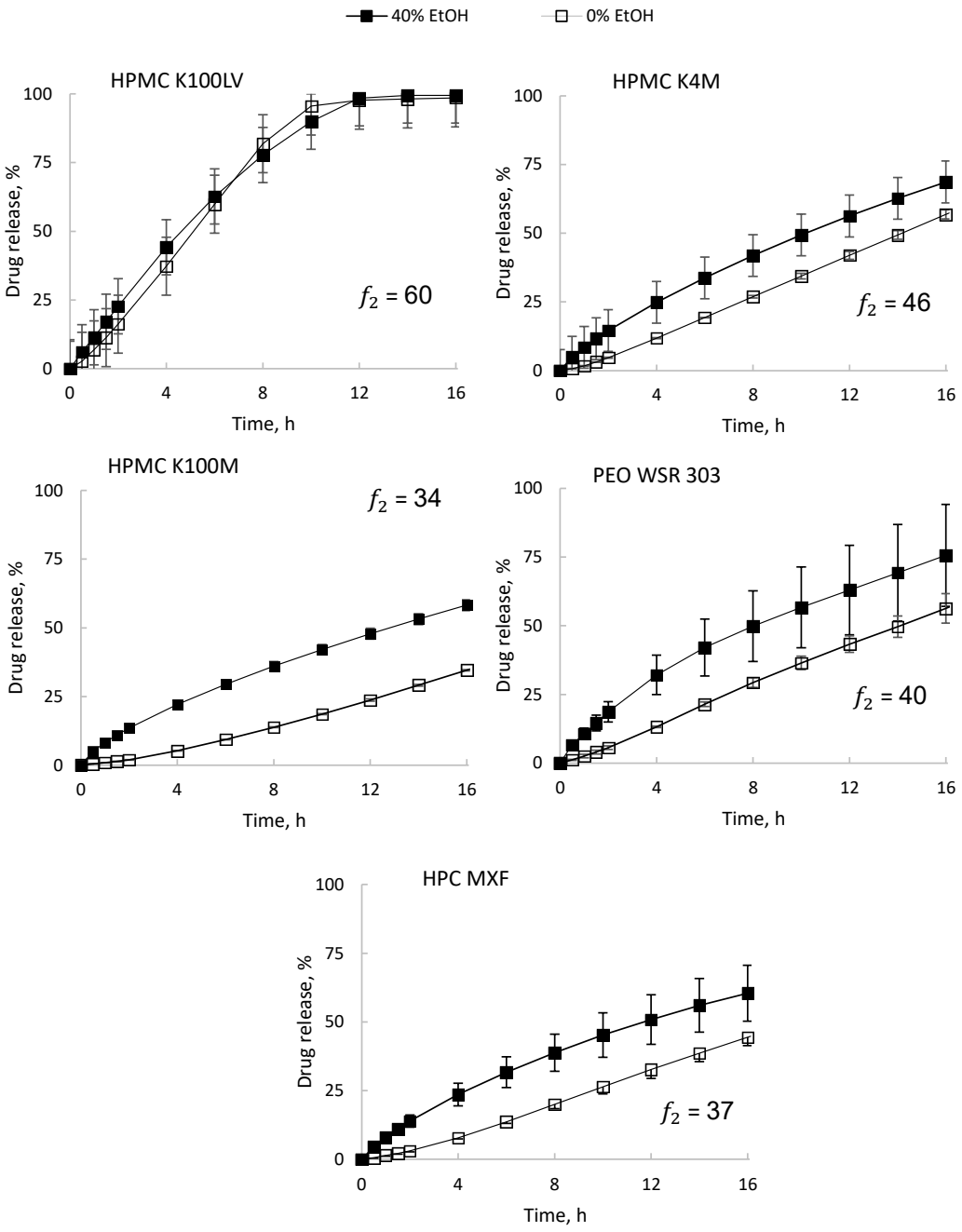


Fig. 34 Carbamazepine release from tablets containing hydrophilic matrix polymers in 0% or 40% ethanol.

The viscosity of HPMC had a substantial impact on the release behavior and tablets with a lower molecular weight (K100LV) released the drug completely within 10 h and independent of ethanol content in the medium. With an increase in polymer viscosity the release rate dropped. However, the release rate dropped more for 0% ethanol than for 40% ethanol as can be seen by a decrease

in similarity from HPMC K100LV to HPMC K100M. This may be due to a faster erosion of lower viscosity grades of HPMC [286]. HPMC K100LV led to complete release in 10 hours

The similarity for HPMC K100LV also held for drug-polymer ratios of 30:70 and 70:30 (Fig. 35). Thus, HPMC K100LV is a suitable polymer for ethanolic resistance of poorly soluble drugs. Evidently, the similarity between release in 0% and 40% ethanol increased with increased erosion, thus, release rate.

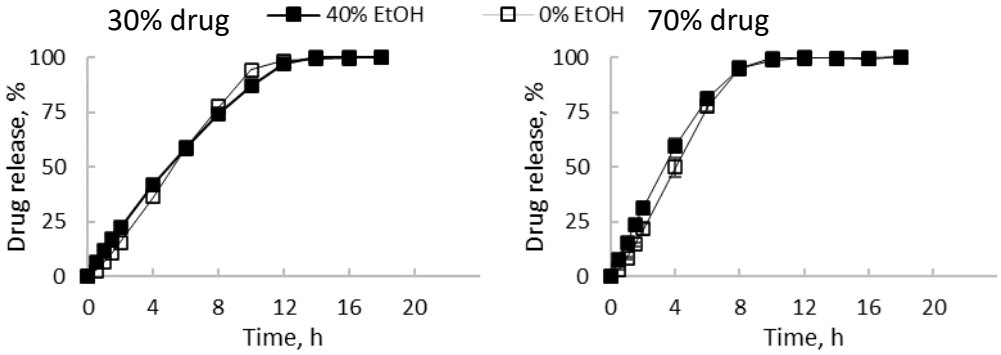


Fig. 35 Carbamazepine release from HPMC K100LV tablets at different ratios in 0 or 40% ethanol.

3.3.1.7 Visual observations of release

To confirm the increased diffusion in 40% ethanol, macroscopic evaluations of HPMC K4M tablets with both paracetamol and carbamazepine were conducted. The images confirmed a change in release behavior for carbamazepine (Fig. 36). As the polymer hydrated, the carbamazepine particles moved outwards with the polymer network to the eroded edge of the tablet. While the particles may change their size and shape in 0% ethanol, they generally reached the outside of the tablet where they left the polymer network and sedimented (Fig. 36a). In 40% ethanol the particles also moved outwards with the polymer, but due to the higher solubility, shrinked and dissolved before reaching the tablet boundary.

Including a coloring pigment in the tablet shows the extent of the polymer network (Fig. 36b). In 0% ethanol only a thin green layer without visible particles can be seen. This layer may be the stagnant boundary layer for the diffusion of the coloring agent and the polymer, or it may be the outer layer of the tablet where the polymer network is too loose to hold the carbamazepine particles. In 40% ethanol this particle-free layer is many times larger.

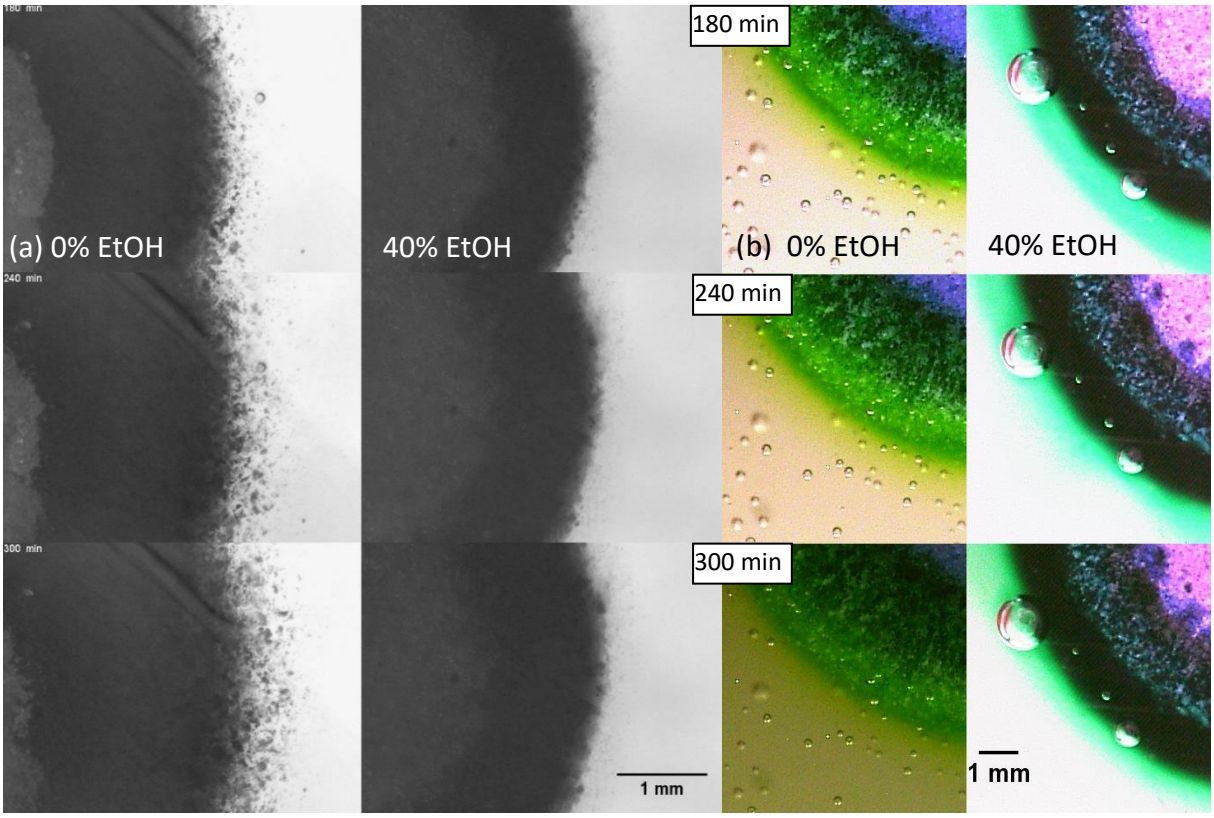


Fig. 36 Photographs of a HPMC K4M tablet with (a) 49.5% Carbamazepine using back lighting and (b) 48.5% Carbamazepine and 2% Patent Blue V with top lighting, placed between two transparent discs in 0 or 40% ethanol.

This was not observed for paracetamol (Fig. 37). The solubility of paracetamol is higher in both 0% and 40% ethanol than that of carbamazepine in 40% ethanol (Table 11). Thus, the solubility threshold where the release of visible particles can be seen is between 0.2 mg/ml and 3.8 mg/ml, i.e., between the solubility in 0% and 40% ethanol for carbamazepine.

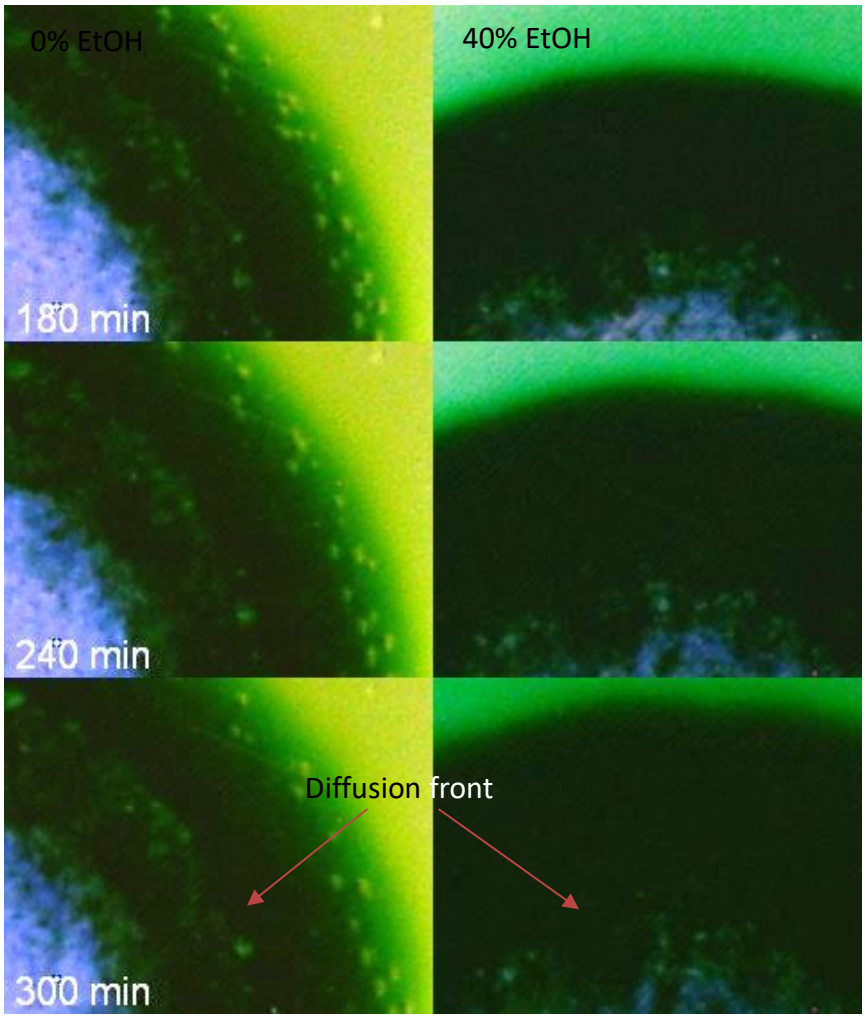


Fig. 37 Photograph of a HPMC K4M tablet with 48.5% paracetamol and 2% Patent Blue V with top lighting, placed between two transparent discs in 0%or 40% ethanol. The brightness was increased by 40%.

Different layers of the tablet are visible, especially for 0% ethanol. A more in depth explanation of the fronts in matrix tablets is given by Colombo et al [2]. The diffusion front, showing the difference between dissolved and undissolved drug, was moved further inwards in 40% ethanol. This implies, that more drug could be dissolved inside the tablet, which can be explained by the higher solubility of paracetamol in 40% ethanol.

This also resulted in a faster hydration of the tablet matrix with paracetamol in 40% ethanol (Fig. 38). HPMC alone hydrated slightly faster in 0% ethanol. Interestingly, substituting half of the paracetamol with lactose accelerated the hydration in 0% ethanol and slowed down the hydration in 40% ethanol. However, the latter may also result from a reduced amount of paracetamol.

Therefore, in hydroethanolic media, lactose does not only slow down the diffusion rate of the drug, but also does not increase the penetration rate of the medium.

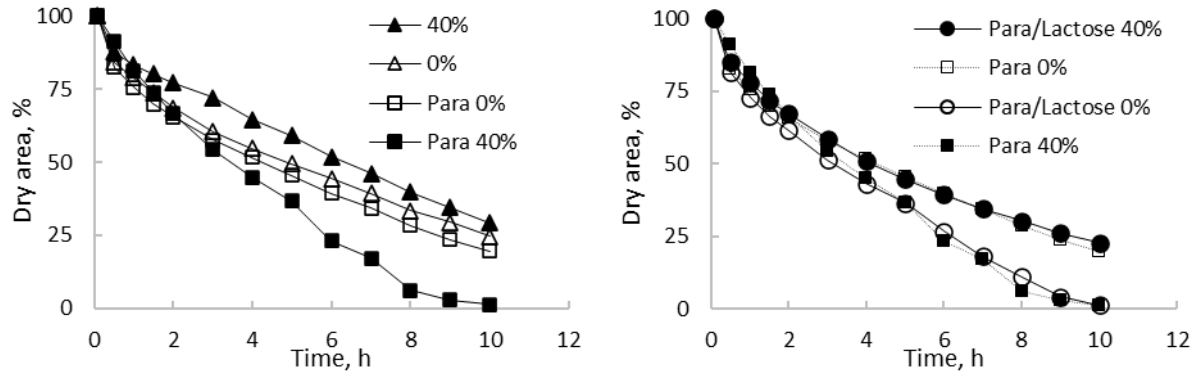


Fig. 38 Dry area of tablets of HPMC K4M with or without paracetamol and lactose in 0 or 40% ethanol

3.3.1.8 Mathematical evaluation of release

A mathematical treatment of release data according to equation 9 demonstrated, that the release mechanism of paracetamol did not change (Table 12). The %-release-via-diffusion did not vary significantly (t (26) =0.631; p=0.532) between 40% ethanol ($\bar{x}$=54.6, std = 21.8) and 0% ethanol ($\bar{x}$=50.0, std = 17.9). Paracetamol was released in a dissolved state in both 0 and 40% ethanol (Chapter: 3.3.1.7, P. 83), but the release rate is still affected by the hydration and disentanglement behavior of the polymer (k_2 in equation 9). Therefore, no clear trend regarding the %-release-via-diffusion could be observed for the more soluble paracetamol when increasing the ethanol concentration.

Applying the mathematical approach to carbamazepine, where the release mechanism in aqueous medium is mainly via erosion, confirmed a change in hydroethanolic medium, at least partially, to diffusion. The %-release-via-diffusion is significantly higher (t (11) =6.234; p< 0.0001) for 40% ethanol ($\bar{x}$=30.6, std = 13.7) than for 0% ethanol ($\bar{x}$=3.2, std = 1.7). This was due to the higher solubility, resulting in a faster dissolution of drug and, therefore, higher concentrations of drug available for diffusion. The %-release-via-diffusion in 40% ethanol increased with increasing viscosity for HPMC. This is due to the reduced erosion rate with increased viscosity [286]. A slower erosion rate allows more time for drug diffusion out of the polymer. Therefore, if the drug is

released via erosion, the viscosity of the polymer is critical to the performance in hydroethanolic media.

T**able 12** Effect of ethanol concentration on the mean-values of the f_2-value, the release exponent and regression coefficient from analysis of the release of paracetamol or carbamazepine from hydrophilic matrix polymers.

			HPMC K100LV		HPMC K4M		HPMC K100M		PEO		HPC	
	EtOH		40%	0%	40%	0%	40%	0%	40%	0%	40%	0%
Paracetamol	f_2-value		40.4		47.7		45.3		39.9		54	
	Values Peppas-Sahlin	k1	6.24	3.27	3.24	2.18	4.51	2.87	5.59	2.52	3.75	4.87
		k2	0.07	0.21	0.12	0.11	0.03	0.08	0.03	0.17	0.05	0.01
		R²	0.97	0.99	0.98	0.99	0.99	0.99	0.97	0.99	0.99	0.98
		% Diffusion	91	62	70	59	92	72	94	57	85	97
Carbamazepine	f_2=-value		60.3		45.8		33.7		39.5		36.8	
	Values Peppas-Sahlin	k1	0.01	0.01	0.64	0.01	0.92	0.04	1.15	0.05	0.89	0.01
		k2	0.31	0.27	0.12	0.11	0.08	0.07	0.12	0.11	0.09	0.09
		R²	1.00	0.97	1.00	0.98	1.00	0.96	1.00	0.99	1.00	0.98
		% Diffusion	7	5	31	2	45	5	46	5	43	2

* R² refers to the fit of the calculated release curve to the experimental data until 60% of drug is release

** as calculated with equation 10

3.3.1.9 Influence of fillers on the release of carbamazepine from hydrophilic matrices

For paracetamol, the inclusion of fillers resulted in similar release (Chapter: 3.3.1.4, P. 75). Applying this knowledge to carbamazepine resulted also in similar release with both lactose and MCC (Fig. 39). The %-release-via-diffusion increased from 0% to 40% for MCC (0: 1.7%; 40: 32.8%), but not for lactose (0: 65.5%; 40: 49.5%). Thus, lactose is a suitable filler in hydrophilic matrix tablets not only for paracetamol, but also for carbamazepine. It enables the drug to be released via diffusion even for poorly soluble drugs. MCC accelerated the erosion without changing the underlying release mechanism.

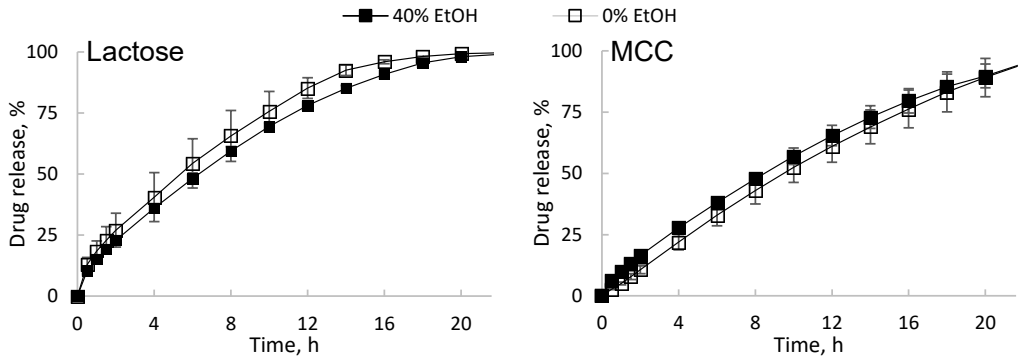


Fig. 39 Release of carbamazepine from a tablet consisting of 49.5% carbamazepine, 24.25 % HPMC K4M and 24.25% filler in 0 or 40% ethanol.

There are drawbacks associated with tablets relying on erosion for release, as the hydrodynamic conditions can greatly affect the release rate [102-104]. The knowledge of the behavior of different fillers enables different approaches to combine the resistance to hydroethanolic media and the resistance to mechanical stress.

3.3.2 Insoluble polymers

3.3.2.1 Release of paracetamol from insoluble polymers

Insoluble polymers differ from hydrophilic polymers, in that they do not dissolve. Release is thus only possible via diffusion and not via erosion.

Eudragit® RS was an unsuitable matrix polymer in hydroethanolic media as tablets prepared with this polymer disintegrated in 40% ethanol (Fig. 40).

The performance of the insoluble ethylcellulose in hydroethanolic media has been widely investigated as a coating material [24, 40], but not as a matrix former. The release of paracetamol from matrix tablets prepared with ethylcellulose was accelerated in 40% ethanol. Ethylcellulose is soluble in hydroethanolic mixtures above 50% ethanol [41] and can swell in media with lower ethanol content promoting release acceleration.

Kollidon® SR was previously successful as matrix former for tramadol, demonstrating similar release in hydroethanolic media [190]. This behavior was also confirmed for paracetamol with a higher solubility ratio (Fig. 40). Kollidon® SR is a combination of water and ethanol insoluble polyvinylacetate and soluble polyvinylpyrrolidone (PVP). Upon dissolution, PVP can, however, also increase the viscosity of the medium inside the tablets and thereby reduce the diffusivity [3]. The kinematic viscosity of a 5% PVP solution in 40% ethanol of 6.39 $\frac{mm}{s}$ was 2.5 times higher than that of 0% ethanol with 2.55 $\frac{mm}{s}$. Therefore, the diffusion in 40% ethanol is likely reduced by the presence of the PVP. Kollidon® SR is suitable to produce ethanol-resistant matrix tablets of paracetamol.

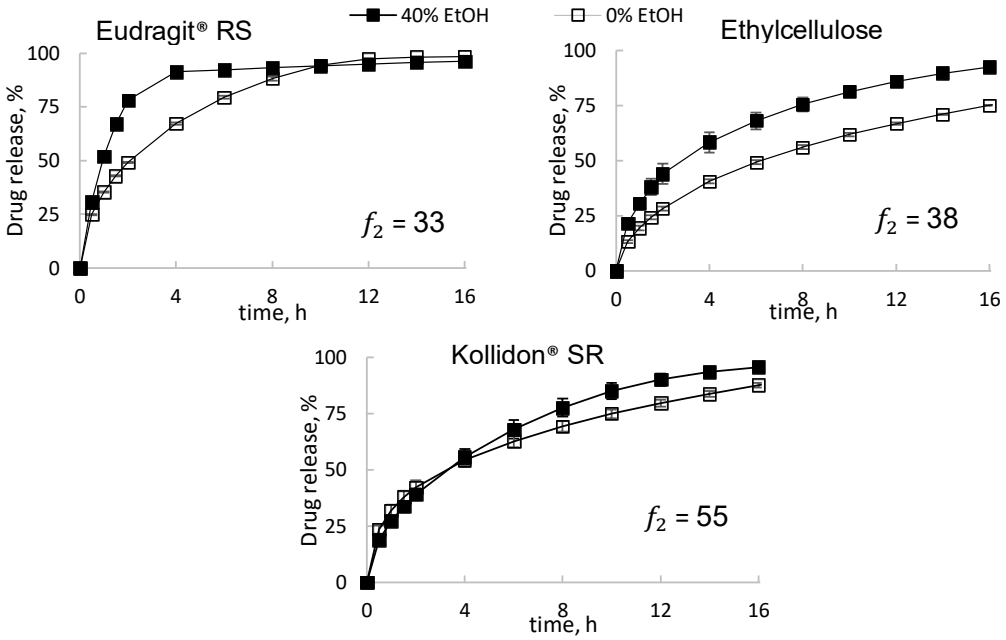


Fig. 40 Paracetamol release from matrices containing different hydrophobic polymers in 0 and 40% ethanol.

The different affinity of ethylcellulose and Kollidon® SR towards ethanol is reflected in the medium uptake (Fig. 41). Tablets of ethylcellulose took up more medium in 40% ethanol compared to 0% ethanol but remained insoluble. With a higher medium content in the tablets the diffusion is likely increased [13], which, however, can also be associated with swelling and a porosity reduction [174]. Tablets of ethylcellulose showed no signs of erosion in either medium and remain insoluble. The medium uptake of tablets with Kollidon® SR was higher in 0% ethanol and the tablets showed a larger amount of leaching, likely of the soluble PVP, compared to 40% ethanol. This supports the reduced diffusion of the PVP, specifically in 40% ethanol.

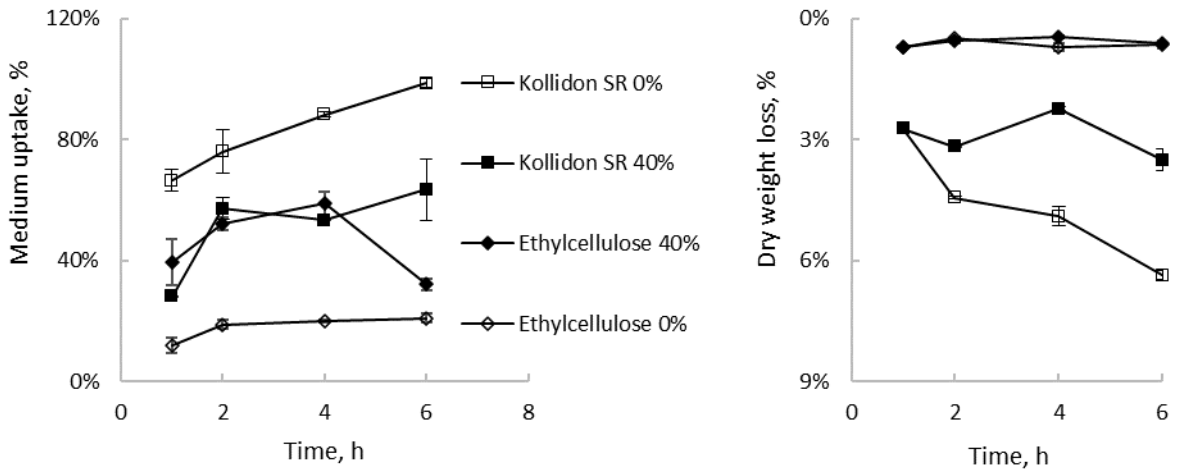


Fig. 41 Medium uptake and dry weight loss (leaching) of tablets of Kollidon® SR and ethylcellulose after immersion in 0 or 40% ethanol.

The release from insoluble polymers is based on percolation theory [3] and thus on the space between the matrix particles. Ethylcellulose is available in different particle sizes, which may also affect the release in 40% ethanol. The FP-grade is a micronized powder with a D50 of 5.2 µm and commonly used for matrix tablets. The non-FP standard grade of Ethocel® has a D50 of 164.3 µm. Using the non-FP grade accelerated the release of paracetamol (Fig. 42). The similarity, however, was reduced further (f_2=27). A larger particle size increases the release rate and the percolation threshold [291]. Thus, less drug must dissolve to create a connected network of pores. In tablets with Ethocel® FP this threshold is not passed, whereas it is likely passed in non-FP-tablets. A similar effect of rapid release with 40% ethanol was shown for xanthan gum [23]. The use of larger particle sizes is not a feasible approach to increase the similarity in release to 40% ethanol.

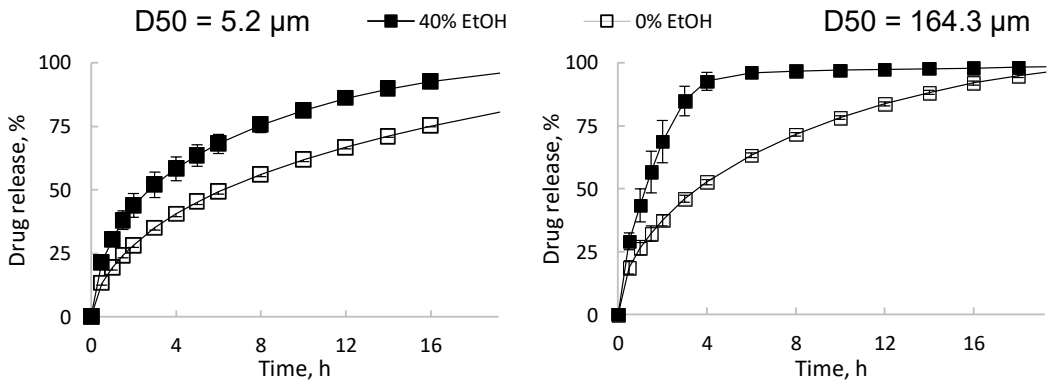


Fig. 42 Release of paracetamol from EC-matrices with different particle sizes in 0 or 40% ethanol.

3.3.2.2 Influence of fillers on the release of paracetamol from insoluble matrices

By inclusion of lactose and decreasing both drug and polymer in the formulation of ethylcellulose-tablets a similar release was achieved (Fig. 43). Interestingly, the release in 20% ethanol was even slower which can be explained by two opposing non-linear effects. One is the decreasing solubility of lactose, as described above, counteracting the increased solubility of paracetamol. The other is an increase in medium permeation of ethylcellulose with increasing ethanol content [23].

For Kollidon® SR, the inclusion of lactose reduced the matrix integrity leading to tablet disintegration in 0% ethanol. The tablets did, however, not disintegrate in 40% ethanol. While this formulation cannot be considered sustained release, there may be future applications to avoid immediate drug release if ethanol is present in the stomach.

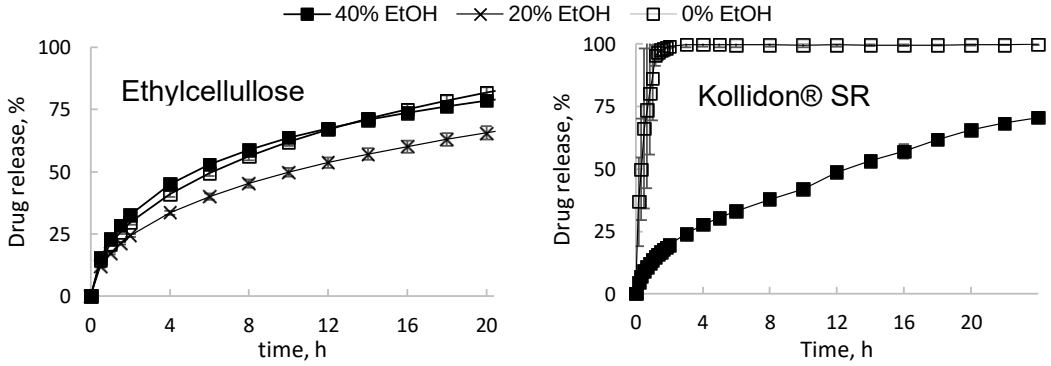


Fig. 43 Release of paracetamol from a tablet consisting of 35% matrix polymer, 30% drug and 33% lactose in 0, 20 or 40% ethanol.

3.3.2.3 Release of carbamazepine from insoluble polymers

For carbamazepine, both Kollidon® SR (f_2=32) and ethylcellulose (f_2=23) led to greatly accelerated release in 40% ethanol (Fig. 44). The low solubility of the drug in aqueous media resulted in a very slow release. The release in 40% ethanol was similar for both polymers, but the release in 0% ethanol from ethylcellulose was much slower than from Kollidon® SR. This is because of the diffusion driven release, which is obviously accelerated due to the remarkable increase in drug solubility in hydroethanolic media. Tablets of Kollidon® SR, despite the slower leaching of PVP in 40% ethanol (Fig. 10), led to a smaller difference, but a non-similar release, nonetheless.

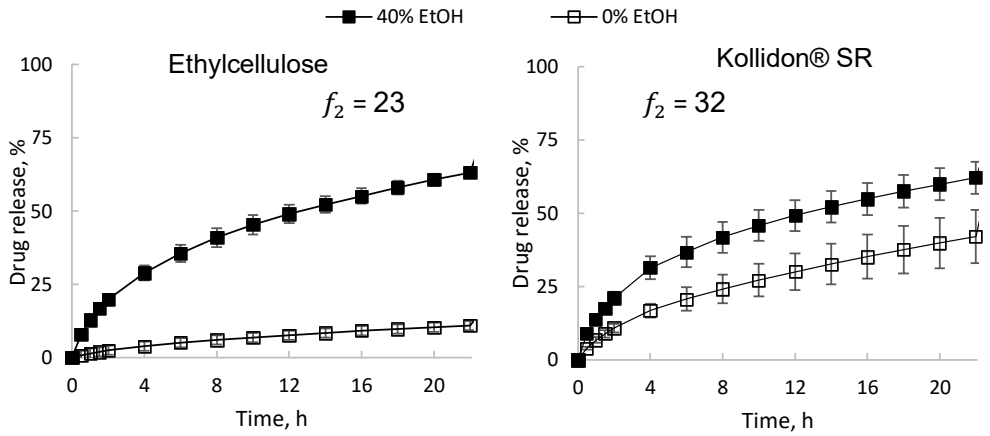


Fig. 44 Release of carbamazepine from tablets with insoluble matrix polymers in 0 and 40% ethanol.

The inclusion of lactose, as described for paracetamol, was not sufficient to achieve similar release profiles from either Kollidon® SR or ethylcellulose (Fig. 45). The addition of lactose led to an overall increase in carbamazepine release, however, did not improve the similarity for 0 and 40% ethanol.

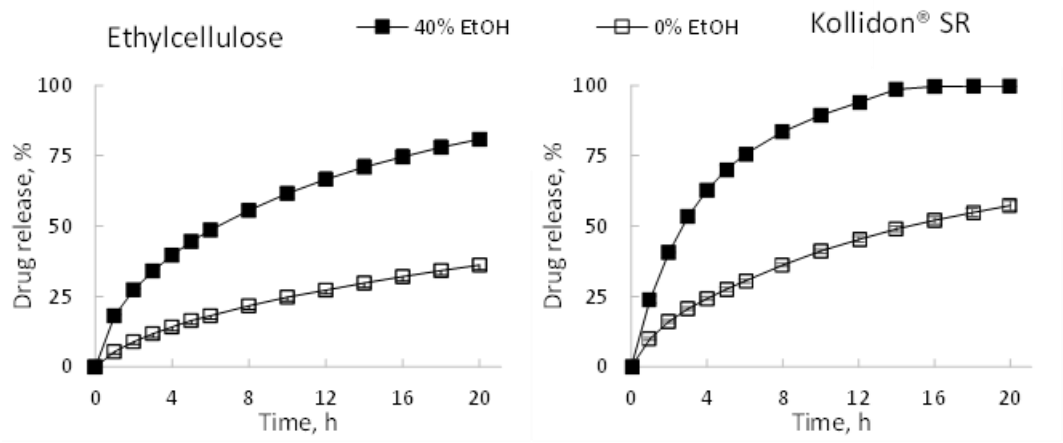


Fig. 45 Release of carbamazepine from tablets consisting of 30% drug, 35% matrix polymer and 33% lactose in 0 and 40% ethanol.

Even a further reduction in drug content to 10% with increasing lactose did not lead to similar release from Kollidon® SR (Fig. 46). Interestingly, this led to a further reduction in release in 0% ethanol but accelerated the release in 40% ethanol.

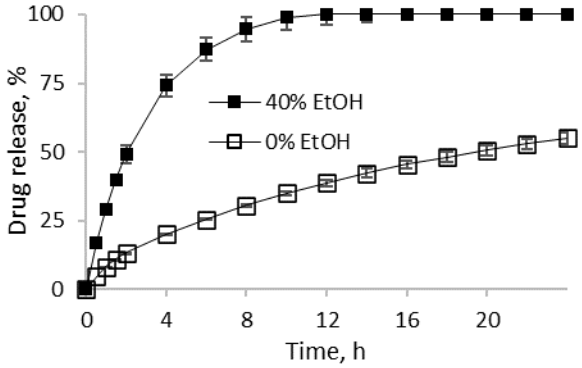


Fig. 46 Release of carbamazepine from tablets of 10% drug, 35% Kollidon® SR and 53% lactose in 0 and 40% ethanol.

The solubility and thus the dissolution of lactose is higher than that of carbamazepine in both media. This is in contrast to paracetamol, where the solubility compared to lactose is much higher in 40%. Thus, the equilibrating effect of lactose may be only given for drugs, which have a higher

solubility than the lactose itself. Insoluble polymers should not be used for ethanolic resistance of poorly soluble drugs like carbamazepine.

3.3.2.4 Release of metoprolol from insoluble polymers

As both tablets of ethylcellulose and Kollidon® SR performed differently depending on the solubility of the drug, they were additionally tableted with the highly soluble metoprolol tartrate. Tablets of ethylcellulose led to similar release (f_2=71), whereas tablets of Kollidon® SR showed faster release in 0% ethanol (Fig. 47). The release in 0% ethanol from Kollidon® SR is too rapid to be considered extended-release.

Interestingly, the tablets of Kollidon® SR disintegrated after 3 h in 40% ethanol but remained intact in 0% ethanol. This may be due to the presence of metoprolol inside the tablet in 40% ethanol, as in 0% ethanol the metoprolol is already completely released at this point. In the ethylcellulose tablets the metoprolol dissolved rapidly and left pores inside the polymer network. The higher medium uptake in ethylcellulose did not accelerate the metoprolol release, as the ethanol could also swell the ethylcellulose-chains and reduce the pore size. For a highly soluble drug like metoprolol, ethylcellulose is a suitable matrix polymer whereas Kollidon® SR is not suitable to achieve similar release.

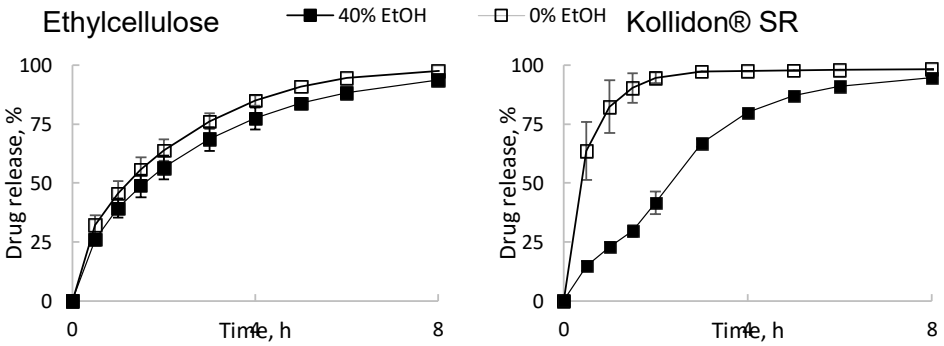


Fig. 47 Release of metoprolol from insoluble matrix polymers in 0 and 40% ethanol.

3.3.3 Conclusion

Drug with a high solubility ratio, e.g., a 20 times higher solubility in hydroethanolic media compared to aqueous media are likely to have an accelerated release from both hydrophilic and insoluble polymers. For the sparingly soluble paracetamol, a similar release can be achieved by using hydrophilic polymers with a low media content like HPC MXF or by including fillers such as lactose. The use of insoluble polymers leads to similar release if the polymer has a lower media uptake in hydroethanolic media or if lactose is included. For the very sparingly soluble carbamazepine, the higher solubility in hydroethanolic media can shift the release mechanism from erosion-dominated to diffusion-dominated. A similar release is only achievable using hydrophilic polymers with a high erosion rate or by combining hydrophilic polymers with fillers such as lactose. Both approaches may lead to a faster release, but this may be adjusted e.g., by varying the dosage form size. Insoluble polymers are not suitable to achieve similar release for a poorly soluble drug like carbamazepine. This new understanding will allow a more targeted approach to the issue of ethanol intake with matrix tablets.

3.4 The behavior of extended-release pellets in aqueous and hydroethanolic media

Another approach to achieve an extended-release formulation is by applying coatings to a drug-containing core. This allows the separation and independent formulation of (drug) core and (polymer) coating and the use of smaller formulation sizes. Coating a pharmaceutical dosage form can have many advantages, including moisture protection, avoiding drug-drug interaction or protection from light [292]. The use of insoluble polymers as coating materials further reduces the drug release, leading to an extended release of the drug.

3.4.1 Comparison of different coating polymers

Among polymers used for the formulation of extended-release (ER) pellets are the insoluble Eudragit® RS, Kollicoat® SR and ethylcellulose, which, however, differ in their swelling ability in release media. These provide sufficient retardation of drug release from coated pellets including freely soluble e.g., propranolol HCl. However, the release in hydroethanolic media can increase depending on core, coating material and the drug used.

To differentiate the swelling of coating and of core in the release medium, the behavior of untreated microcrystalline cellulose (MCC) cores was investigated (Fig. 48). The MCC cores swelled relatively fast in aqueous medium and slightly or remarkably slower in 20 and 40% ethanol, respectively. This can be explained by the different affinity of cellulose chains to water and ethanol. Water diffuses through the microfibril bundles of the MCC more effectively than ethanol [293], resulting in increased liquid-retention and swelling [294]. The swelling of the MCC core is a part of the release mechanism from coated pellets, resulting in stretching or (micro)rupturing of the coating [295]. The swelling rate was slower in hyperosmolar medium (i.e., with of addition 3% NaCl), but equated in extent the 30% swelling in isosmotic medium. The exception was medium with 40 % ethanol with nearly similar swelling behavior in both iso- and hyperosmolar media (Fig. 48).

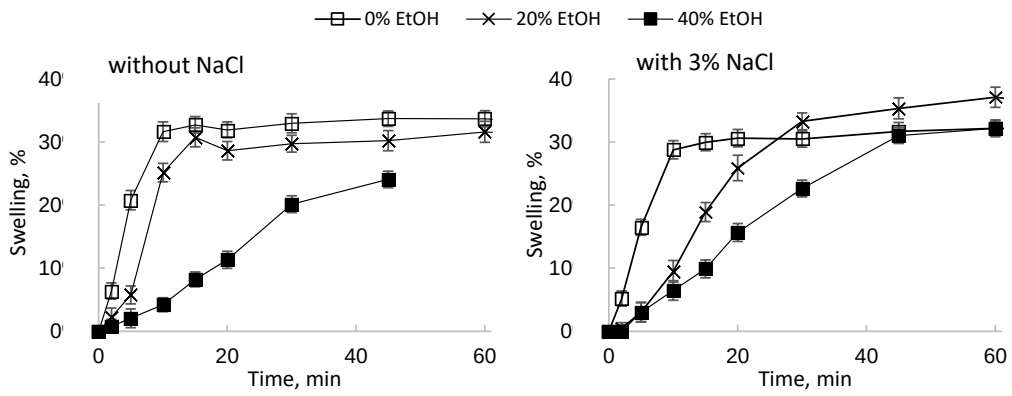


Fig. 48 Swelling % of MCC cores in 0 or 40% ethanol.

The release of freely soluble propranolol HCl from MCC based pellets coated with Eudragit® RS increased in both 20 and 40% ethanol, when compared with aqueous medium (Fig. 49). In the presence of ethanol, the coating swelled by 70% and disintegrated, exposing the pellet core fully to the medium and resulting in an immediate release (Fig. 49). This is similar to the behavior of Eudragit® RS in matrix tablets (Fig. 40). Thus, Eudragit® RS can be considered unsuitable for ethanol-resistant coatings.

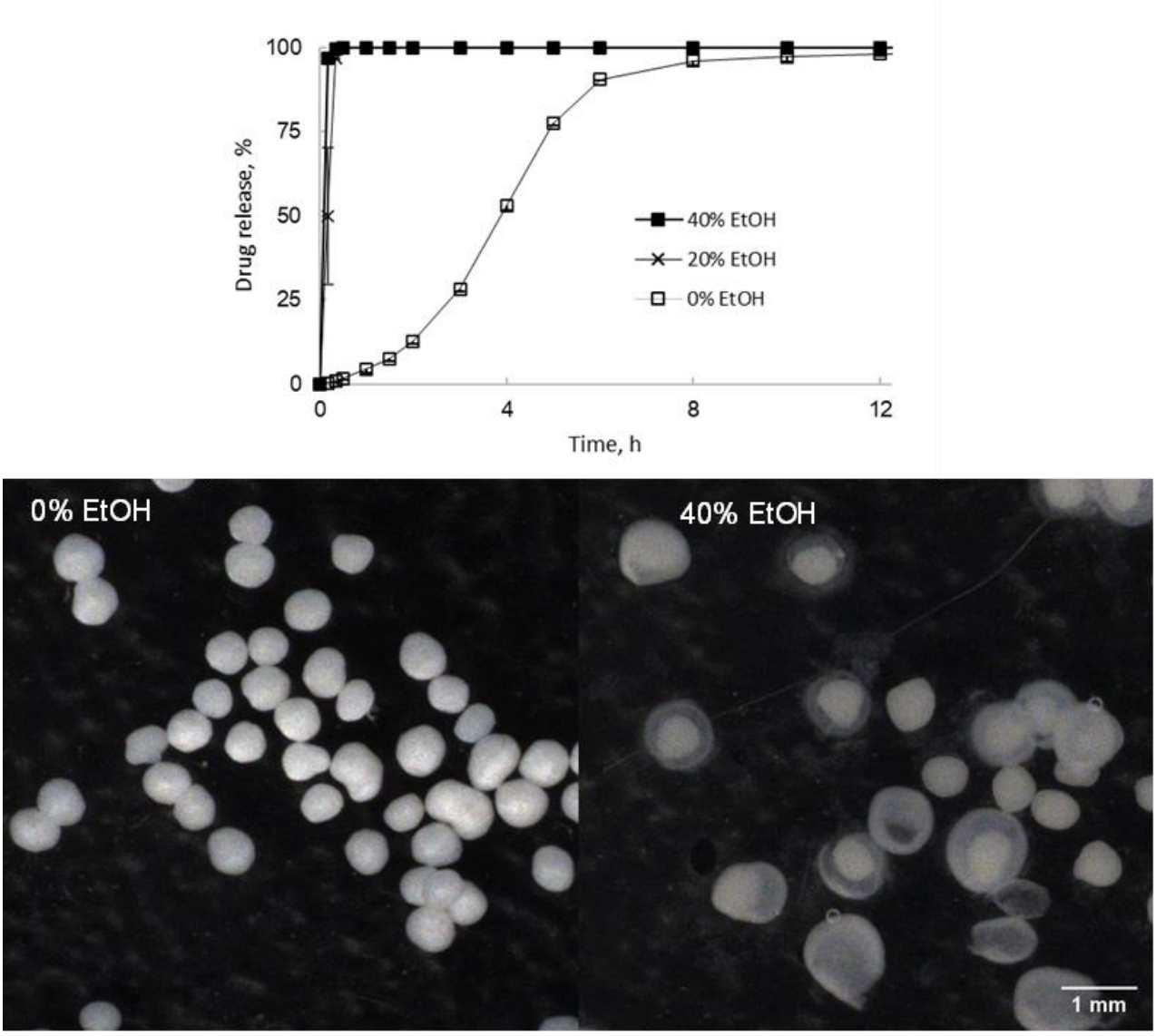


Fig. 49 Drug release and macroscopic pictures (2 h) of propranolol HCl pellets coated with Eudragit® RS in 0 or 40% ethanol.

The release of propranolol HCl also increased in 20% and 40% ethanol from pellets coated with Kollicoat® SR 30D (Fig. 50). An extensive coating swelling, approximately 70% and similar to Eudragit RS, even without disintegration, explained the immediate release (Fig. 50). Also, a sticking tendency of Kollicoat® SR 30D coated pellets was observed in ethanol-containing media. Kollicoat® SR 30D can, likewise, be considered as unsuitable for ethanol-resistant coatings. This result is in contrast to the matrix tablets prepared from Kollidon® SR, a matrix former with similar composition, which showed similar release for the paracetamol (Fig. 40). This discrepancy can be explained by the comparatively higher surface area and shorter diffusion pathway in the case of

coated pellets. Therefore, the effect of ethanol in the medium can also depend on the morphology and geometry of the dosage form.

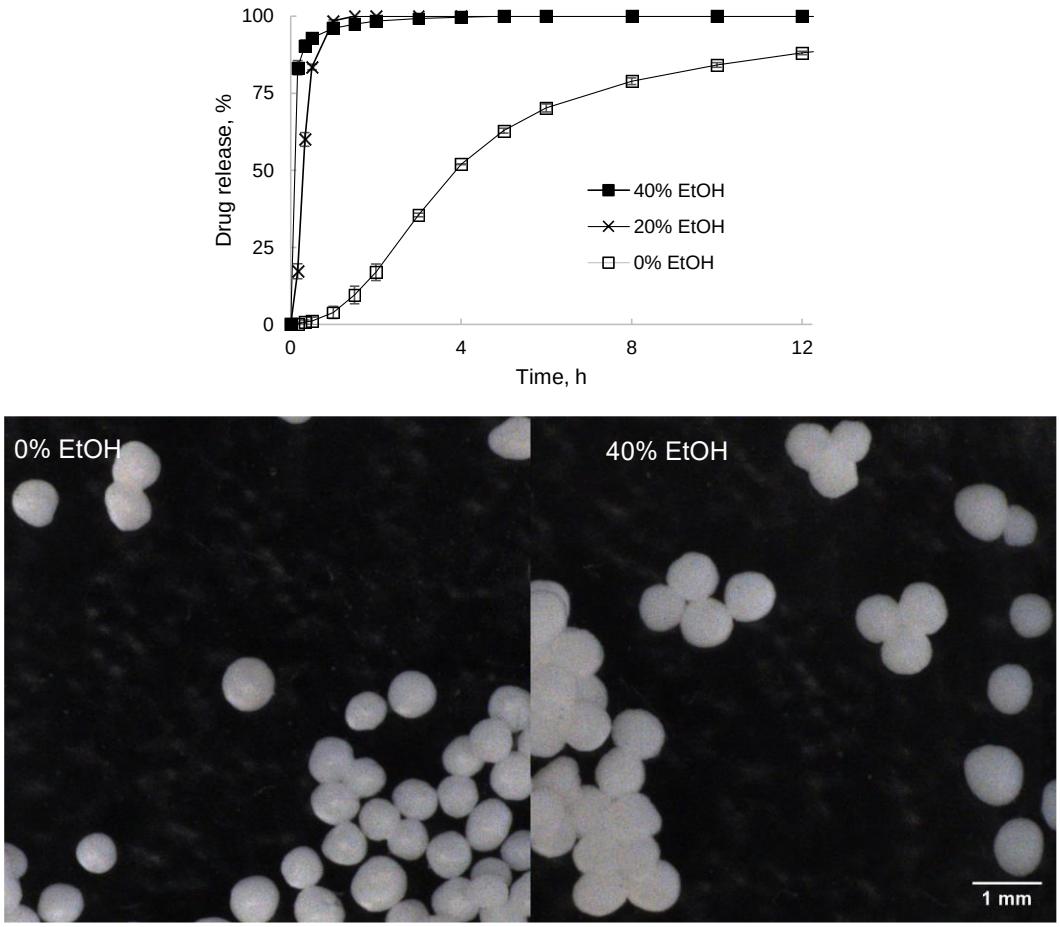


Fig. 50 Drug release and macroscopic pictures (2 h) of propranolol HCl pellets coated with Kollicoat® SR in 0 or 40% ethanol.

A release of propranolol HCl independent of ethanol content was achieved from pellets coated with ethylcellulose (Fig. 51). However, in contrast to aqueous medium and 20% ethanol, the release profile for 40% ethanol differed only slightly, but taking into consideration the similarity of $f_2 = 59$, it can be considered as similar. This is probably due to a smaller swelling difference (~ 23 %) between aqueous medium and 40% ethanol.

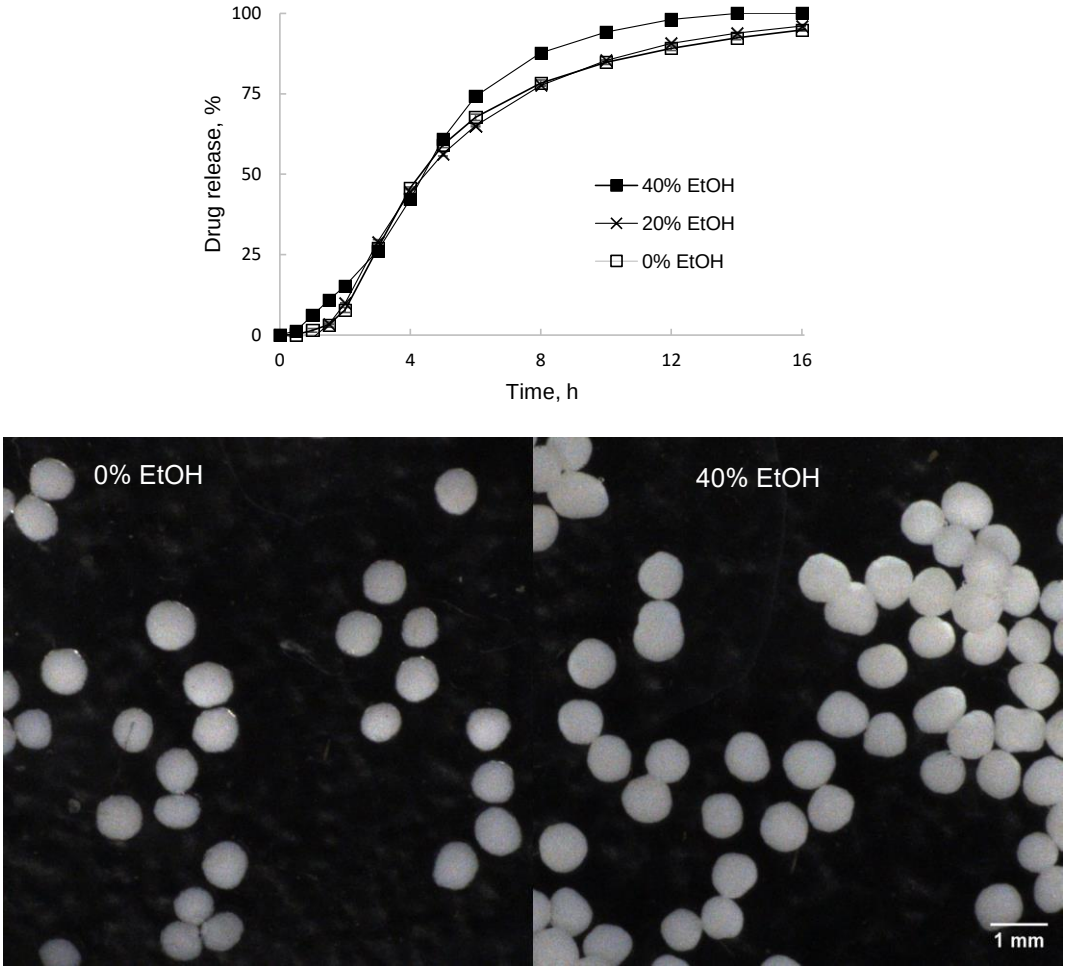


Fig. 51 Drug release and macroscopic pictures (2 h) of propranolol HCl pellets coated with ethylcellulose in 0 or 40% ethanol.

Despite all three tested coating polymers being soluble in ethanol, the accelerated release in hydroethanolic media was only evident for Kollicoat® SR and Eudragit® RS which can be explained by their extensive swelling difference compared to ethylcellulose, approx. 70 vs. 23 %, respectively.

3.4.2 Release of different drugs from ethylcellulose

Since drug solubility would strongly determine the release behavior from pellets coated with ethylcellulose in hydroethanolic media, other drugs, namely, very soluble metoprolol tartrate and slightly soluble theophylline were investigated (Table 11).

The release of metoprolol tartrate decreased with increasing ethanol concentration (Fig. 52). This cannot be explained by the solubility since metoprolol tartrate has the highest solubility in all investigated media. In 40% ethanol, the ethylcellulose coating of metoprolol tartrate pellets was transparent (Fig. 52) while pure ethylcellulose films were opaque. This could indicate an interaction between ethylcellulose and metoprolol e.g. a non-covalent binding as reported previously for ethanol with ethylcellulose [174] or other, enteric polymers [178], as well as indomethacin and ethylcellulose [296].

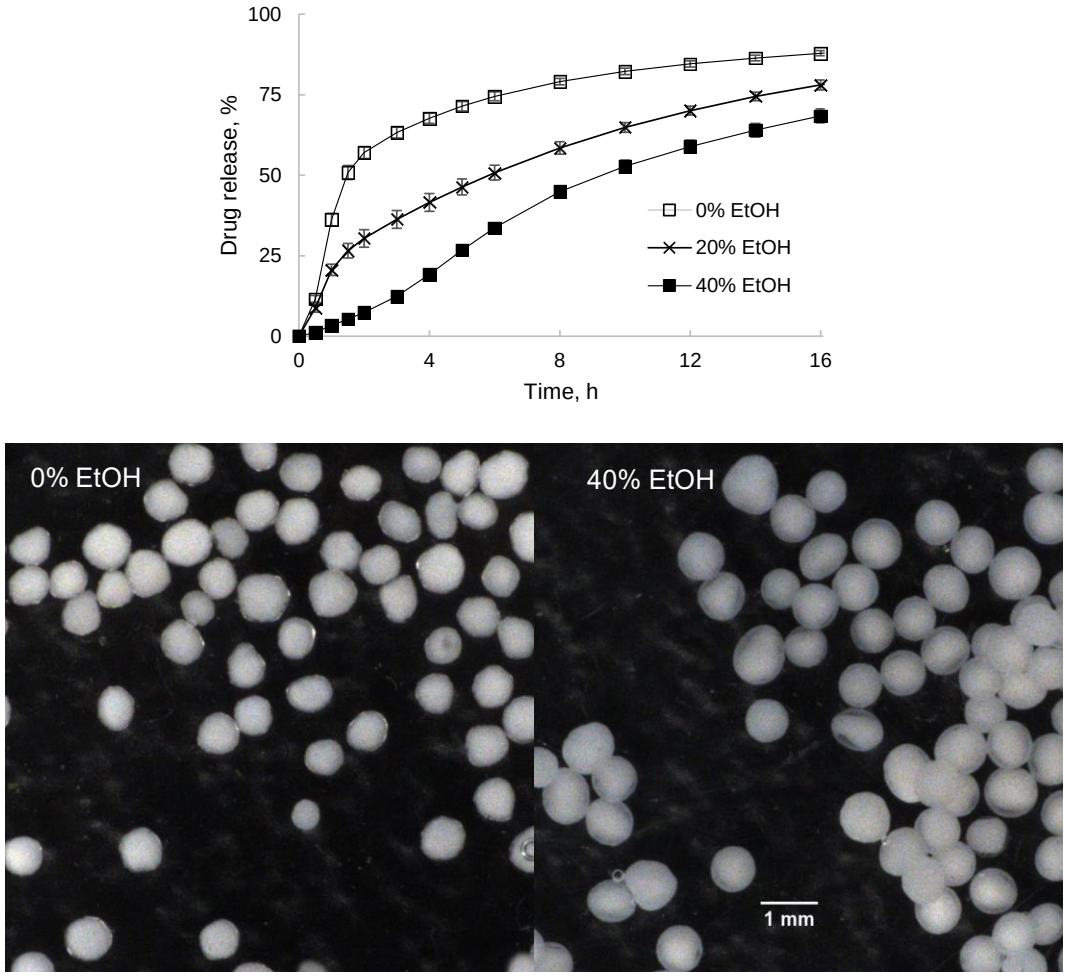


Fig. 52 Drug release and macroscopic pictures (2 h) of metoprolol HCl pellets coated with ethylcellulose in 0 or 40% ethanol.

The partition coefficient in 40% ethanol for ethylcellulose is slightly higher for metoprolol compared to theophylline and propranolol (Fig. 53), but the difference seems unlikely to be solely

responsible for this interaction. Further investigations into this issue are required before the validity of this finding to alcohol effects can be confirmed.

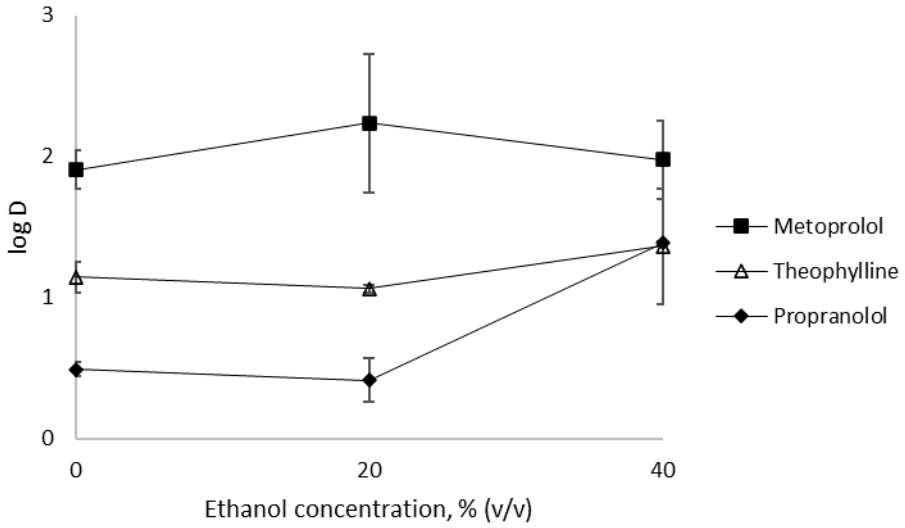
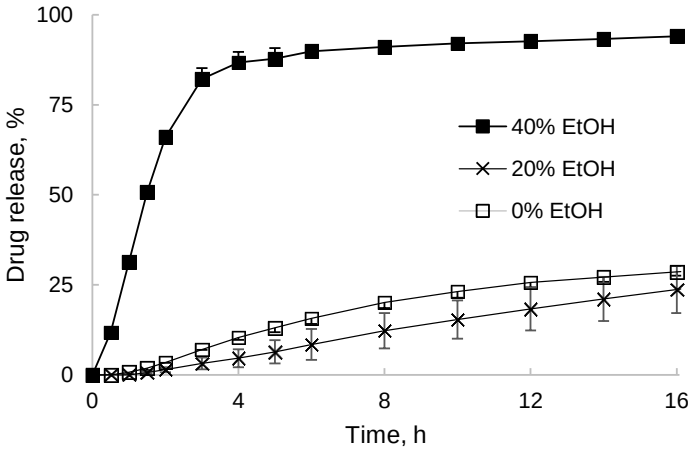


Fig. 53 Partition coefficient log D (log ($\frac{k_{polymer}}{k_{medium}}$)) for ethylcellulose 0, 20 or 40% ethanol.

In case of theophylline, the release was very slow in 0% and 20% ethanol but increased significantly in 40% ethanol (Fig. 54). This difference suggests a change in the release mechanism. Pellets of theophylline swelled stronger in 40% ethanol when compared with 0% ethanol. The theophylline molecule is smaller and more lipophilic than propranolol and metoprolol [297]. These properties can be either alone or both the reason for the accelerated release.



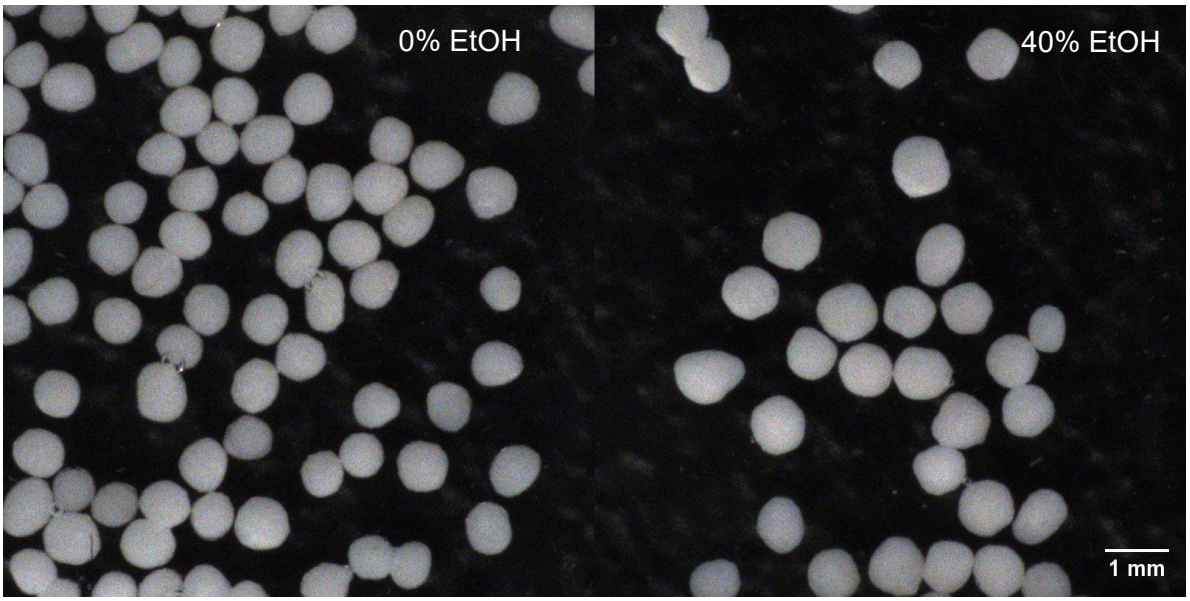


Fig. 54 Drug release and macroscopic pictures (2 h) of theophylline pellets coated with ethylcellulose in 0 or 40% ethanol.

To assess, whether the accelerated release in 40% ethanol for theophylline can be due to an increased diffusion through the polymer, the diffusion of dissolved theophylline through an ethylcellulose film was measured. The diffusion rate was similar for 40% and 20% ethanol, whereas only very little drug was released in 0% ethanol (Fig. 55). In contrast to aqueous medium, where diffusion always followed a zero order kinetic [298], the first hour showed a reduction in release rate prior to the zero-order release rate in hydroethanolic media. This is due to swelling of the polymer and (partial) closing of pores. The similar rate for 40% and 20% ethanol indicates, that other factors are important for the accelerated release in 40% ethanol. The water

permeation of ethylcellulose films in 40% ethanol was reported to be greatly higher compared to 20% [174]. Furthermore, pellet swelling, and mechanical properties of the ethylcellulose-film are also important for this difference.

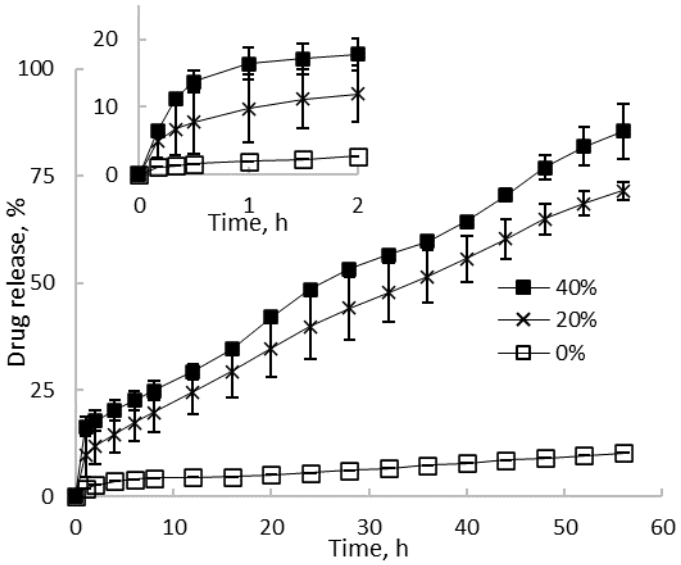


Fig. 55 Release of theophylline from a diffusion cell through a casted ethylcellulose film (25-55 µm thickness) in 0, 20 or 40% ethanol.

3.4.3 Swelling and medium uptake of ethylcellulose coated pellets

Medium uptake of ethylcellulose coated pellets increased significantly in 40 % ethanol for all investigated drugs (Fig. 56), due to the above discussed swelling of the coating. This may also increase its permeability. Pellets of propranolol HCl swelled the most, which may be the result of the larger medium uptake. Pellets of metoprolol showed a decrease in swelling after 4 h, which may be due to an increase in drug release at this timepoint.

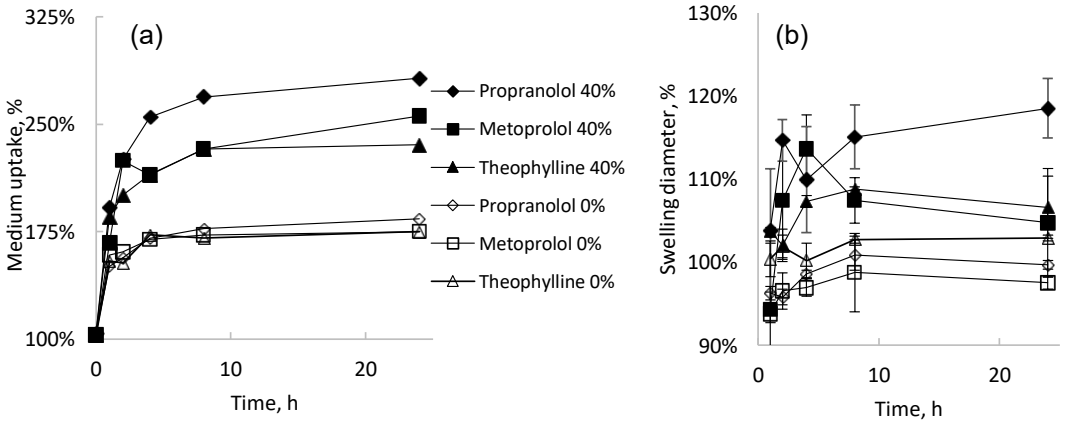


Fig. 56 (a) Medium uptake and (b) swelling of MCC pellets layered with metoprolol tartrate, propranolol HCl or theophylline and coated with 30% ethylcellulose 10 in 0 or 40% ethanol. Magnification of dry pellets in comparison to wet pellets due to different refractive indices is responsible for the swelling diameter below 100%.

Interestingly, the ethylcellulose coated pellets selectively took up more ethanol, as can be demonstrated with propranolol HCl. The w/w concentration of ethanol inside pellets after 90 min was approximately 32 %, which is double the concentration in the release medium ~ 16 % (Fig. 57). Taking into consideration the reduced swelling of the MCC cores in ethanol-containing media (Fig. 48), the ethanol uptake can be attributed to the coating and explain the increase of the coating permeability and faster release.

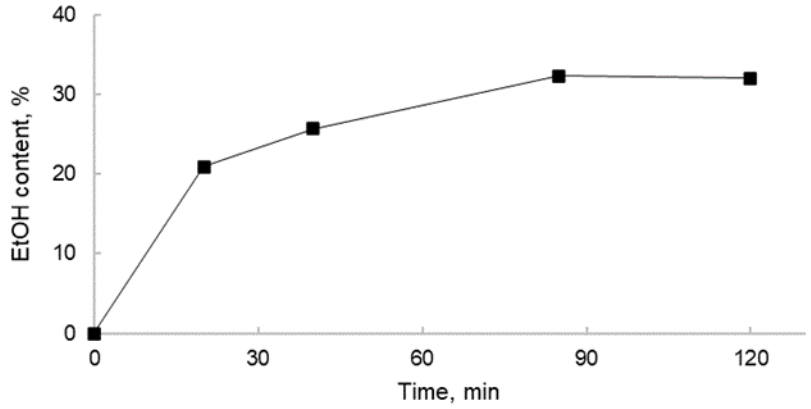


Fig. 57 Ethanol content (measured via GC) of medium uptake (measured gravimetrically) of MCC pellets layered with propranolol HCl and coated with ethylcellulose in 20% ethanol. The 20% (v/v) ethanol ~ 16% (w/w) ethanol.

3.4.4 Mechanical properties of ethylcellulose films

ethylcellulose is known to be brittle and may form channels if the coating ruptures [55]. The rupturing of the coating is more likely if it has a low puncture strength and low elongation. The mechanical properties, such as puncture strength and elongation, decreased with increasing ethanol amount, especially in 40 % ethanol (Table 13). Therefore, the brittleness of ethylcellulose in 40 % ethanol caused faster rupturing and, thus, faster release.

Table 13 Mechanical properties of dry and wet films of ethylcellulose after 2 h immersion in 0, 20 or 40% ethanol

	Puncture strength, MPa	**Elongation, %**
Dry	0.59	1.2
0% ethanol	0.45	1.6
20% ethanol	0.35	1.5
40% ethanol	0.15	0.8

However, ethanol may also act as a plasticizer for ethylcellulose. A plasticizing effect due to the medium is known e.g. for Eudragit® L 30 D, where a much higher elongation to rupture is found in wet- compared to dry state [55]. A plasticizer would increase the polymer mobility and allow it to close spaces, i.e., pores and cavities, left by the particles and could also cause a closing of pores in-situ. A similar effect was seen for the water diffusion through ethylcellulose-hydroxypropyl cellulose (HPC) films [174]. The ethylcellulose swells in the presence of ethanol and closes the pores left by the dissolution of HPC.

This pore closing appears likely, considering the loss of isopropanol from pellets in different media (Fig. 58). The ethylcellulose -coating, prepared from an aqueous isopropanol solution, will have micro-pores as a result of polymer coacervation [298]. Thus, the loss of isopropanol through the pores is fast. In hydroethanolic media, the pores close over time due to the plasticizing effect of ethanol, resulting in an initially similar isopropanol loss, but with a plateau after 2 hours (which corresponds to the plateau observed in the ethanol uptake).

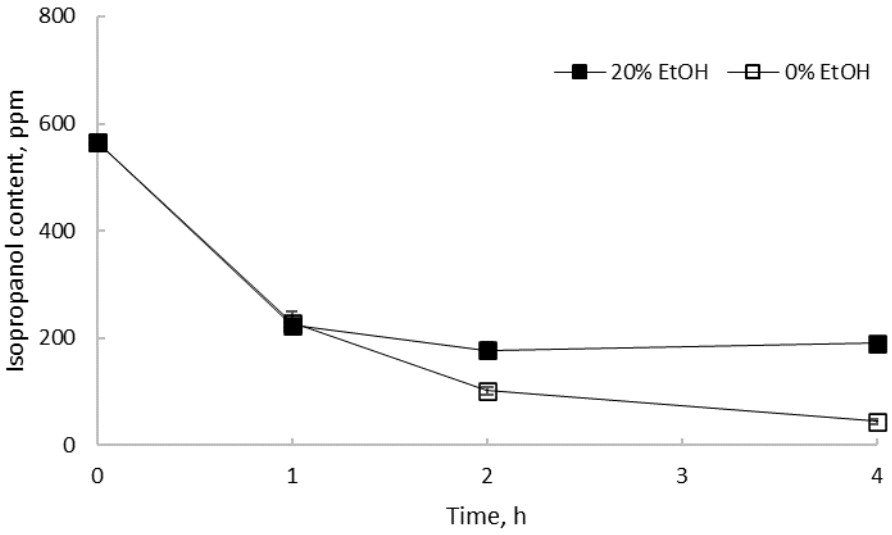


Fig. 58 Isopropanol content of propranolol pellets coated with 40% ethylcellulose after immersion in 0.1 N HCl substituted with 0 and 20% ethanol.

3.4.5 Influence of osmolality on release

Because of the osmotic release mechanism, the addition of osmotically active agent to the release media will decrease the release [52]. In fact, the addition of 3% NaCl resulted in nearly full suppression of release in 0 or 20 % ethanol (Fig.59) which confirmed the purely osmotically driven release.

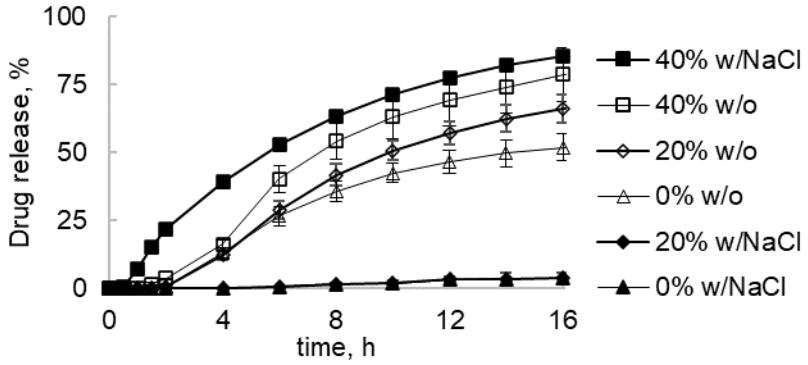


Fig.59 Effect of 3% NaCl on drug release from MCC pellets layered with propranolol and coated with 40% ethylcellulose in 0, 20 or 40% ethanol.

In 40% ethanol, the release of propranolol HCl was not suppressed by addition of 3% NaCl, but also changed from osmotic, with a typical sigmoidal shape, to diffusion-based, following a square root of time kinetic (Fig. 60, $R^2 = 0.995$).

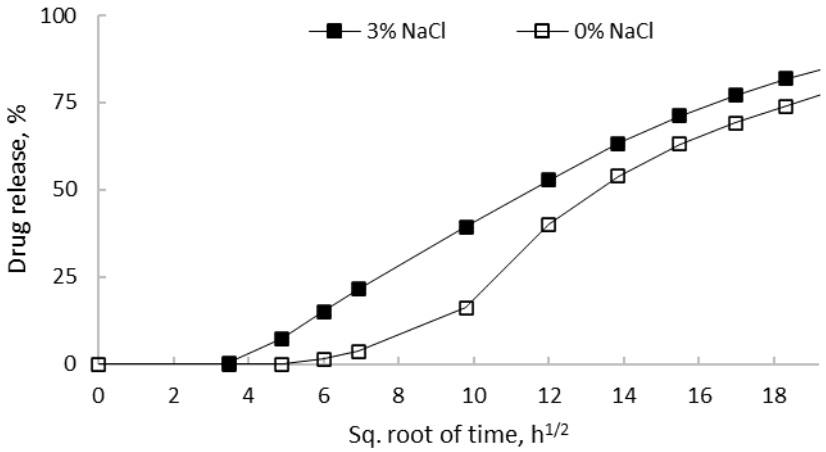


Fig. 60 Drug release from MCC pellets layered with propranolol and coated with 40% ethylcellulose in 40% ethanol vs. square root of time at different NaCl concentrations

The swelling of MCC, while still being slower than in 0% and 20% ethanol, was not slowed down by the addition of NaCl in 40% ethanol (Fig. 48). NaCl can also affect the release via diffusion by a reduction of drug solubility [299]. The solubility of propranolol HCl is decreased in presence of NaCl (Table 14). However, this reduction would not result in a complete stop of release.

Table 14 Solubility [mg/ml] of propranolol HCl 0% and 20% ethanol with different additives.

Additive	0% EtOH	20% EtOH
-	135.0	170.5
10% NaCl (w/w)	5.8	10.7
10% Sucrose (w/w)	88.3	137.0
5% HPMC E5 (w/w)	103.2	160.9

3.4.6 Influence of coating level on release

The mechanisms governing the release of propranolol from ethylcellulose -coated pellets led to a similar release at 30% coating level. Different coatings levels however led to different release profiles, both in terms of lag time and slope (Fig. 61).

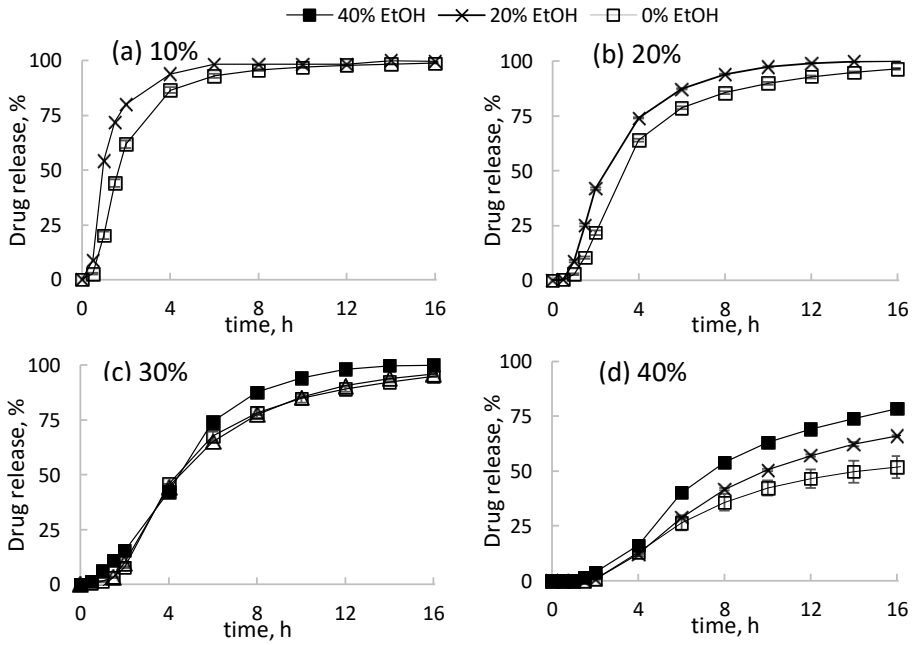


Fig. 61 Drug release from MCC pellets layered with propranolol and coated ethylcellulose at different coating levels in 0, 20 or 40% ethanol.

The mean dissolution time (MDT) of propranolol HCl was lower in 20% ethanol at lower coating levels of 10% and 20%, but similar at 30% and 40% coating (Fig. 62). The MDT is a standardized measure of the timepoint, where 50% of the drug is released. A low value indicates a faster release. In 40% ethanol, the release was similar at 30% coating and faster at 40% coating.

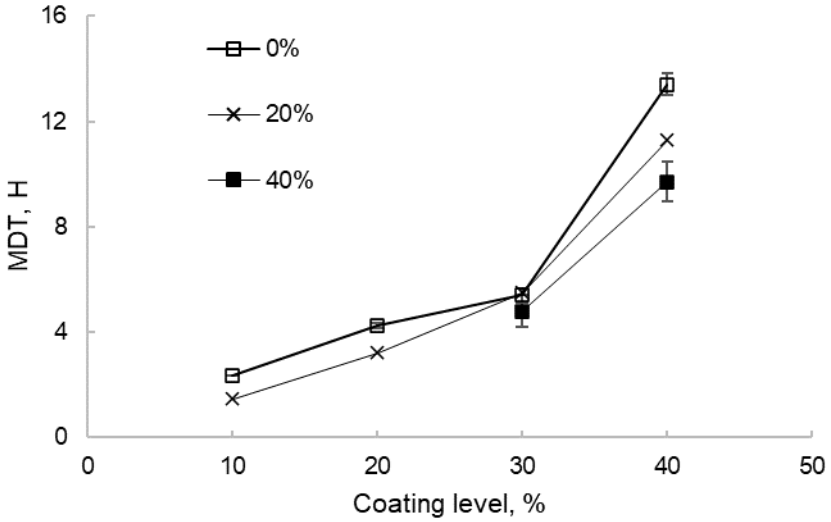


Fig. 62 Effect of coating level on MDT of propranolol pellets in 0, 20 or 40% ethanol.

With increasing coating level, the swelling capacity of the core remains constant, but the pressure required to rupture the coating increases [300] and can be, at some point, insufficient for adequate release. Therefore, the faster medium uptake and increased wettability would explain the faster release in 20% ethanol at low coating levels. At 30% coating level, wettability becomes less important, and the release occurs mainly due to the rupturing effect induced by the core swelling. At 40% coating, the coating is stronger, and ruptures are not sufficient for complete release. Thus, the similar release in the investigated media observed at 30% coating cannot be extrapolated to other coating levels.

To investigate the effect of core, theophylline was layered onto MCC and sugar cores. Theophylline release from MCC cores was similar at coating levels of 10% (f_2 = 70) and 30% (f_2 = 61) for 0 and 20% ethanol (Fig. 63). At 20% coating level release was faster in 0% compared to 20% ethanol (f_2 = 44). This contrasts with sugar cores, where release was faster in 20% ethanol at all coating levels (f_2 = 40, 37 or 33 for 10, 20 or 30% coating level, respectively). Both MCC and sugar cores create pressure against the coating. MCC is insoluble but swells, stronger in aqueous medium (Fig. 48). The sugar core dissolves in all investigated media creating an osmotic pressure once the volume in the core is larger than the displaceable volume [54]. The dissolution of sugar is associated with a volume contraction [301] which is lower in water-ethanol mixtures compared

to pure water [302]. The lower contraction and the higher medium permeation [174] can explain the faster release in 20% ethanol from sugar cores.

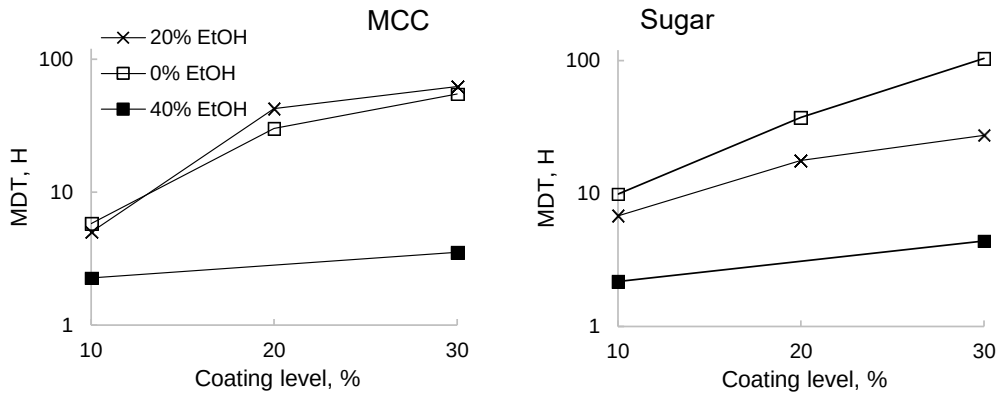


Fig. 63 Effect of coating level and core type on MDT of theophylline pellets in 0, 20 or 40% ethanol

The original curves also indicated a strong reduction in slope of the release curve in 0 and 20% ethanol and less effect in 40% ethanol (Fig. 64). Thus, the use of ethylcellulose alone is likely not suitable to achieve similar release in 40% ethanol at any coating level.

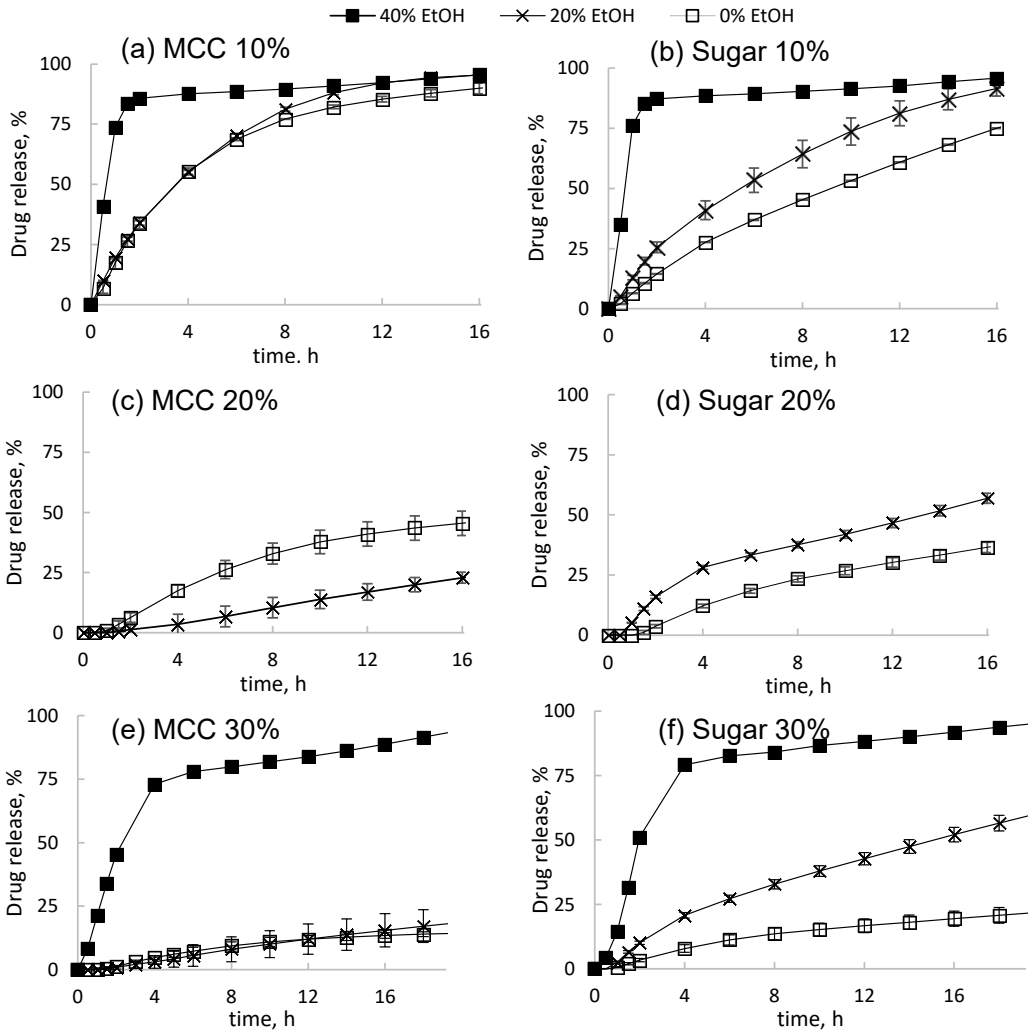


Fig. 64 Drug release from MCC or sugar bead pellets layered with theophylline and coated with different levels of ethylcellulose in 0, 20 or 40% ethanol.

3.4.7 Influence of hydrophilic polymers in the coating on release behavior

The addition of hydrophilic polymers has been used to match the release [170] or the water permeability [174] in aqueous and hydroethanolic media from ethylcellulose .

Introduction of HPC into an ethylcellulose -coating accelerated the release (Fig. 65). The release in 0% ethanol was still slower than in hydroethanolic media, but interestingly there was no difference between 20% and 40% ethanol, irrespective of the coating level. An increase of coating thickness from 30% w/w (f_2=20.8) to 45% w/w (f_2=23.0) reduced the difference between 20% ethanol and 0% ethanol-containing media only slightly. Following the conclusions given by

Larsson et al. [174], the swelling of ethylcellulose in 40% ethanol partially closed the pores created by the HPC. In 20% ethanol this swelling may be insufficient to close the pores, leading to similar release. For theophylline, the inclusion of HPC was not suitable to achieve similar release for hydro- and aqueous media.

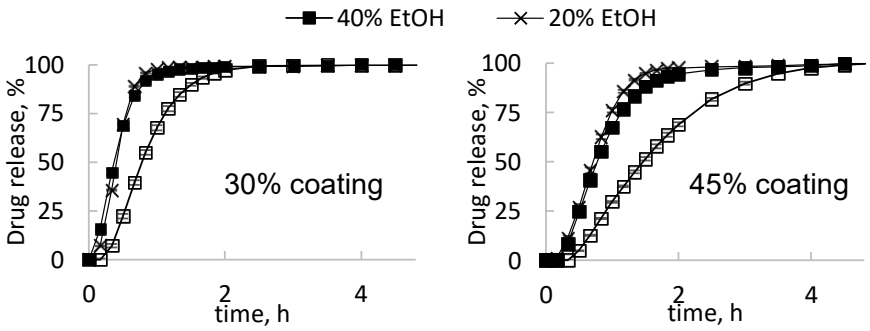


Fig. 65 Drug release from MCC pellets layered with theophylline and coated with 30% or 45% Ethocel® 10: Klucel LF (65:35) in 0, 20 or 40% ethanol.

3.4.8 Conclusion

Kollicoat® SR and Eudragit® RS are not suitable to prevent alcohol-induced accelerated release. ethylcellulose can be used to achieve release unaffected by ethanol up to 20% ethanol as required by the EMA. The release mechanism of the drugs may change from osmotically driven to a diffusion-based release in 40% ethanol. At this concentration similar release is only achievable for drugs of higher solubility like metoprolol and propranolol. However, there is acceptable concern, whether a prolonged exposure to such a high concentration in the stomach, especially for multiple unit dosage forms, will happen in-vivo. A similar release with ethylcellulose is also a function of coating level and core type. MCC cores should be preferred over sugar cores to avoid accelerated release in hydroethanolic media.

3.5 The behavior of enteric-coated pellets in aqueous and hydroethanolic media

Enteric coatings are utilized to not release the drug in the acidic pH of the stomach and to release the drug in the intestine. The protection of the gastric mucosa from the drug or the protection of the drug from the acidic pH of the stomach are the main reasons for applying an enteric coating [79]. Further applications include colonic targeting [73] and mixed coatings to counteract a reduced intestinal drug solubility [64]. Contrasting with extended-release formulations where the concern is dose-dumping, enteric pellets are rather at risk of sub-therapeutic drug-plasma levels, if the drug degrades prior to absorption.

A coating is referred to as enteric-resistant in this work if less than 10% drug is released, usually over a period of two hours. This is based on the recommendations of the Ph. Eur. [303].

3.5.1 Methacrylic acid-methyl-methacrylate-copolymer (Eudragit® L)

Eudragit® L is a polymethacrylate designed for enteric coatings and was introduced to the market in 1955 [304]. It is available both with 30% solid contents as an aqueous dispersion and as plain powder for redispersion in water or dissolution in organic solvents. Plasticizers are necessary for the aqueous dispersions, whereas they are not always needed for organic solutions [304]. The water soluble plasticizers triacetin and triethyl citrate (TEC) are the best due to their small molecular size [305]. The minimum layer thickness to achieve enteric-resistance for Eudragit® L is 40-50 µm (4-5 mg dry polymer/cm²). Eudragit® L has been used together with insoluble polymers for ethanolic resistance [208, 210, 306], but this leads to the previously mentioned issue of slow release in the intestine.

The release of propranolol from pellets coated with Eudragit® L showed near-instantaneous release in 20% ethanol (Fig. 66). An increase in coating level led to a slower release in 0% ethanol, whereas there was nearly no effect visible for 20% ethanol. This rapid release from dosage forms coated with Eudragit® L was also observed in recent reports [178] and in commercial products (Chapter: 3.2.1; Fig. 10, Fig. 12). Eudragit® L is not a suitable polymer to achieve ethanolic resistance for 20% ethanol.

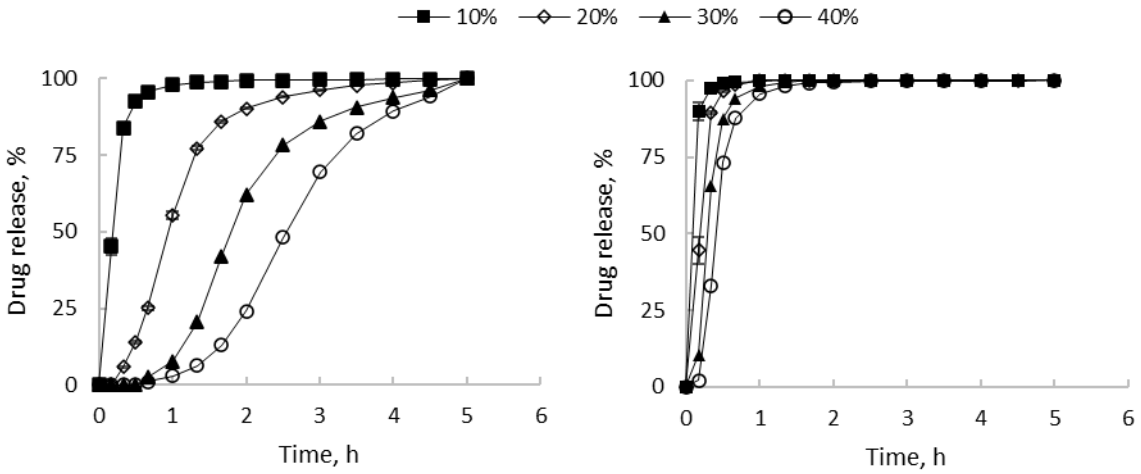


Fig. 66 Release of propranolol HCl from pellets coated with Eudragit® L at different coating levels in 0 or 20% ethanol.

3.5.2 Polyvinyl acetate phthalate (PVAP)

Sureteric® is an aqueous dispersion of PVAP and thus allows the inclusion of water-soluble polymers. As the inclusion of guar gum in an ethylcellulose coating can lead to similar release in aqueous and hydroethanolic media [170], this approach was evaluated for the aqueous Sureteric®. To avoid a premature release due to dissolution of the guar gum, guar gum was only included in the second coating. Thus, a bottom coating of 20% Sureteric® without guar gum was coated again with 20% Sureteric®-Guar gum (90:10, w/w). This mixture was however insufficient to achieve acidic resistance in 0% ethanol and showed rapid release in 20% ethanol (Fig. 67).

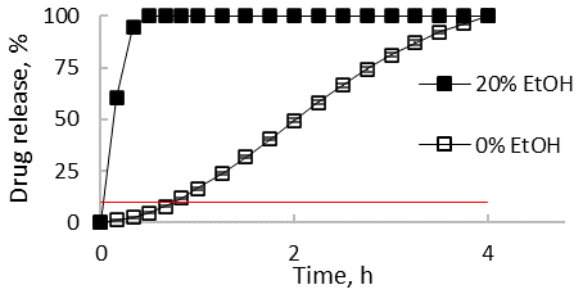


Fig. 67 Release of propranolol from pellets coated with 20% Sureteric® and 20% Sureteric®/Guar gum (90:10, w/w) in 0 or 20% ethanol.

In the coating of aqueous dispersions, curing is often required to achieve complete coalescence of the polymer particles on the pellet surface [292]. The curing of the Sureteric® coated pellets however only had a minor effect on release (Fig. 68). Thus, the poor release-sustaining-effect could not be ascribed to an insufficient bonding of the polymer particles on the pellet surface due to insufficient curing. Instead, the guar gum may have simply dissolved and led to pores in the coating.

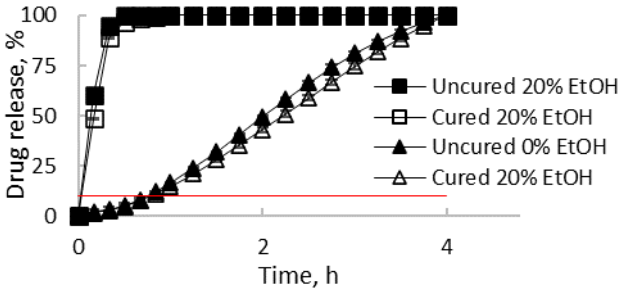


Fig. 68 Release of propranolol from pellets coated with 20% Sureteric® and 20% Sureteric®/Guar gum (90:10, w/w) in 0 or 20% ethanol. Pellets were either not cured or cured for 22 h at 50°C.

To slow down the release of guar gum and to achieve ethanolic resistance, 20% Sureteric® was coated on top of the previous coatings, resulting in three coating layers. This was sufficient to achieve acidic resistance and slow down the release in 20% ethanol (Fig. 69). The top coating avoided premature dissolution of the guar gum in the second coating by reducing the diffusion rate, increasing the local concentration, and thus slowing down further dissolution of the polymer.

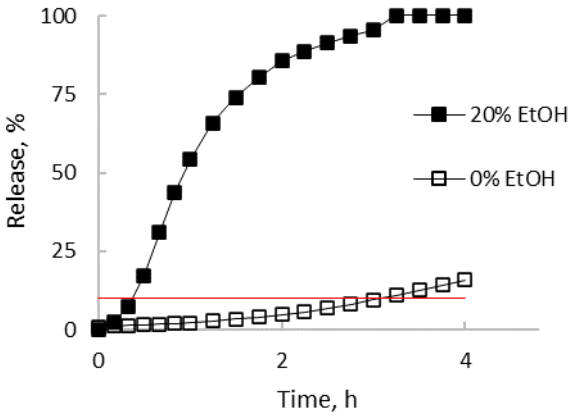


Fig. 69 Release of propranolol from pellets coated with 20% Sureteric®, 20% Sureteric®/Guar gum (90:10, w/w) and 20% Sureteric® in 0 or 20% ethanol.

An additional curing had no effect on the release of these 3-layered pellets (Fig. 70). However, due to the considerable amounts of coating material and the still present accelerated release this combination is not a feasible approach to target ethanol-induced dose dumping.

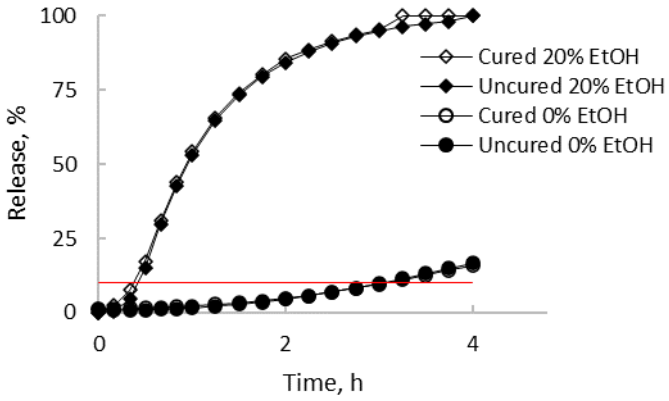


Fig. 70 Release of propranolol from pellets coated with 20% Sureteric®, 20% Sureteric®/Guar gum (90:10, w/w) and 20% Sureteric® in 0 or 20% ethanol. Pellets were either not cured or cured for 22 h at 50 °C.

3.5.3 Hydroxypropyl methylcellulose-phthalate (HPMCP)

3.5.3.1 The behavior of HPMCP-coated pellets layered with propranolol HCl

HPMCP consists of Hydroxypropyl methylcellulose (HPMC) esterified with phthalic-acid and marketed by Shin-Etsu for dissolution at different pH. While coating of micro ground HPMCP in

an aqueous dispersion can achieve enteric-resistance, at higher coating levels [80], no aqueous dispersion is commercially available and HPMCP is recommended to be prepared from an organic solution. It was tested at different coating levels (Table 15).

Table 15 Coating level and coating amount of propranolol-HPMCP pellets

Feret diameter of layered pellets	914 ± 20 µm
Circularity	0.88 ± 0.1
40% coating level	9.2 mg/cm²
30% coating level	6.9 mg/cm²
20% coating level	4.6 mg/cm²
10% coating level	2.3 mg/cm²

The release of propranolol from HPMCP-coated pellets showed enteric-resistance in 0% ethanol above a coating level of 20% (Fig. 71). As HPMCP can be coated from an ethanolic solution it is soluble in ethanol [178]. The 20% ethanol were not sufficient to dissolve the HPMCP, but swelling was possible. This allowed both medium penetration and premature release. The curve of release followed a sigmoidal shape. Such a shape has also been described for a system comprising Eudragit® RS and succinic acid [71]. This system had been linked to an osmotic pumping mechanism [307]. Thus, it is possible, that the release from HPMCP has at least partially an osmotic mechanism. Considering the size increase observed for Duloxetine Aurobindo in hydroethanolic media (Fig. 13), this osmotic release may result from a strong media uptake prior to the onset of release.

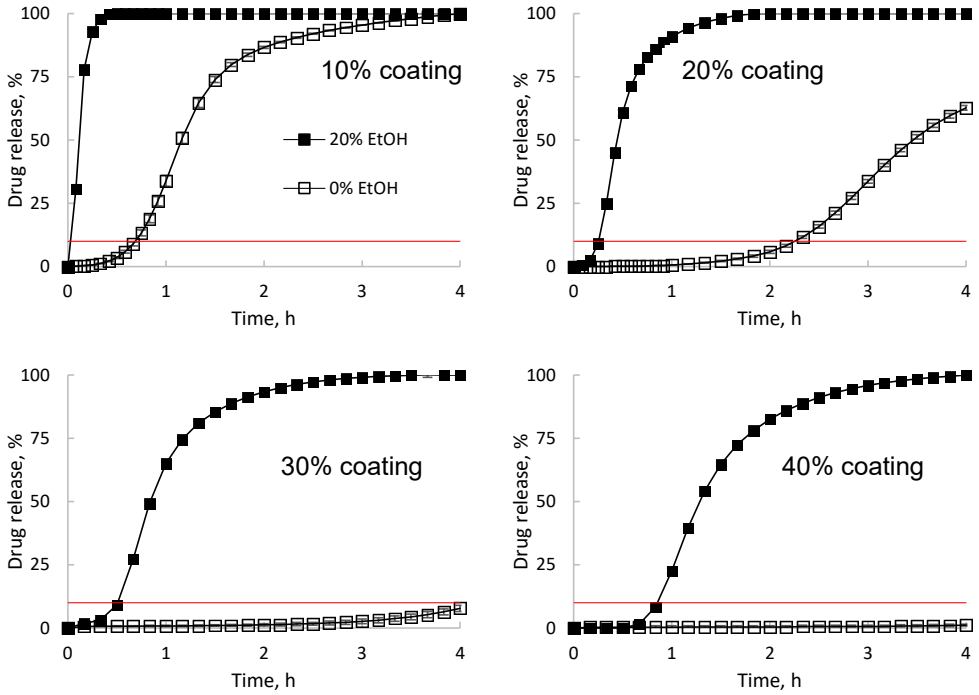


Fig. 71 Release of propranolol from HPMCP-coated pellets at different coating level in 0 or 20% ethanol.

The loss of residual isopropanol content from pellets, originating from the coating solution, can inform about the permeability or potential porosity of the coating. A rapid loss of isopropanol may result from a high porosity of the coating, enabling a fast diffusion of the isopropanol into medium. Pellets coated with HPMCP showed a faster loss of isopropanol in 20% ethanol (Fig. 72) compared to 0% ethanol. The presence of ethanol can increase the permeability of polymer coatings [174] towards water vapor as well as increase the porosity of enteric polymers [178]. Both effects can also apply to isopropanol and explain the faster loss of isopropanol from the pellets, especially in contrast to ethylcellulose (Fig. 58). This would imply a higher chance for the medium to penetrate the core.

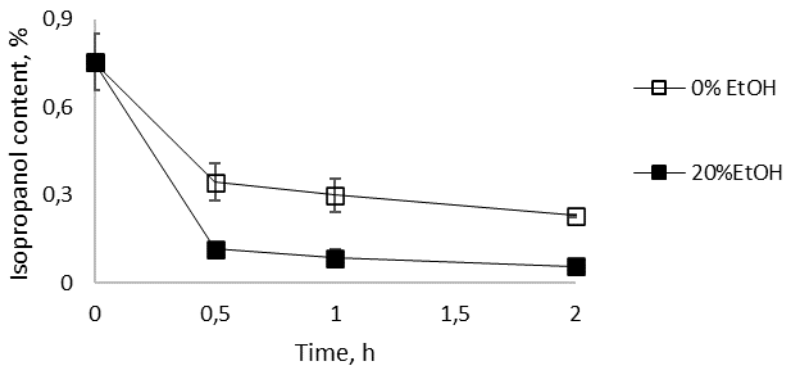


Fig. 72 Isopropanol content in 0 and 20% ethanol of propranolol pellets coated with HPMCP.

If the medium penetrates faster into the core in the presence of ethanol, this would result in a higher medium uptake. The pellets took up media in both aqueous and hydroethanolic media (Fig. 73). However, the medium uptake in aqueous media plateaued af89ter 30 min, whereas the medium uptake in 20% ethanol increased linearly with time. There was only minor difference between the media regarding the dry mass loss, which is likely mostly caused by drug dissolution. The accelerated release observed earlier is thus due to an increased swelling and not polymer dissolution or disintegration.

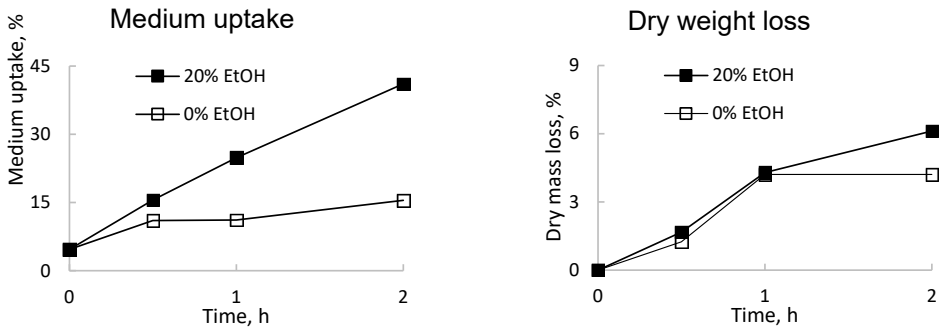


Fig. 73 Medium uptake and dry weight loss in 0 and 20% ethanol of layered pellets of propranolol coated with HPMCP.

The resulting premature release in 20% ethanol showed a clear increase of t_{10} with increasing coating level (Fig. 74). The t_{10} refers to the time point where approximately 10% of the drug is released and thus the timeframe in which formulation may be considered as enteric-resistant. The slope of the curve decreased with increasing lag time.

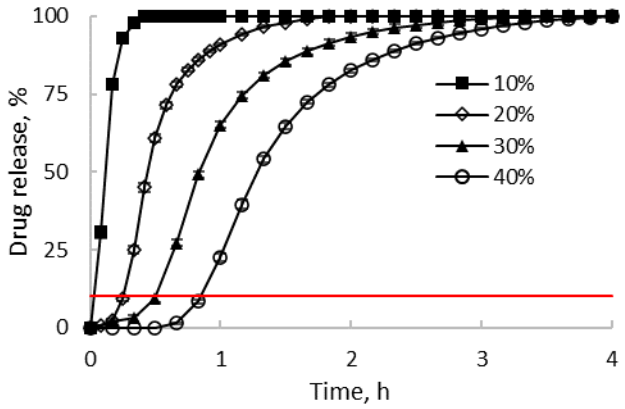


Fig. 74 Release of propranolol from HPMCP-coated pellets at different coating levels in 20% ethanol.

This observed t_{10} depended linearly on the coating level for a specific pellet size. This allows determining the required amount of coating level to achieve enteric-resistance with

$$\boldsymbol{Coat_{Amt} = 0.124\, T_{10} + 2.176} \qquad \text{equation 18}$$

with T_{10} being the required t_{10} in min and $Coat_{Amt}$ being the required coating amount in mg/cm². For 120 min this would require a coating amount of 17.1 mg/cm² or 74.2% coating level.

As there are drawbacks associated with a very thick layer of enteric polymer regarding the dissolution in the intestine [84], a larger pellet core was chosen instead.
Cellets® are also MCC cores but the tested batch was of a larger size (1.25 mm - 1.4 mm). At the same coating level, they thus had a larger coating amount per surface area. This resulted in enteric-resistance in 20% ethanol already at 30% coating level (Fig. 75). The relationship between t_{10} and coating level differed from the Celphere® 507 pellets used previously (Fig. 71).

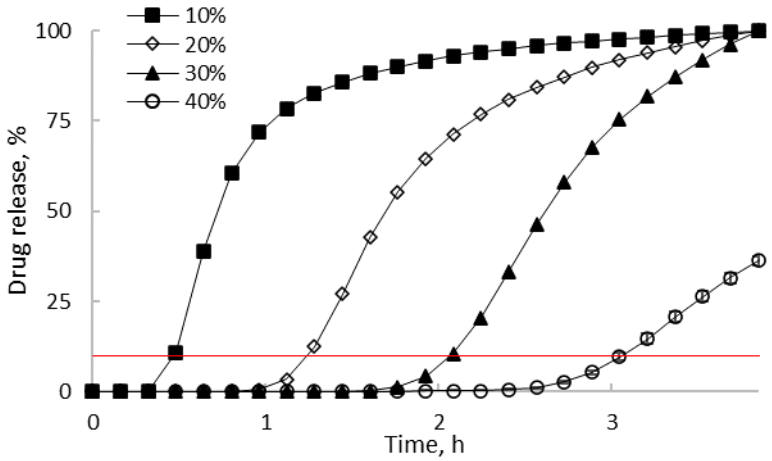


Fig. 75 Effect of coating level on drug release in 0 or 20% ethanol from propranolol from Cellets® coated with HPMCP.

Cellets® showed a steeper relationship between lag time and coating level than Celphere® 507 (Fig. 76). Therefore, another factor, besides the coating level, was responsible for the difference in t_{10}. As the two pellet types differ in their size, the surface-to-volume ratio may explain some of these differences. It has been used in the past to calculate the lag time of pellets coated with ethylcellulose [300].

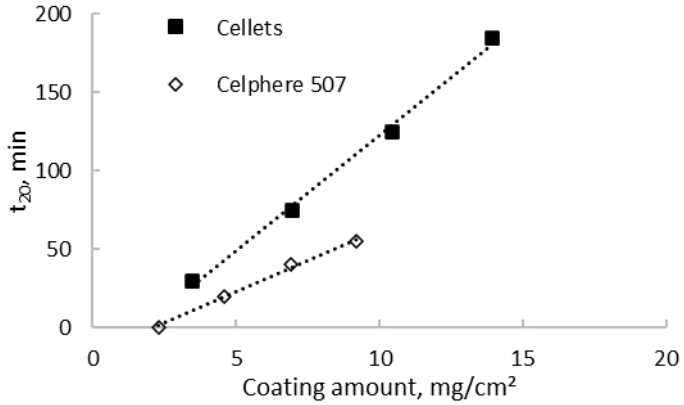


Fig. 76 t_{10} vs. coating amount for propranolol-HPMCP pellets in 20% ethanol.

A drawback associated with a linear relationship as in equation 18 is the possibility of negative values at low coating levels. Instead, the t_{10} should asymptotically approach zero. A power law was used to achieve this asymptotical approach and allow the inclusion of the surface-to-volume ratio:

$$T_{10} = (b \frac{Coat_{Amt}}{\frac{A}{V}})^{c}$$ equation 19

Where A is the surface area, V is the pellet volume and $\frac{A}{V}$ thus the surface-to-volume ratio. The surface-to-volume ratio was 4.3 for Cellets® and 6.6 for Celphere® 507.b and c are dimensionless fitted constants, which may differ depending on the drug solubility, the polymer type, and the core type.

Fitting b and c to the data from Fig. 76 resulted in equation 20:

$$T_{10} = (13.33 \frac{Coat_{Amt}}{\frac{A}{V}})^{1.39}$$ equation 20

The calculated t_{10} fitted well to the experimental data of both pellet types (Fig. 77a) and the residual errors showed no trend (Fig. 77b). Thus, equation 20 is suitable to describe the relationship between coating amount, surface-to-volume ratio and t_{10}. It should be noted that the error is rather high for the low data points, where, despite the presence of a coating amount, there was nearly no lag time. This may be due to an incomplete coating, which would result in a different release mechanism [60].

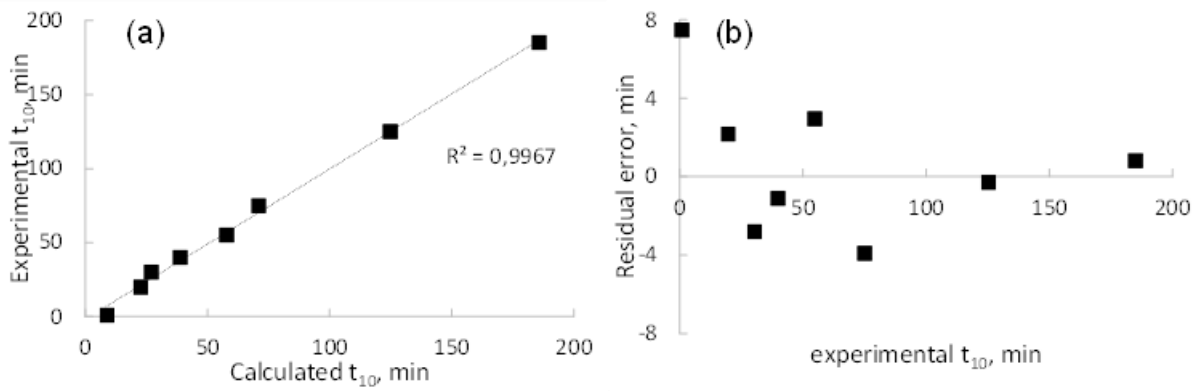


Fig. 77 (a) Calculated vs. experimental t_{10} of HPMCP pellets in 20% ethanol. (b) residual error

To verify the validity of equation 20, it was tested on a separate set of data not included in the creation of the equation. A subset of the propranolol-layered Celphere® 507 was sieved to yield pellets of a mean size of 819 µm and a surface-volume ratio of 7.3. The resulting curve showed

good fit with a R^2 of 0.995 (Fig. 78). The largest difference can be observed for the lowest coating amount, where a rapid release was seen in-vitro. However, as these low coating amounts do not provide enteric-resistance, they are unlikely to be of interest to formulation scientists. The presented equation can be a time-saving approach to determine the required amount of coating polymer to avoid premature release in hydroethanolic media. It can be applied to calculate the t_{10} of propranolol from HPMCP coated pellets of different sizes.

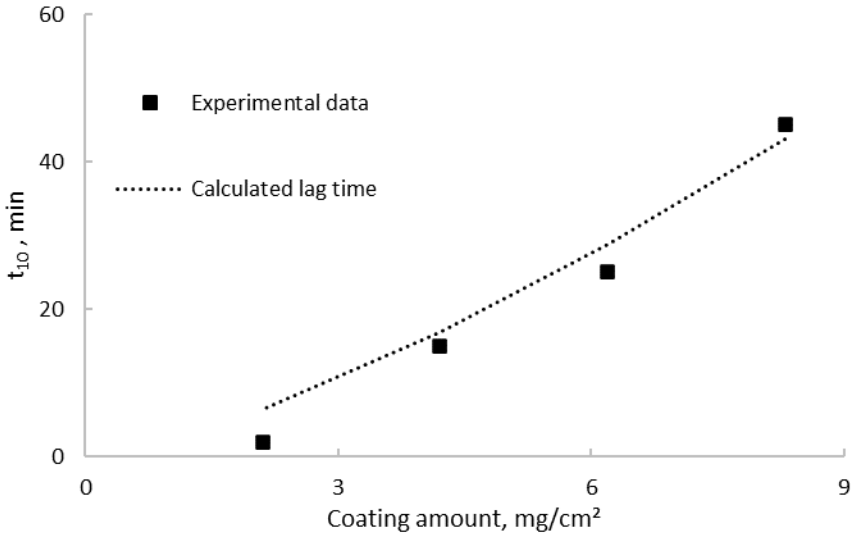


Fig. 78 Calculated vs. experimental t_{10} of test-subset of HPMCP pellets in 20% ethanol.

Adjusting the coating amount and fitting the t_{10} to achieve enteric-resistance even in the presence of ethanol is one possible approach for enteric dosage forms. However, the difference in release between 0% and 20% ethanol is still very large. Cellets® with 40% HPMCP had a lag time of 3.1 h in 20% ethanol, but over 18 h in 0% ethanol, without a change in medium pH (Fig. 79). Thus, while increasing the coating amount may be sufficient to enable enteric-resistance in-vivo, it will not result in a similar release. Instead, the inclusion of a subcoating was evaluated as a possible approach to reduce the difference in release.

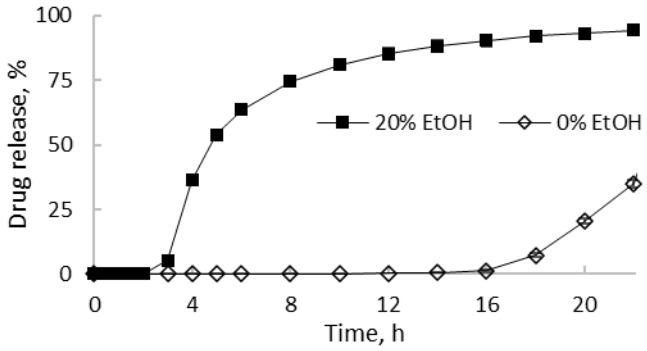


Fig. 79 Release of propranolol from Cellets® coated with HPMCP in 0 or 20% ethanol.

3.5.3.2 The effect of a HPMC sub-coating on the release of enteric coated pellets

A subcoating is commonly applied when using enteric polymers. The subcoating can protect the drug from the acid groups of the enteric polymer [80, 308], reduce the moisture uptake [309] or can affect the release in the intestine [310].

HPMC E5 was chosen as a subcoating material due to its widespread use and because HPMC was little affected by ethanol in the media (Chapter 3.3.1, P. 68). A 3% HPMC-subcoating was chosen to achieve a protection of the content from the enteric polymer. This led to a release profile (Fig. 80) with an accelerated release in 20% ethanol similar to the non-subcoated pellets.

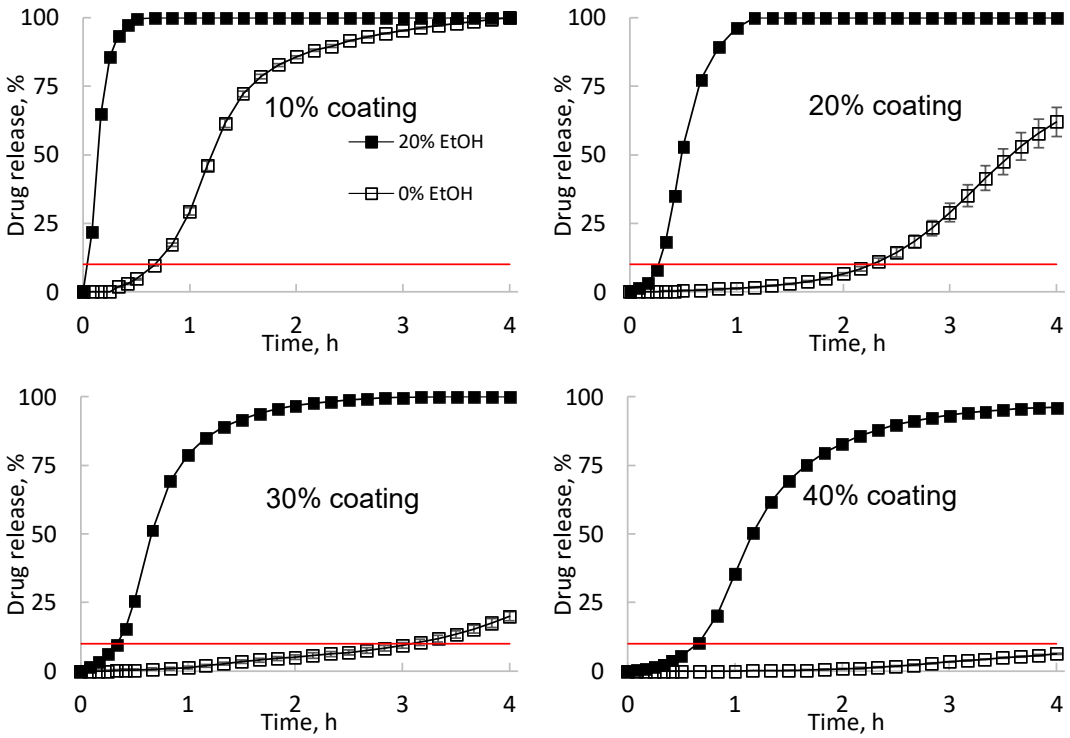


Fig. 80 Effect of a 3% HPMC E5 subcoating and coating level on propranolol release from HPMCP-coated pellets in 0 and 20% ethanol.

A direct comparison between subcoated and non-subcoated pellets showed a reduction in lag time in 20% ethanol (40% coating level) and in 0% ethanol (30% and 40%). The slope of the release is less steep in 20% ethanol. Thus, a slight shift in release mechanism, to a more linear type of release due to the presence of the HPMC E5 subcoating may be possible, but larger amounts of polymer are required, to profoundly affect the release curve.

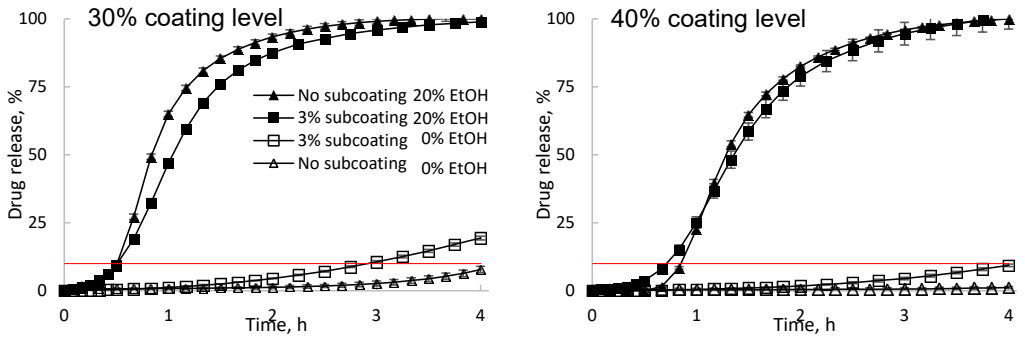


Fig. 81 Effect of 3% HPMC-sub coating on drug release from HPMCP coated propranolol pellets in 0 and 20% ethanol.

The usage of 50% HPMC resulted in a reduction in the accelerated release in 20% ethanol (Fig. 82). After 2 hours around 15% of the drug was released in 20% ethanol, which is only slightly above the desired value of 10% release. This low amount of released drug translates to a low risk of ethanolic dose dumping in-vivo.

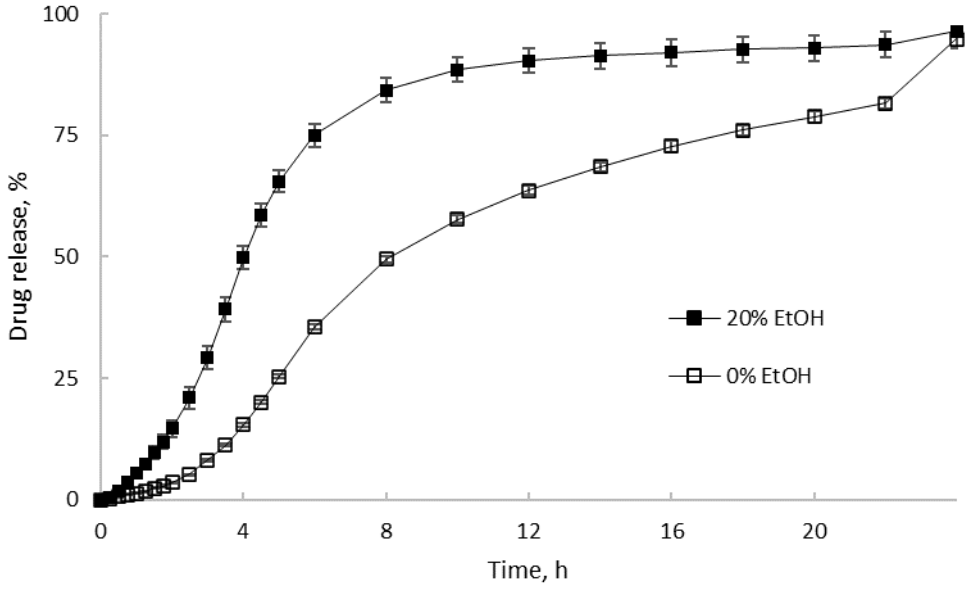


Fig. 82 Effect of 50% HPMC-sub coating on drug release from HPMCP coated propranolol pellets in 0 and 20% ethanol.

Both the use of a larger coating amount as well as the application of a subcoating can reduce the risk associated with the concomitant intake of ethanol and enteric coated pellets. However, both methods can also decrease the release rate in the intestine [310]. A sufficiently fast release in PBS

6.8 was observed from both Cellets® and subcoated Celphere® (Fig. 83). The Cellets® had a slightly longer lag time, whereas the subcoated pellets took longer to reach 100% release. However, both formulations released over 80% of the drug in 30 minutes and can thus be considered suitable enteric dosage forms.

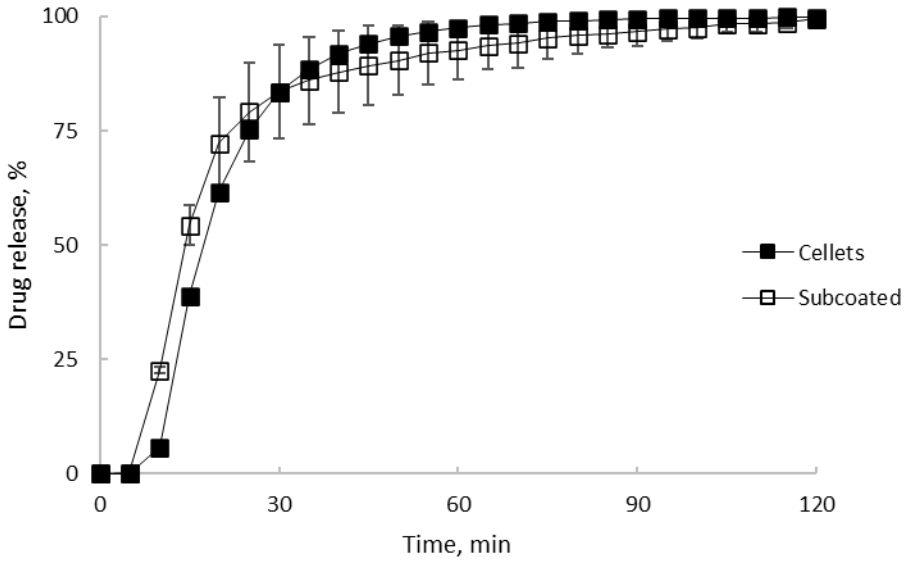


Fig. 83 Release of propranolol in PBS 6.8 from Cellets® or 50% sub coated Celphere® pellets coated with HPMCP.

3.5.3.3 The behavior of HPMCP-coated pellets layered with theophylline

Theophylline is less soluble than propranolol (Table 11) and may thus differ in its release behavior. Less than 10% coating level were required to achieve enteric-resistance in 0% ethanol (Fig. 84). In 20% ethanol, the release was accelerated compared to 0% ethanol, but it was slower than for propranolol (Fig. 71). The release of theophylline in 20% ethanol followed a zero-order release rate. This can be explained by the low solubility of theophylline and the possibility of a diffusion through the coating. Not all the theophylline could be dissolved at once, resulting in a constant concentration gradient and, therefore, zero order release.

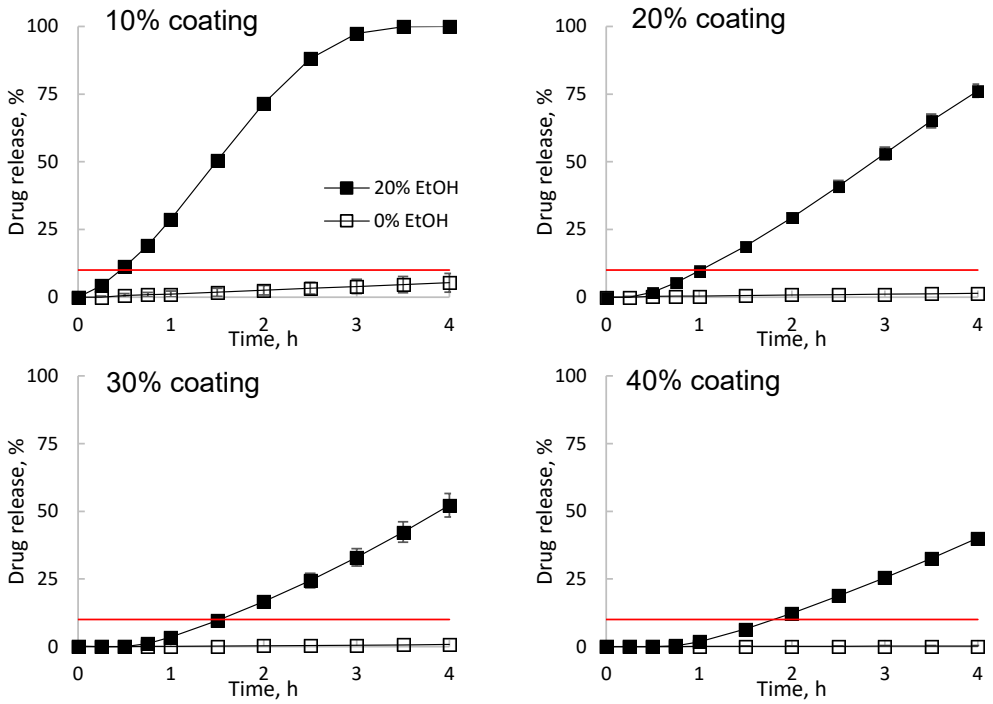


Fig. 84 Effect of coating level on release of theophylline layered onto MCC pellets in 0 or 20% ethanol.

The coating level affected both the release rate and the lag time (Fig. 85). With increasing coating level, the medium takes longer to penetrate and swell the coating. According to Fick's law of diffusion, the diffusion of the drug, the rate limiting step for the release after the lag time, is similarly reduced with increasing coating amount [30].

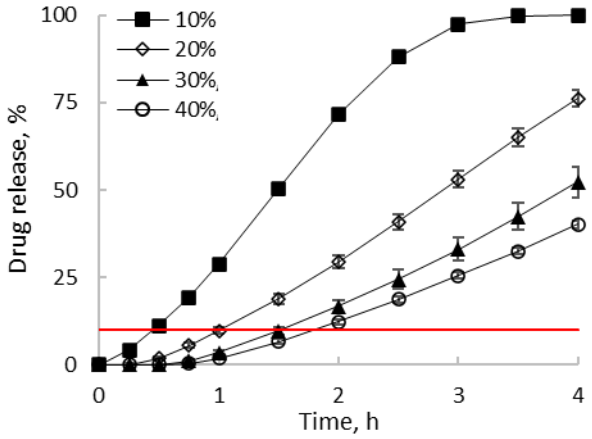


Fig. 85 Effect of coating level on release of theophylline layered onto MCC pellets in 20% ethanol.

As the accelerated release of propranolol in comparison to theophylline could be linked to a higher degree of swelling, the medium uptake of pellets layered with either drug was compared

(Table 16). The wet and dry weight of propranolol and theophylline were similar until 40 min, which is slightly before the onset of release. When the release started, at 85 and 120 min, the difference in wet weight between the drugs was increased. This can be attributed to the solubility and the different release mechanism: propranolol has a higher solubility and is released with an osmotic mechanism, which will likely result in micro ruptures of the coating. In contrast, theophylline has a low solubility. The inside of the pellet will quickly be saturated with a large amount of the theophylline still being undissolved. Thus, the osmotic pressure created by the theophylline is smaller than that of the propranolol, which will result in less medium taken up. The plateauing of the wet weight despite the release indicated, that theophylline can diffuse through the swollen polymer.

Table 16 Normalized wet and dry weight of propranolol and theophylline pellets coated with 40% HPMCP in 20% ethanol

	Wet weight		Dry weight		Wet weight / dry weight	
min	Propranolol	Theophylline	Propranolol	Theophylline	Propranolol	Theophylline
20	129.1	127.4				
40	138.3	137.6	94.6	95.5	146.14	144.2
85	164.3	147.4	90.0	93.9	182.6	156.9
120	171.2	144.2	89.4	93.3	191.5	154.6

The release rate of theophylline depended on the position of the drug inside the pellet. A layered pellet shows a faster relative release rate than a matrix pellet [61]. This behavior also applies to an enteric coating. Using a matrix core resulted in enteric-resistance even in 20% ethanol at a coating level of 30% (Fig. 86).

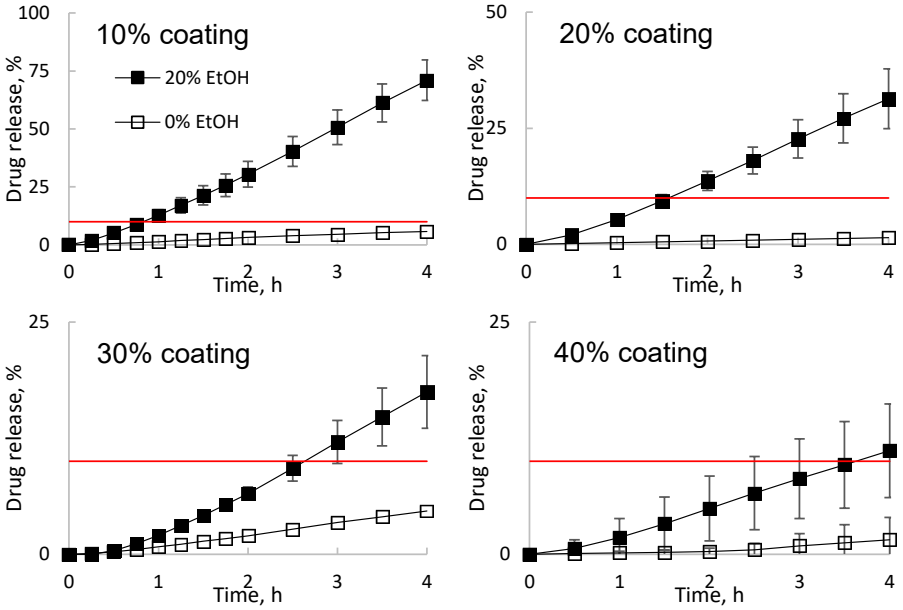


Fig. 86 Effect of coating level on release of theophylline from matrix pellets in 0 or 20% ethanol.

An increase of the coating level specifically led to a decrease in the steepness of the slope of release in 20% ethanol, whereas the onset of release, the point where drug first appears on the outside of the pellet coating, appears to be less affected by a further increase from 30% coating to 40% coating (Fig. 87). The same was observed for the layered pellets (Fig. 85). This may be the result of prior membrane swelling by the hydroethanolic media, which would facilitate the diffusion, and which may be less affected by the change in coating thickness than the drug diffusion.

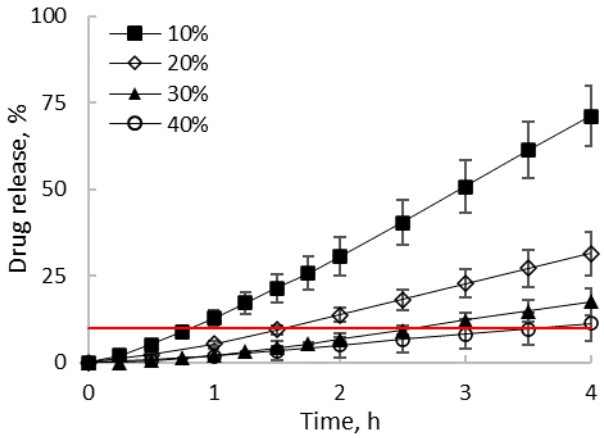


Fig. 87 Effect of coating level on release of theophylline from matrix pellets in 20% ethanol.

By comparing the zero-order release rate of theophylline with the sigmoidal shape of propranolol, it appears likely, that the release mechanism of propranolol and theophylline differs. The power-equation nicely described the t_{10} of propranolol-layered pellets (equation 20, Fig. 77). However, the t_{10} of theophylline matrix pellets followed a linear function and the layered theophylline pellets led to a square root type of function (Fig. 88). Therefore, applying the same power-equation to this type of system would result in a systematic error.

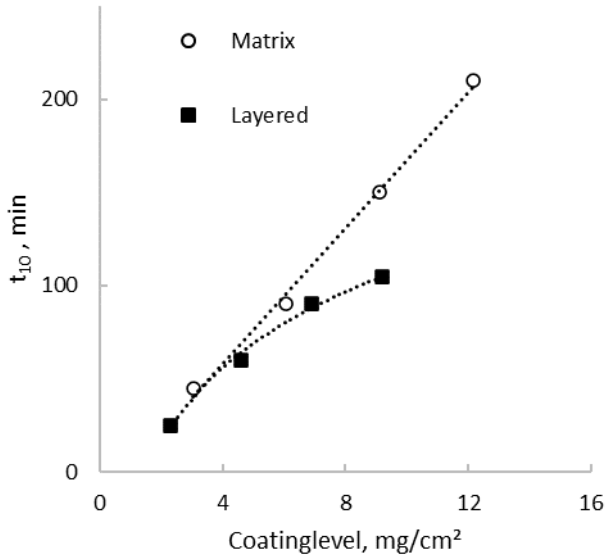


Fig. 88 Coating amount vs. t_{10} of theophylline layered pellets coated with HPMCP in 20% ethanol.

This difference in behavior can be attributed to the different release mechanisms. For the release by osmotic pumping the coating strength increases with increasing coating amount, whereas the

medium uptake decreases [300] (see also Chapter: 3.4.6, P. 110). In contrast, for a drug released via diffusion the t_{10} can be linear to coating thickness [311]. There are also some studies suggesting the lag-time of single substance diffusion depends on the square of the thickness [312, 313], which would result in a square root-dependency as observed (Fig. 88). Therefore, the shape of the relationship between t_{10} and coating amount depends not only on the release mechanism, but also on the distribution of the drug in the core.

As the drug solubility had a profound impact on the behavior in (acidic-) hydroethanolic media, it was important to clarify, if this also negatively affected the release at neutral pH. Matrix pellets were slightly slower in release, but both matrix and layered pellets released more than 75% of the drug in 30 minutes in PBS 6.8, which can be considered sufficiently fast release.

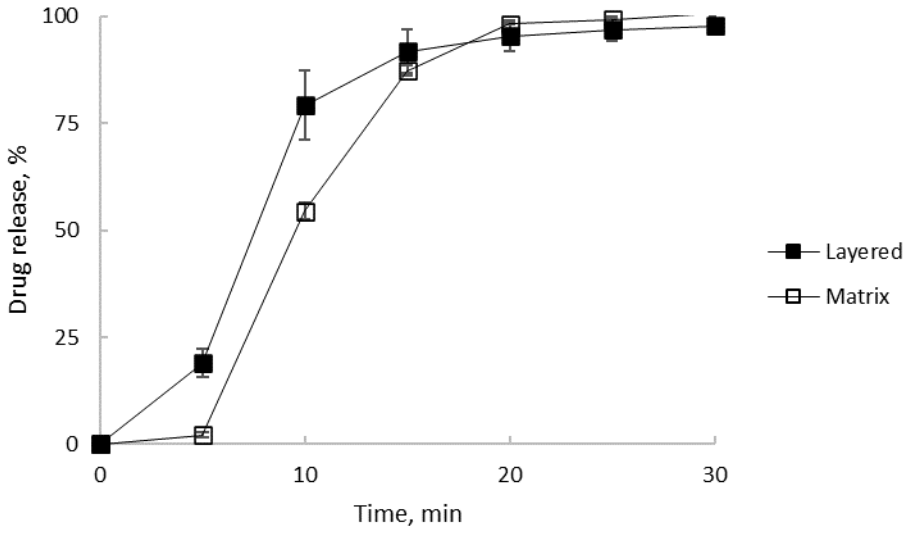


Fig. 89 Release of theophylline in PBS from layered and matrix pellets coated with 40% HPMCP in PBS 6.8.

Of all evaluated dosage forms, enteric-coated pellets are the most susceptible to an accelerated release in hydroethanolic media. The different requirements, compared to extended-release dosage forms, render the drugs of higher solubility like propranolol to be more challenging than drugs of lower solubility like theophylline. The use of a sufficiently thick coating, a subcoating or a drug-matrix-core can increase the lag time even in 20% ethanol, resulting in formulations that meet the European Medicines Agency (EMA) requirements.

4 Summary

The safety and efficacy of modified release drug formulations depend on their ability to allow a reproducible release that is affected as little as possible by external influences. These influences include the prandial status of a patient, the gastrointestinal motility as well as the concomitant intake of ethanol. Ethanol is a substance with a substantial risk of addiction and a risk of pharmacodynamic and pharmacokinetic interactions. It can additionally affect the modified release characteristics of drug formulations, by accelerating the release or even leading to dose dumping with potential toxic side effects. Despite being a regulatory requirement for drug applications, only little is known about the mechanisms of how ethanol can cause accelerated release.

The aim of this work was to identify formulation parameters that can affect the release in hydroethanolic media and possible approaches to mitigate this.

The effects of hydroethanolic media were assessed in-vitro according to the Food and Drug Administration (FDA) guidelines in a paddle apparatus in 0.1 N HCl containing 0, 20 or 40% ethanol. A basket apparatus was employed for the determination of medium uptake and, after drying in an oven, dry weight during the release testing. The swelling and visual observation of the pellets was performed with a macroscope without agitation. The ethanol content was evaluated using gas chromatography. The release profiles of matrix tablets and preliminary literature data were empirically fitted to determine the amount of release via diffusion. The preliminary literature data was evaluated using multiple imputation followed by multiple linear regression.

To summarize the finding of the published literature, a multiple linear regression with the ratio of the mean release time, the similarity value, and the ratio of the amount of release via diffusion was conducted. Accelerated release in hydroethanolic media was associated with a high partition coefficient of the drug, the use of a coating and a smaller dosage form size. The use of melting or granulation reduced the accelerated release. The amount of ethylcellulose for coated systems and of Kollidon® SR for matrix systems was associated with less accelerated release, whereas formulations with calcium stearate had a higher likelihood of accelerated release. There was very

little correlation between the accelerated release and the ratio of the release via diffusion, therefore this method cannot be used to predict accelerated release.

The effects of hydroethanolic media were assessed on commercial products. Four enteric products of duloxetine HCl gave similar release in 0.1 N HCl and PBS 6.8, but different release profiles and release mechanisms depending on the ethanol content. Pellets coated with Eudragit® L showed the fastest release in both 20% and 40% ethanol due to a rapid disintegration of the coating. The originator product Cymbalta®, using Hydroxypropyl methylcellulose-acetate-succinate (HPMCAS), showed only little size increase before the coating ruptured, whereas pellets coated with hydroxypropyl methylcellulose phthalate (HPMCP) showed a large size increase without any rupturing. Mini tablets coated with HPMCAS showed sufficient resistance in 20% ethanol, but not in 40% ethanol. Therefore, the release in hydroethanolic media may differ strongly between bioequivalent dosage forms and a change between these products for a patient with a history of alcohol abuse should not be recommended.

Furthermore, two extended-release formulations of doxazosin mesylate, an enteric coated matrix tablet and an osmotic tablet, were compared in different media. For the coated matrix tablet, the release increased, due to the disintegration of the coating with increasing ethanol content in 0.1 N HCl but was highest in pH 6.8 buffer. The osmotic tablet showed a strong increase in release with increasing ethanol content, but only after a lag time of 2 hours, which explains the absence of such findings in in-vivo studies.

Matrix tablets of hydroxypropyl methylcellulose K4M (HPMC) with metoprolol tartrate, theophylline, propranolol HCl, paracetamol or carbamazepine were prepared and tested in hydroethanolic media. Paracetamol and carbamazepine were further tableted with the hydrophilic polymers hydroxypropyl cellulose (HPC), polyethylenoxide (PEO), HPMC K100LV and K100M as well as with microcrystalline cellulose (MCC) and lactose. Later, the effect of the insoluble polymers Kollidon® SR, Eudragit® RS and ethylcellulose, alone and in combination with lactose for similar release in aqueous and hydroethanolic medium were investigated.

The accelerated release in 40% ethanol depended on the solubility ratio between hydroethanolic and aqueous media and not the solubility itself. The increased solubility ratio can increase the diffusional release of the drugs. For paracetamol, a higher medium uptake of polymers was

associated with more accelerated release, due to the increased drug dissolution and the use of HPC resulted in similar release at low and equivalent polymer amounts. However, at high polymer amounts the release in aqueous and hydroethanolic media was not similar for HPC, but for HPMC and PEO. The inclusion of both fillers, MCC and lactose, led to similar release for paracetamol, but lactose decreased the difference more strongly. Carbamazepine always released faster in 40% ethanol except for HPMC K100LV, where the erosion rate matched the diffusion rate, irrespective of drug loading. This was due to a shift in release mechanism from erosion-driven in aqueous media to a more diffusion-driven release in hydroethanolic media. The inclusion of both lactose and MCC led to similar release in 0% and 40% ethanol for carbamazepine also with HPMC K4M.

The release of paracetamol from tablets of insoluble polymers was only similar for Kollidon® SR, whereas the tablet prepared with Eudragit® RS completely disintegrated. The inclusion of lactose led to similar release for ethylcellulose. For carbamazepine, no combination of an insoluble polymer with any amounts of lactose provided similar release, emphasizing that these polymers are not suitable for very sparingly soluble drugs in hydroethanolic media.

For all evaluated drugs robust matrix formulations could be developed, either by choice of polymer or by the inclusion of appropriate fillers.

Enteric and extended-release coatings were applied onto pellets coated with propranolol.

The propranolol HCl release from pellets coated with Kollicoat® SR and Eudragit® RS increased significantly in 20 and 40% ethanol. For ethylcellulose-coated pellets, the effect of ethanol in the medium on release depended on the aqueous solubility of the drug and the coating ethylcellulose level. Increasing ethanol content in the medium, the release of metoprolol tartrate decreased due to drug-ethylcellulose interaction and the release of other drugs, e.g., theophylline increased due to selective uptake of ethanol by the coating. For propranolol HCl, the release was almost unchanged at 30% and 40% coating but increased for lower coating levels (10-20%). The osmotic release mechanism for propranolol HCl pellets coated with ethylcellulose was confirmed by release suppression in hyperosmotic media. The release mechanism of the drug changes from an osmotically driven mechanism to a diffusion-based release in 40% ethanol. At this concentration similar release is only achievable for drugs of higher solubility. ethylcellulose, as coating material

in combination with MCC cores, can be used to achieve release unaffected by ethanol up to 20% ethanol. Thereby, the coating level must equate the aqueous drug solubility.

All evaluated enteric formulations showed an increase in lag time and a reduction in slope with increasing coating strength. Both Eudragit® L and Sureteric® with guar gum did not allow appropriate enteric-resistance at reasonable coating amounts or rapidly disintegrated in 20% ethanol. HPMCP-coated pellets showed a linear relationship between coating amount and t_{10} in 20% ethanol. By including the surface to volume ratio of different-sized pellets an empiric equation was established to determine the timepoint at which 10% of the drug are released (t_{10}). This equation was successfully applied to calculate the t_{10} of smaller pellets. An appropriate t_{10} of 125 minutes was achieved at a coating amount of 10.5 $\frac{mg}{cm^2}$ for pellets with a diameter of 1.3 mm. The difference in release between 0% and 20% ethanol could also be reduced by applying a HPMC-subcoating. Both approaches did not impair the rapid release at pH 6.8.

HPMCP pellets layered with theophylline required less coating material to achieve enteric-resistance and showed a reduction in accelerated release compared to propranolol. Matrix pellets of theophylline were resistant to both 0.1 N HCl and 20% ethanol at 30% coating level. These pellets still showed rapid release at pH 6.8.

For each type of formulation, different approaches may be considered to avoid accelerated release in hydroethanolic media. However, except for the cases, where the release-modifying polymer itself rapidly dissolves or disintegrates in the release medium, hydroethanolic media mostly enhance the diffusion of the drug. They hereby allow a diffusion-driven release even if the release mechanism in aqueous media is different. Appropriate measures therefore focus either on increasing the drug release in aqueous media or reducing the diffusion in hydroethanolic media.

5 Zusammenfassung

Die Sicherheit und Effektivität von Arzneiformen mit veränderter Freisetzung hängen von ihrer Eigenschaft ab, eine reproduzierbare Freisetzung zu gewährleisten, die so wenig wie möglich durch externe Faktoren beeinflusst wird. Diese Faktoren beinhalten den prandialen Status eines Patienten, die gastrointestinale Motilität sowie die gleichzeitige Einnahme von Ethanol. Ethanol ist eine Substanz mit einem hohen Abhängigkeitsrisiko und einem Risiko für pharmakodynamische und pharmakokinetische Wechselwirkungen. Es kann zusätzlich die veränderte Wirkstofffreisetzung beeinflussen, indem es die Arzneistofffreigabe beschleunigt oder sogar zu einem Dose-dumping mit potenziell toxischen Nebenwirkungen führt. Obwohl es eine Zulassungsvoraussetzung für Arzneimittelanträge ist, ist bisher nur wenig bekannt über die Mechanismen, wie Ethanol zu einer beschleunigte Arzneistofffreisetzung führt.

Das Ziel dieser Arbeit war die Identifikation von Formulierungsparametern, die die Arzneistofffreisetzung in hydroethanolischen Medien beeinflussen und mögliche Herangehensweise diese zu vermeiden.

Der Einfluss von hydroethanolischen Medien wurde in-vitro untersucht gemäß den Food and Drug Administration (FDA)-Richtlinien in einer Blattrührer-Apparatur in 0.1 N HCl mit 0, 20 oder 40% ethanol. Eine Drehkörbchen Apparatur wurde für die Bestimmung der Mediumsaufnahme sowie, nach Trocknung in einem Ofen, dem Trockengewicht während der Freisetzung verwendet. Das Quellverhalten und die visuelle Untersuchung erfolgten mittels Makroskop ohne Agitation. Der Ethanol-Gehalt wurde mittels Gas Chromatographie ermittelt. Die Freisetzungsprofile von Matrixtabletten und der vorhandenen Literatur wurden empirisch angepasst, um die Menge der Freisetzung mittels Diffusion zu bestimmen. Die vorhandenen Literaturdaten wurden ausgewertet mittels multipler Imputation gefolgt von multipler linearer Regression.

Um die Ergebnisse der bisher veröffentlichten Studien zusammenzufassen, wurde eine multiple lineare Regression mit dem Verhältnis der mittleren Auflösungszeit, dem Ähnlichkeitswert (f_2) und dem Verhältnis der Menge an Freisetzung via Diffusion durchgeführt. Eine beschleunigte Freisetzung in hydroethanolischen Median war assoziiert mit einem großen Verteilungskoeffizienten des Arzneistoffes, der Verwendung eines Überzuges und eine kleinere Arzneiformgröße. Die Verwendung von Schmelz- oder Granulierverfahren reduzierte die

beschleunigte Freisetzung. Die Menge an Ethylcellulose in überzogenen Formulierungen und an Kollidon® SR in Matrixformulierungen war assoziiert mit weniger beschleunigter Freisetzung, wohingegen Formulierungen mit Calcium Stearat eine höhere Wahrscheinlichkeit für beschleunigte Freisetzung hatten. Es gab wenig Korrelation zwischen der beschleunigten Freisetzung und dem Verhältnis der Freisetzung mittels Diffusion, daher eignet sich diese Methode nicht, um eine beschleunigte Freisetzung vorherzusagen.

Der Einfluss von hydroethanolischen Medien wurde an kommerziellen Produkten ermittelt. Vier enterische Produkte von Duloxetin HCl führten zu ähnlichen Freisetzungen in 0.1 N HCl und PBS 6.8, aber unterschiedlichen Freisetzungsprofilen und -mechanismen in Abhängigkeit des Ethanolgehaltes. Mit Eudragit®L überzogene Pellets zeigten die schnellste Freisetzung sowohl in 20% als auch in 40% ethanol aufgrund eines rapiden Zerfalls des Überzuges. Das Ursprungsprodukt Cymbalta®, aus Hydroxypropylmethylcellulose-Acetat-Succinat (HPMCAS), zeigte nur leichte Größenzunahme bevor der Überzug rupturierte, wohingegen mit Hydroxypropylmethylcellulose-Phthalat (HPMCP) überzogene Pellets ein starkes Größenwachstum ohne Anzeichen von Rupturierung zeigte. Mit HPMCAS überzogene Mini-tabletten zeigten ausreichenden Schutz in 20% ethanol, aber nicht in 40% ethanol. Daher kann sich die Freisetzung in hydroethanolischen Medien zwischen bioäquivalenten Darreichungsformen stark unterscheiden und ein Austausch dieser Produkte bei Patienten mit Alkoholmissbrauch in der Anamnese sollte nicht empfohlen werden.

Des Weiteren wurden zwei Retardformulierungen von Doxazosin Mesylate, eine enterisch überzogene Matrixtablette und eine osmotische Tablette, in verschiedenen Medien verglichen. Für die überzogene Matrixtablette beschleunigte sich die Freisetzung mit dem Zerfall des Überzuges mit steigendem Ethanolgehalt in 0.1 N HCl, aber war am höchsten im pH 6.8 Puffer. Die osmotische Tablette zeigte eine starke Zunahme der Freisetzung mit steigendem Ethanolgehalt, aber erst nach einer Verzögerungszeit von 2 Stunden, was die Abwesenheit solcher Erkenntnisse in in-vivo Studien erklärt.

Matrixtabletten von Hydroxypropylmethylcellulose K4M (HPMC) mit Metoprolol Tartrat, Theophyllin, Propranolol HCl, Paracetamol und Carbamazepin wurden hergestellt und in hydroethanolischen Medien getestet. Paracetamol und Carbamazepin wurden des Weiteren mit den hydrophilen Polymeren Hydroxypropylcellulose (HPC), Polyethylenoxid (PEO), HPMC K100LV

und K100M sowie mit mikrokristalliner Cellulose (MCC) und Lactose tablettiert. Später wurden zudem der Einfluss der unlöslichen Polymere Kollidon® SR, Eudragit® RS und ethylcellulose, allein und in Kombination mit Lactose auf eine ähnliche Freisetzung in wässrigen und hydroethanolischen Medien hin untersucht.

Die beschleunigte Freisetzung in 40% Ethanol hing von dem Verhältnis der Löslichkeiten und nicht der Löslichkeit selbst ab. Eine erhöhtes Löslichkeitsverhältnis kann die Freisetzung der Arzneistoffe mittels Diffusion erhöhen. Für Paracetamol war eine größere Mediumsaufnahme der Polymere assoziiert mit mehr beschleunigter Freisetzung, aufgrund einer stärkeren Arzneistoffauflösung und die Verwendung von HPC resultierte in ähnlichen Freisetzungsprofilen bei niedrigen und äquivalenten Polymermengen. Bei großen Polymermengen war die Freisetzung hingegen nicht mehr ähnlich für HPC, jedoch für HPMC und PEO. Die Inkludierung von beiden Füllstoffen, MCC wie Lactose, führte zu ähnlicher Freisetzung für Paracetamol, aber Lactose reduzierte den Unterschied stärker. Carbamazepin wurde immer schneller freigesetzt in 40% ethanol, außer bei HPMC K100LV, wo die Erosionsrate der Diffusionsrate angepasst war, unabhängig von der Arzneistoffmenge. Dies lag an einer Verschiebung von erosions-basierter Freisetzung in wässrigen Medien zu einer vermehrt Diffusion-basierten Freisetzung in hydroethanolischen Medien. Die Inkludierung sowohl von Lactose als auch von MCC führte zu ähnlicher Arzneistofffreisetzung in 0% und 40% ethanol für Carbamazepin auch mit HPMC K4M.

Die Freisetzung von Paracetamol aus Tabletten aus unlöslichen Polymeren war nur ähnlich für Kollidon® SR, wohingegen die Tabletten, die mit Eudragit® RS hergestellt wurden, komplett zerfielen. Die Inkludierung von Lactose führte zu ähnlicher Freisetzung für ethylcellulose. Für Carbamazepine, keine Kombination eines unlöslichen Polymeres mit jeglicher Menge an Lactose erlaubte eine ähnliche Freisetzung, was hervorhebt, dass diese Polymere nicht für sehr schlecht lösliche Polymere in hydroethanolischen Medien geeignet sind.

Für alle evaluierten Arzneistoffe konnten robuste Matrixformulierungen entwickelt werden, entweder durch die Wahl des Polymers oder durch die Inkludierung geeigneter Füllstoffe.

Enterische- und Retardüberzüge wurden auf Pellets mit Propranolol aufgetragen.

Die Freisetzung von Propranolol HCl von Pellets mit einem Überzug aus Kollicoat® SR und Eudragit® RS war signifikant erhöht in 20 und 40% ethanol. Für Ethylcellulose-überzogene Pellets, hing der Einfluss von Ethanol im Medium auf die Arzneistofffreisetzung stark von der wässrigen Löslichkeiten des Arzneistoffes und dem Überzugslevel des ethylcellulose ab. Eine Erhöhung des Ethanolgehaltes im Medium reduzierte die Freisetzung von Metoprolol Tartrat aufgrund von Arzneistoff-Ethylcellulose-Interaktionen. Für Propranolol HCl, die Freisetzung war nahezu unverändert bei 30% und 40% Überzug, aber war erhöht für niedrigere Überzugsmengen (10-20%). Der osmotische Freisetzungsmechanismus von Ethylcellulose-überzogenen Propranolol HCl Pellets wurde bestätigt durch die Unterdrückung der Freisetzung in hyperosmotischem Medium. Der Freisetzungsmechanismus änderte sich von osmotischer Freisetzung zu einer Diffusion-basierten Freisetzung in 40% ethanol. Bei dieser Konzentration ist eine ähnliche Freisetzung nur möglich für Arzneistoffe mit höherer Löslichkeit. Ethylcellulose, als Überzugsmaterial in Verbindung mit MCC-Kernen, kann verwendet werden, um eine Freisetzung zu erzielen, die unabhängig ist von bis zu 20% ethanol. Hierbei muss das Überzugslevel der wässrigen Arzneistofflöslichkeit angepasst werden.

Alle evaluierten enterischen Formulierungen zeigten eine Zunahme der Verzögerungszeit und eine Reduktion der Steigung mit Zunahme der Überzugsstärke. Sowohl Eudragit® L wie auch Sureteric® mit Guarkernmehl erlaubten keine geeignete Magensaft-resistenz oder zerfielen rapide in 20% ethanol. HPMCP-überzogene Pellets zeigten ein lineares Verhältnis zwischen der Überzugsmenge und dem Zeitpunkt, an dem 10% des Arzneistoffes freigesetzt wurden (t_{10}) in 20% ethanol. Durch die Hinzunahme des Oberflächen-Volumen-Verhältnis wurde eine empirische Gleichung zur Ermittlung der Verzögerungszeit identifiziert. Diese Gleichung wurde erfolgreich angewandt, um die t_{10} kleinerer Pellets zu berechnen. Eine ausreichende Verzögerungszeit von 125 Minuten wurde erzielt mit einer Überzugsmenge von 10.5 $\frac{mg}{cm^2}$ für Pellets mit einem Durchmesser von 1.3 mm. Der Unterschied in der Freisetzung zwischen 0% und 20% ethanol konnte auch reduziert werden durch die Applikation einer HPMC-Zwischenschicht. Beide Ansätze behinderten nicht die schnelle Arzneistofffreisetzung bei pH 6.8.

Für jede Art der Formulierung sollten verschiedene Ansätze in Betracht gezogen werden, um eine beschleunigte Freisetzung in hydroethanolischen Medien zu vermeiden. Jedoch, außer in den Fällen, in denen das Freisetzungs-modifizierende Polymer selber im Freisetzungsmedium schnell

zerfällt oder sich auflöst, verstärken hydroethanolische Medien vorrangig die Diffusion des Arzneistoffes. Sie erlauben hiermit eine diffusions-gesteuerte Freisetzung selbst dann, wenn der Freisetzungsmechanismus in wässrigen Medien anders ist. Geeignete Maßnahmen fokussieren daher eine Erhöhung der Arzneistofffreisetzung in wässrigen Medien oder eine Reduktion der Diffusion in hydroethanolischen Medien.

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7 Appendices

7.1 Appendix A – Script for equation fitting

Appendix B contains the python script used for calculating the constants in the Peppas-Sahlin equation (equation 11, equation 12). The current setting was used for the literature evaluation (with the command IterateFolders()). The setting for the experimental data did not include a lag time. The burst release was added in at an earlier time point, but not used for the final evaluation.

```
import numpy as np
import matplotlib.pyplot as plt
import open3d as o3d
import math
import csv
import os
from pathlib import Path


timeintervals = 100
#m.time = np.linspace(0, timeframe, timeintervals)

def IterateFolders():
    global path, results, pathabbreviation
    results = {}
    results["Sample name"] = ["Samplename"]
    results["Ethanol content"] = ["Ethanol content"]
    results["Diffusion-Constant"] = ["Diffusion-Constant"]
    results["Exponent"] = ["Exponent"]
    results["Case-II-constant"] = ["Case-II-constant"]
    results["Burst-release"] = ["Burst-release"]
    results["Lag-time"] = ["Lag-time"]
    results["Determination-coefficient"] = ["Determination-coefficient"]
    results["Total-percent-Diffusion"] = ["Total-percent-Diffusion"]
    print(results)
    path_of_the_directory = '\Raw data'
    paths = Path(path_of_the_directory).glob('**/*.csv')
    pathabbreviations = []
    for path in paths:
        print(path)
        pathabbreviation = path
        givePowerLaw()
def DataFromCsv():
    global first_col2, sec_col2, third_col2, fourth_col2, fifth_col2, sixth_col2
    csv_file = np.genfromtxt(path,  # enter Data path
                             delimiter=';', dtype="str")  # , usecols=np.arange(0,3))

    # The timepoints in the CSV-File should start with 0,0, otherwise Errors may arise in the calculation
```

```
first_row = csv_file[0, :].tolist()  # Complete first column
first_row2 = []
print(first_row2)

first_col = csv_file[:, 0].tolist()  # Complete first column
first_col2 = []
col_length = 30

for i in first_col[2:col_length]:  # Replacing commas by points
    x = i.replace(",", ".")
    try:
        x = (float(x))
    except ValueError:
        print(x)
    first_col2.append(x)
print(first_col2)  # + ")")
sec_col = csv_file[:, 1].tolist()
sec_col2 = []
for i in sec_col[2:col_length]:  # Replacing commas by points
    x = i.replace(",", ".")

    try:
        x = float(x)
    except ValueError:
        print(x)
    sec_col2.append(x)
print(sec_col2)  # + ")")

third_col = csv_file[:, 2].tolist()
third_col2 = []
for i in third_col[2:col_length]:
    x = i.replace(",", ".")
    try:
        x = float(x)
    except ValueError:
        print(x)
    third_col2.append(x)
print(third_col2)  # + ")")

fourth_col = csv_file[:, 3].tolist()
fourth_col2 = []
for i in fourth_col[2:col_length]:
    x = i.replace(",", ".")
    try:
        x = float(x)
    except ValueError:
        print(x)
    fourth_col2.append(x)
print(fourth_col2)  # + ")")
try:
    fifth_col = csv_file[:, 4].tolist()
    fifth_col2 = []
    for i in fifth_col[2:col_length]:
        x = i.replace(",", ".")
        try:
            x = float(x)
```

```
            except ValueError:
                print(x)
            fifth_col2.append(x)
        print(fifth_col2)  # + ")")
        sixth_col = csv_file[:, 5].tolist()
        sixth_col2 = []
        for i in sixth_col[2:col_length]:
            x = i.replace(",", ".")
            try:
                x = float(x)
            except ValueError:
                print(x)
            sixth_col2.append(x)
        print(sixth_col2)  # + ")")
    except:
        print("Only 3 columns")
    print("\n\n\n")


def adjust_Korsmeyer_peppas():
    global adjusted_paracetime, adjusted_paracet40ethanol, adjusted_paracetHCl,
adjusted_comparison, mean, res, exponent_calculated, Comparison_parameter

    comparison_time = timevalues # Time parameter to evaluate
    exponent_calculated = [0.4501]



    adjusted_paracetime = []
    adjusted_paracet40ethanol = []
    adjusted_paracetHCl = []
    adjusted_comparison = []
    for i in range(len(comparison_time)):
        if Comparison_parameter[i] < 60:
            adjusted_paracetime.append(comparison_time[i])
            adjusted_comparison.append(Comparison_parameter[i])
    mean = sum(adjusted_comparison) / len(adjusted_comparison)
    res = sum((ii - mean) ** 2 for ii in adjusted_comparison)

# Korsmeyer Peppas equation according to Ford et al, used for comparison purposes
def korsmeyer_peppas():
    regressionlist = []
    adjust_Korsmeyer_peppas()
    for i in range(1,350):
        for j in range(45,101):
            for b in range(0,10):
                for l in range(0,10):
                    bulkconc = []
                    #bulkconc = m.Var(value=0, lb=0, ub=100)  #
Intermediate(bulksolubility/MediaVolumeGC)
                    kinetic_constant = i/100      # Kinetic constant for Korsmeyer Peppas
                    diffusional_exponent = j/100   # Diffusional exponent according to Korsmeyer Peppas
                    burst = float(b)
                    lag = (float(l))
                    print(i)
                    print(j)
                    print("\n")
```

```
            for timepoint in adjusted_paracetime:
                lagged_timepoint = timepoint-lag if timepoint-lag >= 0 else 0
                currentconc = (kinetic_constant)*((lagged_timepoint)**diffusional_exponent)+burst
                bulkconc.append(currentconc)

            def regressioncoefficient():
                                # Calculation of the regression coefficient
                global regressionarray2
                bulkconc2 = np.array(bulkconc)
                #  bulkconc2 = bulkconc.astype(float)
                #  paracetHCl2 = paracetHCl.astype(float)
                #  regression = np.corrcoef(paracet40ethanol, bulkconc2.astype(float))
                # regrestopass=float(regression[0,1])
                totalsum = 0
                for datapoint in range(len(adjusted_paracetime)):
                    x_add = (abs(adjusted_comparison[datapoint]) - abs(bulkconc[datapoint]))**2
                    totalsum = totalsum + x_add
                regressionlist.append(([float(i),float(j), float(b), float(l), float(totalsum/res)]))
            regressioncoefficient()
# plot results

minRegression = (min([sublist[-1] for sublist in regressionlist]))
print(minRegression)
for sublist in regressionlist:
    if sublist[-1] == minRegression:
        bulkconc2 = []
        # bulkconc = m.Var(value=0, lb=0, ub=100)  # Intermediate(bulksolubility/MediaVolumeGC)
        kinetic_constant = sublist[0] / 100  # Kinetic constant for Korsmeyer Peppas
        diffusional_exponent = sublist[1] / 100  # Diffusional exponent according to Korsmeyer Peppas
        burst = sublist[2]   # Burst release according to Korsmeyer Peppas
        lag = sublist[3]   # lag time according to Korsmeyer Peppas
        print("Kinetic Constant " + (str(kinetic_constant)))
        print("Diffusional constant " + (str(diffusional_exponent)))
        print("Burst release " + (str(burst)))
        print("Lag time " + (str(lag)))
        print("Determination coefficient " + (str(1-(sublist[-1]))))
        for timepoint2 in adjusted_paracetime:
            lagged_timepoint2 = timepoint2 - lag if timepoint2 - lag >= 0 else 0
            currentconc2 = kinetic_constant * (lagged_timepoint2 ** diffusional_exponent) + burst
            bulkconc2 = np.append(bulkconc2, currentconc2)
#bulkconc = np.delete(bulkconc, [0])
plt.figure(1)
plt.plot(adjusted_paracetime, bulkconc2, "b")
plt.plot(adjusted_paracetime, adjusted_comparison, "yo")
plt.plot(adjusted_paracetime, adjusted_paracetHCl, "bo")
# plt.plot(m.time, solubilityGC, "r")
# plt.plot(m.time, releasedifference, "y")
plt.xlabel("Time(min)")
plt.ylabel("Concentration(mg/L)")
plt.legend(["Parameter 1", "40% ethanol", "0% ethanol"])  #
plt.show()

plt.figure(2)
plt.plot([sublist[-5] for sublist in regressionlist], [sublist[-1] for sublist in regressionlist], "b")
# plt.plot(m.time, solubilityGC, "r")
# plt.plot(m.time, releasedifference, "y")
plt.xlabel("Time(min)")
```

```
    plt.ylabel("Concentration(mg/L)")
    plt.legend(["Parameter 1", "40% ethanol", "0% ethanol"])  #
    plt.show()

def peppas_sahlin():
    global results, pathabbreviation
    regressionlist = []
    adjust_Korsmeyer_peppas()
    for i in range(1, 5001, 10):
        for j in range(1, 5001, 10):
            for m in range(0, 1):
                for b in range(0, 1):
                    for l in range(0, 120, 5):
                        bulkconc = []
                        #bulkconc = m.Var(value=0, lb=0, ub=100)  #
Intermediate(bulksolubility/MediaVolumeGC)
                        diffusion_constant = i/100      # Diffusion constant for Siepmann Peppas
                        caseII_constant = j/1000        # Case-II part according to Siepmann Peppas
                        exponent = exponent_calculated[0] # m/100   # Diffusional exponent according to
Siepmann Peppas
                        burst = float(b)
                        lag = (float(l))
                        for timepoint in adjusted_paracetime:
                            lagged_timepoint = timepoint-lag if timepoint-lag >= 0 else 0
                            currentconc = ((diffusion_constant) * (
                                    (lagged_timepoint) ** exponent) + caseII_constant * lagged_timepoint ** (
                                            2 * exponent) + burst)
                            bulkconc.append(currentconc)

                        """for timepoint in adjusted_paracetime:
                            lagged_timepoint = timepoint-lag if timepoint-lag >= 0 else 0
                            currentconc = (diffusion_constant)*((lagged_timepoint)**exponent)+
caseII_constant*lagged_timepoint**(2*exponent) + burst
                            bulkconc.append(currentconc)"""
                        def regressioncoefficient():
                            global regressionarray2
                            bulkconc2 = np.array(bulkconc)
                            #bulkconc2 = bulkconc.astype(float)
                            #paracetHCl2 = paracetHCl.astype(float)
                            #regression = np.corrcoef(paracet40ethanol, bulkconc2.astype(float))
                            # regrestopass=float(regression[0,1])
                            totalsum = 0
                            for datapoint in range(len(adjusted_paracetime)):
                                x_add = (abs(adjusted_comparison[datapoint]) - abs(bulkconc[datapoint]))**2
                                totalsum = totalsum + x_add

                            regressionlist.append(([float(diffusion_constant),
                                                    float(caseII_constant),
                                                    float(exponent),
                                                    float(b),
                                                    float(l),
                                                    float(totalsum/res)]))
                        regressioncoefficient()
        # plot results

    minRegression = (min([sublist[-1] for sublist in regressionlist]))
    print(minRegression)
```

```
   for sublist in regressionlist:
      if sublist[-1] == minRegression:
         bulkconc2 = []
         # bulkconc = m.Var(value=0, lb=0, ub=100)  # Intermediate(bulksolubility/MediaVolumeGC)
         diffusion_constant = sublist[0]   # Kinetic constant for Korsmeyer Peppas
         caseII_constant = sublist[1]  # Diffusional exponent according to Korsmeyer Peppas
         exponent = sublist[2]     # Exponent accodring to Siepmann Peppas
         burst = sublist[3]   # Burst release according to Korsmeyer Peppas
         lag = sublist[4]   # lag time according to Korsmeyer Peppas
         print("Diffusion Constant " + (str(diffusion_constant)))
         print("Exponent " + (str(exponent)))
         print("Case-II constant" + (str(caseII_constant)))
         print("Burst release " + (str(burst)))
         print("Lag time " + (str(lag)))
         print("Determination coefficient " + (str(1-(sublist[-1]))))
         determinationCoefficient = (str(1-(sublist[-1])))

         fickian_contribution = []
         fickian_contribution_totalamount = 0
         for timepoint in adjusted_paracetime:
            lagged_timepoint = timepoint - lag if timepoint - lag >= 0 else 0
            currentconc = (diffusion_constant) * (
                  (lagged_timepoint) ** exponent) + caseII_constant *
lagged_timepoint**(2*exponent)+burst
            bulkconc2.append(currentconc)

            lagged_timepoint = timepoint - lag if timepoint - lag >= 0 else 0


            fickian_contributionparameter =
1/(1+caseII_constant/diffusion_constant*lagged_timepoint**exponent)
            fickian_contribution.append(fickian_contributionparameter*100)
            current_index = adjusted_paracetime.index(timepoint)
            if timepoint >= lag and timepoint !=0:
               fickian_contribution_add=(timepoint-adjusted_paracetime[current_index-1])*\

((fickian_contribution[current_index]+fickian_contribution[current_index-1])/2)
               fickian_contribution_totalamount =
fickian_contribution_totalamount+fickian_contribution_add
         fickian_contribution_totalpercent =
fickian_contribution_totalamount/(adjusted_paracetime[-1]*100)
   #bulkconc = np.delete(bulkconc, [0])
   try:
      print("Total percent Diffusion: "+ str(fickian_contribution_totalpercent))
   except UnboundLocalError:
      print("this is the sublist")
      print(sublist[-1])
      determinationCoefficient = 0
      fickian_contribution_totalpercent = 0
      print(pathabbreviation)
   results["Ethanol content"].append(etohcont)
   results["Sample name"].append(pathabbreviation)
   results["Diffusion-Constant"].append(diffusion_constant)
   results["Exponent"].append(exponent)
   results["Case-II-constant"].append(caseII_constant)
   results["Burst-release"].append(burst)
   results["Lag-time"].append(lag)
```

```
    results["Determination-coefficient"].append(float(determinationCoefficient))
    results["Total-percent-Diffusion"].append(fickian_contribution_totalpercent)
    if (caseII_constant) == "":
        StopIteration
        print(pathabbreviation)


def korsmeyer_peppas_analytical():
    regressionlist = []
    adjust_Korsmeyer_peppas()
    for i in range(100,151):
        for j in range(41,101):
            for b in range(0,21):
                for l in range(0,21):
                    bulkconc = []
                    #bulkconc = m.Var(value=0, lb=0, ub=100)  #
Intermediate(bulksolubility/MediaVolumeGC)
                    kinetic_constant = i/100      # Kinetic constant for Korsmeyer Peppas
                    diffusional_exponent = j/100   # Diffusional exponent according to Korsmeyer Peppas
                    burst = float(b)
                    lag = (float(l))
                    print(i)
                    print(j)
                    print("\n")
                    for timepoint in adjusted_paracetime:
                        lagged_timepoint = timepoint-lag if timepoint-lag >= 0 else 0
                        currentconc = (kinetic_constant)*((lagged_timepoint)**diffusional_exponent)+burst
                        bulkconc.append(currentconc)

                    def regressioncoefficient():
                        global regressionarray2
                        bulkconc2 = np.array(bulkconc)
                        #bulkconc2 = bulkconc.astype(float)
                        #paracetHCl2 = paracetHCl.astype(float)
                        #regression = np.corrcoef(paracet40ethanol, bulkconc2.astype(float))
                        # regrestopass=float(regression[0,1])
                        totalsum = 0
                        for datapoint in range(len(adjusted_paracetime)):
                            x_add = (abs(adjusted_comparison[datapoint]) - abs(bulkconc[datapoint]))**2
                            totalsum = totalsum + x_add
                        regressionlist.append(([float(i),float(j), float(b), float(l), float(totalsum/res)]))
                    regressioncoefficient()
    # plot results

    minRegression = (min([sublist[-1] for sublist in regressionlist]))
    print(minRegression)
    for sublist in regressionlist:
        if sublist[-1] == minRegression:
            bulkconc2 = []
            # bulkconc = m.Var(value=0, lb=0, ub=100)  # Intermediate(bulksolubility/MediaVolumeGC)
            kinetic_constant = sublist[0] / 100  # Kinetic constant for Korsmeyer Peppas
            diffusional_exponent = sublist[1] / 100  # Diffusional exponent according to Korsmeyer Peppas
            burst = sublist[2]   # Burst release according to Korsmeyer Peppas
            lag = sublist[3]   # lag time according to Korsmeyer Peppas
            print("Kinetic Constant " + (str(kinetic_constant)))
            print("Diffusional constant " + (str(diffusional_exponent)))
            print("Burst release " + (str(burst)))
```

```
        print("Lag time " + (str(lag)))
        print("Determination coefficient " + (str(1-(sublist[-1]))))
        for timepoint2 in adjusted_paracetime:
            lagged_timepoint2 = timepoint2 - lag if timepoint2 - lag >= 0 else 0
            currentconc2 = (kinetic_constant) * ((lagged_timepoint2) ** diffusional_exponent) + burst
            bulkconc2 = np.append(bulkconc2, currentconc2)
    #bulkconc = np.delete(bulkconc, [0])
    plt.figure(1)
    plt.plot(adjusted_paracetime, bulkconc2, "b")
    plt.plot(adjusted_paracetime, adjusted_comparison, "yo")
    plt.plot(adjusted_paracetime, adjusted_paracetHCl, "bo")
    # plt.plot(m.time, solubilityGC, "r")
    # plt.plot(m.time, releasedifference, "y")
    plt.xlabel("Time(min)")
    plt.ylabel("Concentration(mg/L)")
    plt.legend(["Parameter 1", "40% ethanol", "0% ethanol"])  #
    plt.show()

    plt.figure(2)
    plt.plot([sublist[-5] for sublist in regressionlist], [sublist[-1] for sublist in regressionlist], "b")
    # plt.plot(m.time, solubilityGC, "r")
    # plt.plot(m.time, releasedifference, "y")
    plt.xlabel("Time(min)")
    plt.ylabel("Concentration(mg/L)")
    plt.legend(["Parameter 1", "40% ethanol", "0% ethanol"])  #
    plt.show()

    def peppas_sahlin():
        regressionlist = []
        adjust_Korsmeyer_peppas()
        for i in range(101, 151, 1):
            for j in range(0, 101, 1):
                for m in range(0, 1):
                    for b in range(0, 11):
                        for l in range(0, 11):
                            bulkconc = []
                            # bulkconc = m.Var(value=0, lb=0, ub=100)  #
Intermediate(bulksolubility/MediaVolumeGC)
                            diffusion_constant = i / 100  # Diffusion constant for Siepmann Peppas
                            caseII_constant = j / 100  # Case-II part according to Siepmann Peppas
                            exponent = exponent_calculated[
                                0]  # m/100   # Diffusional exponent according to Siepmann Peppas
                            burst = float(b)
                            lag = (float(l))
                            print(i)
                            print(j)
                            print("\n")
                            for timepoint in adjusted_paracetime:
                                lagged_timepoint = timepoint - lag if timepoint - lag >= 0 else 0
                                currentconc = (diffusion_constant) * (
                                        (lagged_timepoint) ** exponent) + caseII_constant * lagged_timepoint ** (
2 * exponent) + burst
                                bulkconc.append(currentconc)

                            def regressioncoefficient():
                                global regressionarray2
                                bulkconc2 = np.array(bulkconc)
```

```
                    # bulkconc2 = bulkconc.astype(float)
                    # paracetHCl2 = paracetHCl.astype(float)
                    # regression = np.corrcoef(paracet40ethanol, bulkconc2.astype(float))
                    # regrestopass=float(regression[0,1])
                    totalsum = 0
                    for datapoint in range(len(adjusted_paracetime)):
                        x_add = (abs(adjusted_comparison[datapoint]) - abs(bulkconc[datapoint])) ** 2
                        totalsum = totalsum + x_add

                    regressionlist.append(([float(i),
                                            float(j),
                                            float(exponent),
                                            float(b),
                                            float(l),
                                            float(totalsum / res)]))

                regressioncoefficient()
        # plot results

    minRegression = (min([sublist[-1] for sublist in regressionlist]))
    print(minRegression)
    for sublist in regressionlist:
        if sublist[-1] == minRegression:
            bulkconc2 = []
            # bulkconc = m.Var(value=0, lb=0, ub=100)  # Intermediate(bulksolubility/MediaVolumeGC)
            diffusion_constant = sublist[0] / 100  # Kinetic constant for Korsmeyer Peppas
            caseII_constant = sublist[1] / 100  # Diffusional exponent according to Korsmeyer Peppas
            exponent = sublist[2]  # Exponent accodring to Siepmann Peppas
            burst = sublist[3]  # Burst release according to Korsmeyer Peppas
            lag = sublist[4]  # lag time according to Korsmeyer Peppas
            print("Diffusion Constant " + (str(diffusion_constant)))
            print("Exponent " + (str(exponent)))
            print("Case-II constant" + (str(caseII_constant)))
            print("Burst release " + (str(burst)))
            print("Lag time " + (str(lag)))
            print("Determination coefficient " + (str(1 - (sublist[-1]))))
            fickian_contribution = []
            fickian_contribution_totalamount = 0
            for timepoint in adjusted_paracetime:
                lagged_timepoint = timepoint - lag if timepoint - lag >= 0 else 0
                currentconc = (diffusion_constant) * (
                    (lagged_timepoint) ** exponent) + caseII_constant * lagged_timepoint ** (
                            2 * exponent) + burst
                bulkconc2.append(currentconc)
                fickian_contributionparameter = 1 / (
                        1 + caseII_constant / diffusion_constant * lagged_timepoint ** exponent)
                fickian_contribution.append(fickian_contributionparameter * 100)
                current_index = adjusted_paracetime.index(timepoint)
                if timepoint != 0.0:
                    fickian_contribution_add = (timepoint - adjusted_paracetime[current_index - 1]) * \
                                ((fickian_contribution[current_index] + fickian_contribution[
                                    current_index - 1]) / 2)
                    fickian_contribution_totalamount = fickian_contribution_totalamount +
fickian_contribution_add
            fickian_contribution_totalpercent = fickian_contribution_totalamount /
(adjusted_paracetime[-1] * 100)
    # bulkconc = np.delete(bulkconc, [0])
```

```
        print("Total percent Diffusion: " + str(fickian_contribution_totalpercent))
        plt.figure(1)
        plt.plot(adjusted_paracetime, bulkconc2, "b")
        plt.plot(adjusted_paracetime, adjusted_comparison, "yo")
        plt.plot(adjusted_paracetime, fickian_contribution, "g")
        # plt.plot(m.time, solubilityGC, "r")
        # plt.plot(m.time, releasedifference, "y")
        plt.xlabel("Time(min)")
        plt.ylabel("Concentration(mg/L)")
        plt.legend(["Parameter 1", "Comparison parameter", "Fickian diffusion contribution"])  #
        plt.show()

        plt.figure(2)
        plt.plot([sublist[-5] for sublist in regressionlist], [sublist[-1] for sublist in regressionlist], "b")
        # plt.plot(m.time, solubilityGC, "r")
        # plt.plot(m.time, releasedifference, "y")
        plt.xlabel("Time(min)")
        plt.ylabel("Concentration(mg/L)")
        plt.legend(["Parameter 1", "40% ethanol", "0% ethanol"])  #
        plt.show()

def givePowerLaw():
    global Height, Diameter, Radius, timefrage, timevalues, Comparison_parameter, results, etohcont
    DataFromCsv()
    timevalues = first_col2
    Diameter = 11.07
    Height = 4.54
    timeframe = len(timevalues)
    m.time = timevalues
    Radius = Diameter / 2
    Comparison_parameter = np.array(sec_col2) # Parameter to evaluate
    #korsmeyer_peppas_analytical()
    """results = {}
    results["Diffusion-Constant"] = ["Diffusion-Constant"]
    results["Exponent"] = ["Exponent"]
    results["Case-II-constant"] = ["Case-II-constant"]
    results["Burst-release"] = ["Burst-release"]
    results["Lag-time"] = ["Lag-time"]
    results["Determination-coefficient"] = ["Determination-coefficient"]
    results["Total-percent-Diffusion"] = ["Total-percent-Diffusion"]
    print(results)"""
    if first_col2[1] != "":
        etohcont = "40"
        peppas_sahlin()
    timevalues = third_col2
    Comparison_parameter = np.array(fourth_col2) # Parameter to evaluate
    if third_col2[1] != "":
        etohcont = "20"
        peppas_sahlin()
    timevalues = fifth_col2
    Comparison_parameter = np.array(sixth_col2) # Parameter to evaluate
    etohcont = "0"
    peppas_sahlin()
    with open('output.csv', 'w') as csvfile:
        header_key = results.keys()
        new_val = csv.DictWriter(csvfile, fieldnames=header_key, delimiter=";")
```

```
    new_val.writeheader()
    for new_k in results:
        new_val.writerow({"Diffusion-Constant": new_k, "Diffusion-Constant": results[new_k]})
    """
   "Diffusion-Constant"].append(diffusion_constant)
results["Exponent"].append(exponent)
results["Case-II-constant"].append(caseII_constant)
results["Burst-release"].append(burst)
results["Lag-time"].append(lag)
results["Determination-coefficient"].append(str(determinationCoefficient))
results["Total-percent-Diffusion"]


    for row in results.keys():

        sublist = [results[row][0],results[row][1],results[row][2],results[row][3]]
        sublisting = " ".join([str(i) for i in sublist])
        sublisting2 = str(sublisting.replace(".",","))
        sublisting3 = list(sublisting2.split(" "))
        csvwriter.writerow(sublisting3)"""
```

~~~~~~

7.2 Appendix B – Correlation matrix of variables used in the MLR

The term NaN refers to data that did not appear together in any publication and thus cannot be correlated.
~~~~~~

Variable	Calcium stearate	Carbopol 971 P NF	Carbopol 974 P	Ethylcellulose	Eudragit RS	Glycerol Dibehenate	Guar gum	HPC
Calcium stearate	1.00	-0.06	-0.04	-0.09	-0.08	-0.01	0.11	-0.04
Carbopol 971 P NF	-0.06	1.00	-0.04	-0.10	-0.08	-0.08	-0.05	-0.04
Carbopol 974 P	-0.04	-0.04	1.00	-0.08	-0.06	-0.07	-0.04	-0.03
Ethylcellulose	-0.09	-0.10	-0.08	1.00	-0.13	-0.14	0.25	-0.06
Eudragit RS	-0.08	-0.08	-0.06	-0.13	1.00	-0.12	-0.07	-0.05
Glycerol Dibehenate	-0.01	-0.08	-0.07	-0.14	-0.12	1.00	-0.08	-0.06
Guar gum	0.11	-0.05	-0.04	0.25	-0.07	-0.08	1.00	-0.03
HPC	-0.04	-0.04	-0.03	-0.06	-0.05	-0.06	-0.03	1.00
HPMC	-0.09	-0.09	-0.07	-0.16	-0.13	-0.08	-0.09	-0.06
Hydroxypropylstarch	-0.05	-0.05	-0.04	-0.09	0.65	-0.08	-0.05	-0.04
Kollidon SR	-0.06	-0.06	-0.05	-0.11	-0.09	0.08	-0.06	-0.04
Lactose	-0.06	-0.02	-0.05	-0.10	-0.08	0.10	-0.06	-0.04
Mannitol	-0.03	-0.03	-0.02	-0.05	-0.04	-0.05	-0.03	0.80
MCC	-0.13	-0.10	-0.10	-0.22	-0.13	0.41	-0.12	-0.08
PEO	-0.05	-0.05	-0.04	-0.09	-0.08	-0.08	0.31	0.28
PVA	-0.05	-0.05	-0.04	-0.08	0.34	-0.06	-0.05	-0.03
Povidone	-0.03	-0.03	-0.03	-0.06	-0.05	-0.05	-0.03	-0.02
Propylenglycol alginate	-0.08	-0.08	-0.06	-0.13	0.90	-0.12	-0.07	-0.05
Talc	-0.05	-0.05	-0.04	-0.08	-0.07	-0.07	-0.05	-0.03
Titanium dioxide	0.52	-0.03	-0.02	-0.05	-0.04	-0.05	0.22	-0.02
Xanthan gum	-0.05	-0.05	-0.04	-0.09	-0.07	-0.08	-0.05	-0.03
Size[mm]	-0.32	0.04	-0.02	-0.59	0.10	0.32	-0.29	0.08
Solubility release media[g/L]	0.38	0.07	0.07	-0.13	-0.10	0.01	0.01	-0.01
log D	-0.08	-0.12	-0.15	-0.18	-0.02	-0.03	-0.21	-0.01
40% EtOH solubility[g/L]	0.07	0.11	0.04	-0.27	-0.09	0.11	-0.10	0.04
Solubility ratio 40	-0.03	-0.03	-0.03	-0.06	-0.05	-0.05	-0.03	-0.02
Drug loading (%)	-0.34	0.45	0.37	0.32	0.09	-0.33	-0.01	-0.26
Compression strength [MPa]	NaN	0.19	0.19	NaN	NaN	-0.19	NaN	NaN
Breaking Force [N]	NaN	-0.22	NaN	NaN	NaN	0.47	NaN	NaN
Preparation[Melted]	0.35	-0.02	-0.14	0.58	-0.25	-0.13	0.33	-0.23
Tablet type [Coated=1;matrix=0]	-0.15	-0.15	-0.12	0.67	-0.20	0.17	0.12	-0.10
F2 40	-0.10	0.06	-0.09	0.22	-0.07	0.06	0.13	0.19
ASD 40	0.00	-0.09	-0.03	-0.16	0.03	-0.11	-0.10	-0.07
F2 20	0.19	0.02	-0.15	0.09	-0.19	0.14	0.12	NaN
ASD 20	-0.11	-0.09	-0.02	-0.07	0.12	-0.10	-0.09	NaN
MDT 40	-0.12	0.08	-0.04	-0.11	-0.17	0.12	-0.07	-0.07
MDT 20	0.03	0.14	-0.06	-0.02	-0.11	0.03	-0.14	NaN
MDT 0	0.16	0.01	-0.09	-0.06	-0.16	0.05	-0.07	-0.08
MDT 40/ratio	-0.21	0.17	0.13	-0.12	-0.10	0.09	-0.02	0.01
MDT 20/ratio	-0.08	0.27	0.26	0.01	-0.13	-0.36	0.00	NaN

Variable	HPMC	Hydroxypropyl starch	Kollidon SR	Lactose	Mannitol	MCC	PEO	PVA
Calcium stearate	-0.09	-0.05	-0.06	-0.06	-0.03	-0.13	-0.05	-0.05
Carbopol 971 P NF	-0.09	-0.05	-0.06	-0.02	-0.03	-0.10	-0.05	-0.05
Carbopol 974 P	-0.07	-0.04	-0.05	-0.05	-0.02	-0.10	-0.04	-0.04
Ethylcellulose	-0.16	-0.09	-0.11	-0.10	-0.05	-0.22	-0.09	-0.08
Eudragit RS	-0.13	0.65	-0.09	-0.08	-0.04	-0.13	-0.08	0.34
Glycerol Dibehenate	-0.08	-0.08	0.08	0.10	-0.05	0.41	-0.08	-0.06
Guar gum	-0.09	-0.05	-0.06	-0.06	-0.03	-0.12	0.31	-0.05
HPC	-0.06	-0.04	-0.04	-0.04	0.80	-0.08	0.28	-0.03
HPMC	1.00	-0.09	-0.09	0.35	-0.05	0.32	-0.09	-0.08
Hydroxypropylstarch	-0.09	1.00	-0.06	-0.06	-0.03	-0.09	-0.05	-0.05
Kollidon SR	-0.09	-0.06	1.00	-0.07	-0.03	0.34	-0.06	-0.04
Lactose	0.35	-0.06	-0.07	1.00	-0.03	-0.13	-0.06	-0.05
Mannitol	-0.05	-0.03	-0.03	-0.03	1.00	-0.07	0.24	-0.03
MCC	0.32	-0.09	0.34	-0.13	-0.07	1.00	-0.02	0.11
PEO	-0.09	-0.05	-0.06	-0.06	0.24	-0.02	1.00	-0.05
PVA	-0.08	-0.05	-0.04	-0.05	-0.03	0.11	-0.05	1.00
Povidone	0.04	-0.03	0.05	-0.03	-0.02	0.29	-0.03	0.45
Propylenglycol alginate	-0.13	0.67	-0.09	-0.08	-0.04	-0.12	-0.08	0.36
Talc	0.55	-0.05	-0.05	0.33	-0.03	0.11	-0.05	-0.04
Titanium dioxide	-0.05	-0.03	-0.03	-0.03	-0.02	-0.07	-0.03	-0.03
Xanthan gum	-0.09	-0.05	-0.06	-0.06	-0.03	-0.12	0.04	-0.05
Size[mm]	0.23	0.07	0.30	0.11	0.07	0.48	-0.08	0.08
Solubility dissolution media[g/L]	-0.06	-0.07	-0.02	-0.09	-0.01	-0.03	-0.04	-0.05
log D	0.36	-0.02	-0.02	0.29	-0.01	0.07	-0.01	-0.02
40% EtOH solubility[g/L]	0.24	-0.06	0.07	0.02	0.03	0.12	-0.04	-0.02
Solubility ratio 40	0.26	-0.03	-0.04	0.51	-0.02	-0.06	-0.03	-0.03
Drug loading (%)	-0.17	0.08	-0.24	-0.10	-0.22	-0.36	-0.22	0.04
Compression strength [MPa]	0.14	NaN	-0.21	0.12	NaN	-0.31	0.13	NaN
Breaking Force [N]	0.02	NaN	-0.23	0.06	NaN	0.58	-0.12	-0.23
Preparation[Melted]	0.29	-0.18	-0.20	-0.09	-0.20	0.38	-0.24	0.16
Tablet type [Coated=1;matrix=0]	-0.21	-0.15	0.30	-0.15	-0.08	0.04	-0.14	-0.11
F2 40	-0.02	-0.06	-0.31	0.01	0.11	-0.09	0.06	0.03
ASD 40	-0.06	0.02	0.23	-0.05	-0.06	-0.01	-0.08	-0.04
F2 20	0.07	NaN	NaN	0.08	NaN	0.09	NaN	NaN
ASD 20	-0.10	NaN	NaN	-0.10	NaN	-0.08	NaN	NaN
MDT 40	-0.04	-0.12	0.67	-0.08	-0.06	0.22	-0.05	-0.09
MDT 20	-0.08	NaN	NaN	-0.22	NaN	-0.13	NaN	NaN
MDT 0	0.03	-0.12	0.17	-0.08	-0.08	-0.01	-0.08	-0.10
MDT 40/ratio	-0.07	-0.06	0.61	0.01	0.02	0.30	0.06	-0.01
MDT 20/ratio	-0.02	NaN	-0.52	0.08	NaN	-0.39	NaN	NaN

Variable	Povidone	Propylenglycol-col alginate	Talc	Titanium dioxide	Xanthan gum	Size[mm]	Solubility dissolution media[g/L]	log D
Calcium stearate	-0.03	-0.08	-0.05	0.52	-0.05	-0.32	0.38	-0.08
Carbopol 971 P NF	-0.03	-0.08	-0.05	-0.03	-0.05	0.04	0.07	-0.12
Carbopol 974 P	-0.03	-0.06	-0.04	-0.02	-0.04	-0.02	0.07	-0.15
Ethylcellulose	-0.06	-0.13	-0.08	-0.05	-0.09	-0.59	-0.13	-0.18
Eudragit RS	-0.05	0.90	-0.07	-0.04	-0.07	0.10	-0.10	-0.02
Glycerol Dibehenate	-0.05	-0.12	-0.07	-0.05	-0.08	0.32	0.01	-0.03
Guar gum	-0.03	-0.07	-0.05	0.22	-0.05	-0.29	0.01	-0.21
HPC	-0.02	-0.05	-0.03	-0.02	-0.03	0.08	-0.01	-0.01
HPMC	0.04	-0.13	0.55	-0.05	-0.09	0.23	-0.06	0.36
Hydroxypropylstarch	-0.03	0.67	-0.05	-0.03	-0.05	0.07	-0.07	-0.02
Kollidon SR	0.05	-0.09	-0.05	-0.03	-0.06	0.30	-0.02	-0.02
Lactose	-0.03	-0.08	0.33	-0.03	-0.06	0.11	-0.09	0.29
Mannitol	-0.02	-0.04	-0.03	-0.02	-0.03	0.07	-0.01	-0.01
MCC	0.29	-0.12	0.11	-0.07	-0.12	0.48	-0.03	0.07
PEO	-0.03	-0.08	-0.05	-0.03	0.04	-0.08	-0.04	-0.01
PVA	0.45	0.36	-0.04	-0.03	-0.05	0.08	-0.05	-0.02
Povidone	1.00	-0.05	-0.03	-0.02	-0.03	0.05	0.00	0.01
Propylenglycol alginate	-0.05	1.00	-0.07	-0.04	-0.07	0.10	-0.10	-0.02
Talc	-0.03	-0.07	1.00	-0.03	-0.05	0.07	-0.06	0.30
Titanium dioxide	-0.02	-0.04	-0.03	1.00	-0.03	-0.17	0.33	-0.13
Xanthan gum	-0.03	-0.07	-0.05	-0.03	1.00	-0.13	-0.12	-0.09
Size[mm]	0.05	0.10	0.07	-0.17	-0.13	1.00	-0.04	0.24
Solubility dissolution media[g/L]	0.00	-0.10	-0.06	0.33	-0.12	-0.04	1.00	-0.29
log D	0.01	-0.02	0.30	-0.13	-0.09	0.24	-0.29	1.00
40% EtOH solubility[g/L]	0.05	-0.09	0.28	0.04	-0.17	0.15	0.72	-0.07
Solubility ratio 40	-0.01	-0.05	-0.01	-0.01	-0.03	0.05	-0.09	0.60
Drug loading (%)	0.00	0.10	-0.05	-0.19	0.08	-0.25	-0.18	-0.30
Compression strength [MPa]	NaN	NaN	NaN	NaN	-0.16	-0.04	0.07	-0.05
Breaking Force [N]	-0.41	NaN	NaN	NaN	NaN	0.45	-0.09	0.03
Preparation[Melted]	-0.11	-0.25	-0.15	0.18	-0.13	-0.57	-0.06	0.17
Tablet type [Coated=1;matrix=0]	-0.09	-0.21	-0.13	-0.08	-0.14	-0.31	-0.14	-0.07
F2 40	-0.04	-0.04	-0.11	0.00	0.22	-0.07	-0.02	-0.14
ASD 40	0.00	-0.02	-0.03	-0.05	-0.07	0.02	-0.06	0.29
F2 20	NaN	NaN	0.05	0.08	NaN	-0.03	0.07	-0.26
ASD 20	NaN	NaN	-0.08	-0.06	NaN	0.16	-0.15	0.51
MDT 40	-0.04	-0.16	-0.07	-0.08	-0.05	0.36	-0.06	0.04
MDT 20	NaN	NaN	-0.09	-0.14	NaN	-0.07	-0.20	0.05
MDT 0	-0.08	-0.16	-0.03	-0.08	-0.05	0.07	-0.11	0.25
MDT 40/ratio	0.13	-0.10	-0.09	-0.07	-0.04	0.39	0.09	-0.28
MDT 20/ratio	NaN	NaN	0.02	-0.01	NaN	-0.16	0.06	-0.26

Variable	40% EtOH solubility[g/L]	Solubility ratio 40	Drug loading (%)	Compression strength [MPa]	Breaking Force [N]	Preparation [Melted]	Tablet type [Coated=1; matrix=0]	F2 40
Calcium stearate	0.07	-0.03	-0.34	NaN	NaN	0.35	-0.15	-0.10
Carbopol 971 P NF	0.11	-0.03	0.45	0.19	-0.22	-0.02	-0.15	0.06
Carbopol 974 P	0.04	-0.03	0.37	0.19	NaN	-0.14	-0.12	-0.09
Ethylcellulose	-0.27	-0.06	0.32	NaN	NaN	0.58	0.67	0.22
Eudragit RS	-0.09	-0.05	0.09	NaN	NaN	-0.25	-0.20	-0.07
Glycerol Dibehenate	0.11	-0.05	-0.33	-0.19	0.47	-0.13	0.17	0.06
Guar gum	-0.10	-0.03	-0.01	NaN	NaN	0.33	0.12	0.13
HPC	0.04	-0.02	-0.26	NaN	NaN	0.23	-0.10	0.19
HPMC	0.24	0.26	-0.17	0.14	0.02	-0.29	-0.21	-0.02
Hydroxypropylstarch	-0.06	-0.03	0.08	NaN	NaN	-0.18	-0.15	-0.06
Kollidon SR	0.07	-0.04	-0.24	-0.21	-0.23	-0.20	0.30	-0.31
Lactose	0.02	0.51	-0.10	0.12	0.06	-0.09	-0.15	0.01
Mannitol	0.03	-0.02	-0.22	NaN	NaN	0.20	-0.08	0.11
MCC	0.12	-0.06	-0.36	-0.31	0.58	-0.38	0.04	-0.09
PEO	-0.04	-0.03	-0.22	0.13	-0.12	0.24	-0.14	0.06
PVA	-0.02	-0.03	0.04	NaN	-0.23	-0.16	-0.11	0.03
Povidone	0.05	-0.01	0.00	NaN	-0.41	-0.11	-0.09	-0.04
Propylenglycol alginate	-0.09	-0.05	0.10	NaN	NaN	-0.25	-0.21	-0.04
Talc	0.28	-0.01	-0.05	NaN	NaN	-0.15	-0.13	-0.11
Titanium dioxide	0.04	-0.01	-0.19	NaN	NaN	0.18	-0.08	0.00
Xanthan gum	-0.17	-0.03	0.08	-0.16	NaN	-0.13	-0.14	0.22
Size[mm]	0.15	0.05	-0.25	-0.04	0.45	-0.57	-0.31	-0.07
Solubility dissolution media[g/L]	0.72	-0.09	-0.18	0.07	-0.09	0.06	-0.14	-0.02
log D	-0.07	0.60	-0.30	-0.05	0.03	-0.17	-0.07	-0.14
40% EtOH solubility[g/L]	1.00	-0.13	-0.15	-0.12	-0.03	-0.14	-0.11	-0.09
Solubility ratio 40	-0.13	1.00	-0.14	0.33	0.11	-0.07	-0.08	-0.04
Drug loading (%)	-0.15	-0.14	1.00	0.18	-0.46	0.01	0.10	0.04
Compression strength [MPa]	-0.12	0.33	0.18	1.00	-0.89	0.25	-0.26	-0.07
Breaking Force [N]	-0.03	0.11	-0.46	-0.89	1.00	-0.22	NaN	0.40
Preparation[Melted]	-0.14	-0.07	0.01	0.25	-0.22	1.00	0.27	-0.21
Tablet type [Coated=1;matrix=0]	-0.11	-0.08	0.10	-0.26	NaN	0.27	1.00	-0.04
F2 40	-0.09	-0.04	0.04	-0.07	0.40	0.21	-0.04	1.00
ASD 40	0.01	0.12	-0.09	-0.13	-0.42	-0.21	0.07	-0.69
F2 20	0.17	-0.35	-0.22	-0.25	0.24	0.23	-0.29	0.50
ASD 20	-0.20	0.56	0.14	0.33	-0.30	-0.18	0.16	-0.42
MDT 40	0.05	-0.03	-0.15	-0.04	-0.36	-0.17	0.20	-0.02
MDT 20	-0.03	-0.10	0.05	0.21	-0.50	0.05	-0.06	0.23
MDT 0	0.00	0.03	-0.17	0.02	-0.30	0.00	0.13	-0.01
MDT 40/ratio	0.09	-0.08	-0.01	0.03	-0.20	-0.10	-0.03	-0.07
MDT 20/ratio	0.02	-0.15	0.49	0.35	0.05	0.17	-0.66	0.28

Variable	ASD 40	F2 20	ASD 20	MDT 40	MDT 20	MDT 0	MDT 40/ratio	MDT 20/ratio
Calcium stearate	0.00	0.19	-0.11	-0.12	0.03	0.16	-0.21	-0.08
Carbopol 971 P NF	-0.09	0.02	-0.09	0.08	0.14	0.01	0.17	0.27
Carbopol 974 P	-0.03	-0.15	-0.02	-0.04	-0.06	-0.09	0.13	0.26
Ethylcellulose	-0.16	0.09	-0.07	-0.11	-0.02	-0.06	-0.12	0.01
Eudragit RS	0.03	-0.19	0.12	-0.17	-0.11	-0.16	-0.10	-0.13
Glycerol Dibehenate	-0.11	0.14	-0.10	0.12	0.03	0.05	0.09	-0.36
Guar gum	-0.10	0.12	-0.09	-0.07	-0.14	-0.07	-0.02	0.00
HPC	-0.07	NaN	NaN	-0.07	NaN	-0.08	0.01	NaN
HPMC	-0.06	0.07	-0.10	-0.04	-0.08	0.03	-0.07	-0.02
Hydroxypropylstarch	0.02	NaN	NaN	-0.12	NaN	-0.12	-0.06	NaN
Kollidon SR	0.23	NaN	NaN	0.67	NaN	0.17	0.61	-0.52
Lactose	-0.05	0.08	-0.10	-0.08	-0.22	-0.08	0.01	0.08
Mannitol	-0.06	NaN	NaN	-0.06	NaN	-0.08	0.02	NaN
MCC	-0.01	0.09	-0.08	0.22	-0.13	-0.01	0.30	-0.39
PEO	-0.08	NaN	NaN	-0.05	NaN	-0.08	0.06	NaN
PVA	-0.04	NaN	NaN	-0.09	NaN	-0.10	-0.01	NaN
Povidone	0.00	NaN	NaN	-0.04	NaN	-0.08	0.13	NaN
Propylenglycol alginate	-0.02	NaN	NaN	-0.16	NaN	-0.16	-0.10	NaN
Talc	-0.03	0.05	-0.08	-0.07	-0.09	-0.03	-0.09	0.02
Titanium dioxide	-0.05	0.08	-0.06	-0.08	-0.14	-0.08	-0.07	-0.01
Xanthan gum	-0.07	NaN	NaN	-0.05	NaN	-0.05	-0.04	NaN
Size[mm]	0.02	-0.03	0.16	0.36	-0.07	0.07	0.39	-0.16
Solubility dissolution media[g/L]	-0.06	0.07	-0.15	-0.06	-0.20	-0.11	0.09	0.06
log D	0.29	-0.26	0.51	0.04	0.05	0.25	-0.28	-0.26
40% EtOH solubility[g/L]	0.01	0.17	-0.20	0.05	-0.03	0.00	0.09	0.02
Solubility ratio 40	0.12	-0.35	0.56	-0.03	-0.10	0.03	-0.08	-0.15
Drug loading (%)	-0.09	-0.22	0.14	-0.15	0.05	-0.17	-0.01	0.49
Compression strength [MPa]	-0.13	-0.25	0.33	-0.04	0.21	0.02	0.03	0.35
Breaking Force [N]	-0.42	0.24	-0.30	-0.36	-0.50	-0.30	-0.20	0.05
Preparation[Melted]	0.21	-0.23	-0.18	0.17	0.05	0.00	-0.10	0.17
Tablet type [Coated=1;matrix=0]	0.07	-0.29	0.16	0.20	-0.06	0.13	-0.03	-0.66
F2 40	-0.69	0.50	-0.42	-0.02	0.23	-0.01	-0.07	0.28
ASD 40	1.00	-0.45	0.77	0.03	-0.25	0.08	-0.09	-0.40
F2 20	-0.45	1.00	-0.66	0.25	0.36	0.14	0.12	0.17
ASD 20	0.77	-0.66	1.00	-0.23	-0.26	0.06	-0.31	-0.49
MDT 40	0.03	0.25	-0.23	1.00	0.70	0.64	0.52	-0.35
MDT 20	-0.25	0.36	-0.26	0.70	1.00	0.73	-0.06	0.20
MDT 0	0.08	0.14	0.06	0.64	0.73	1.00	-0.14	-0.39
MDT 40/ratio	-0.09	0.12	-0.31	0.52	-0.06	-0.14	1.00	0.09
MDT 20/ratio	-0.40	0.17	-0.49	-0.35	0.20	-0.39	0.09	1.00

7.3 Appendix C – Correlation coefficients of omitted variables

Variable	Aerosil	Copovidone	Dibutylsebacate	Magnesium stearate	Stearic acid	Weight[mg]	Height[mm]	20% EtOH solubility[g/L]	Coating level[%]
Aerosil	1.00	0.88	0.75	0.99	0.67	-0.01	0.21	0.07	-0.27
Calcium stearate	0.01	-0.02	-0.04	0.00	-0.05	0.12	-0.24	0.17	-0.11
Carbopol 971 P NF	0.16	0.11	0.07	0.17	0.05	-0.08	0.60	0.09	-0.11
Carbopol 974 P	0.10	0.07	0.04	0.12	0.02	-0.22	NaN	0.06	-0.09
Copovidone	0.88	1.00	0.63	0.88	0.53	-0.31	NaN	-0.09	-0.16
Dibutylsebacate	0.75	0.63	1.00	0.73	0.44	0.39	-0.49	-0.27	0.97
Ethylcellulose	0.33	0.25	0.84	0.31	0.13	0.39	-0.54	-0.22	0.99
Eudragit RS	0.19	0.60	0.06	0.20	0.03	-0.30	-0.09	-0.09	-0.16
Glycerol Dibehenate	0.14	0.05	0.00	0.10	0.51	0.13	-0.11	0.07	-0.11
Guar gum	0.64	0.54	0.62	0.62	0.38	0.31	-0.12	-0.07	0.26
HPC	0.02	0.00	-0.02	0.14	-0.02	-0.06	0.19	0.02	-0.07
HPMC	0.14	0.05	0.00	0.14	0.02	-0.02	0.48	0.03	-0.18
Hydroxypropylstarch	0.54	0.74	0.36	0.54	0.30	-0.21	NaN	-0.06	-0.11
Kollidon SR	0.09	0.02	-0.01	0.05	0.61	0.12	NaN	0.03	-0.06
Lactose	0.09	0.04	0.01	0.12	-0.01	-0.08	0.58	-0.05	-0.13
Magnesium stearate	0.99	0.88	0.73	1.00	0.63	-0.34	0.43	0.03	-0.34
Mannitol	0.05	0.03	0.01	0.15	0.00	-0.05	0.18	0.01	-0.06
MCC	0.31	0.18	0.08	0.26	0.50	0.14	0.58	0.04	-0.17
PEO	0.05	0.02	-0.01	0.08	-0.02	-0.07	0.16	-0.05	-0.10
PVA	0.37	0.49	0.23	0.38	0.25	-0.16	NaN	-0.03	-0.09
Povidone	0.67	0.57	0.49	0.67	0.41	-0.08	NaN	0.04	-0.07
Propylenglycol alginate	0.19	0.61	0.05	0.19	0.03	-0.30	NaN	-0.09	-0.16
Stearic acid	0.67	0.53	0.44	0.63	1.00	0.19	NaN	0.04	-0.05
Talc	0.82	0.71	0.60	0.83	0.51	-0.08	0.50	0.04	-0.10
Titanium dioxide	0.14	0.11	0.08	0.14	0.07	0.07	-0.12	0.16	-0.06
Xanthan gum	0.06	0.01	-0.02	0.06	-0.02	-0.31	0.12	-0.15	-0.11
Weight[mg]	-0.01	-0.31	0.39	-0.34	0.19	1.00	-0.28	0.07	0.41
Height[mm]	0.21	NaN	-0.49	0.43	NaN	-0.28	1.00	0.10	-0.58
Size[mm]	0.51	0.11	-0.55	0.28	0.41	0.08	0.92	0.09	-0.61
Solubility dissolution media[g/L]	-0.03	-0.10	-0.20	-0.06	-0.03	0.11	-0.12	0.92	-0.15

Variable	Aerosil	Copovidone	Dibutylsebacate	Magnesium stearate	Stearic acid	Weight[mg]	Height[mm]	20% EtOH solubility[g/L]	Coating level[%]
log D	0.00	-0.02	-0.17	0.00	-0.02	0.11	0.50	-0.21	-0.15
20% EtOH solubility[g/L]	0.07	-0.09	-0.27	0.03	0.04	0.07	0.10	1.00	-0.23
40% EtOH solubility[g/L]	0.09	-0.10	-0.30	0.11	0.08	0.08	0.44	0.92	-0.26
Solubility ratio 40	0.05	-0.05	-0.05	-0.02	-0.05	-0.03	0.42	-0.12	-0.06
Drug loading (%)	-0.25	0.12	0.37	-0.06	-0.32	-0.07	0.05	-0.19	0.31
Compression strength [MPa]	-0.47	NaN	NaN	0.31	-0.29	-0.07	-0.99	-0.05	-0.09
Breaking Force [N]	0.90	NaN	NaN	0.34	NaN	0.14	0.11	-0.01	NaN
Preparation [Melted=1, compressed=0]	-0.46	-0.26	0.57	-0.10	-0.26	0.50	-0.50	-0.09	0.53
Tablet type [Coated=1;matrix=0]	-0.07	-0.21	0.63	-0.43	0.41	0.46	-0.63	-0.14	0.98
F2 40	-0.01	-0.05	0.22	0.20	-0.17	-0.01	0.06	-0.03	0.21
ASD 40	-0.01	0.00	-0.16	-0.15	0.10	0.05	-0.19	-0.02	-0.14
F2 20	0.01	0.01	0.03	0.01	0.02	0.03	0.07	0.12	0.00
ASD 20	-0.08	NaN	-0.05	-0.14	NaN	0.13	-0.21	-0.18	-0.05
MDT 40	0.24	-0.17	-0.10	-0.18	0.66	0.21	0.30	0.02	-0.08
MDT 20	-0.02	NaN	0.05	-0.07	NaN	-0.06	-0.08	-0.06	-0.02
MDT 0	-0.01	-0.17	-0.06	-0.21	0.24	0.27	-0.16	-0.05	-0.03
Coating level[%]	-0.27	-0.16	0.97	-0.34	-0.05	0.41	-0.58	-0.23	1.00
MDT 40/ratio	0.23	-0.09	-0.10	0.05	0.45	0.03	0.45	0.14	-0.13
MDT 20/ratio	-0.34	NaN	0.02	0.45	-0.70	-0.37	0.42	0.09	-0.10

7.4 Appendix D – VIF values for MLR

Original variables		After deletion of variables	
VIF	variable	VIF	variable
3.18	Calcium stearate	2.20	Calcium stearate
3.13	Carbopol 971 P NF	2.28	Carbopol 971 P NF
2.72	Carbopol 974 P	2.04	Carbopol 974 P
210.21	Ethylcellulose*	5.23	Ethylcellulose*
9.16	Eudragit RS	6.60	Eudragit RS
7.59	Glycerol Dibehenate	2.44	Glycerol Dibehenate
2.64	Guar gum	2.21	Guar gum
12.52	HPC	3.10	HPC
3.17	HPMC	2.81	HPMC
3.81	Hydroxypropylstarch	3.35	Hydroxypropylstarch
7.26	Kollidon SR	2.54	Kollidon SR
4.12	Lactose	2.77	Lactose
3.18	Mannitol	2.89	Mannitol
15.86	MCC**	11.39	MCC**
1.82	PEO	1.59	PEO
2.63	PVA	2.36	PVA
4.68	Povidone	3.10	Povidone
15.23	Propylenglycol alginate	7.46	Propylenglycol alginate
12.52	Talc	4.71	Talc
1.69	Titanium dioxide	1.63	Titanium dioxide
1.82	Xanthan gum	1.43	Xanthan gum
15.18	Size[mm]	4.49	Size[mm]
79.71	Solubility dissolution media[g/L]	6.42	Solubility dissolution media[g/L]
3.83	log D	3.02	log D
100.55	40% EtOH solubility[g/L]	7.64	40% EtOH solubility[g/L]
4.26	Solubility ratio 40	2.93	Solubility ratio 40
14.82	Drug loading (%)	7.80	Drug loading (%)
2.93	Compression strength [MPa]	2.09	Compression strength [MPa]
12.19	Breaking Force [N]	5.69	Breaking Force [N]
4.88	Preparation [Melted=1,compressed=0]	4.03	Preparation [Melted=1,compressed=0]
5.72	Tablet type [Coated=1;matrix=0]	3.73	Tablet type [Coated=1;matrix=0]
775.53	Aerosil		
90.73	Dibutylsebacate		
6.05	Height[mm]		
792.14	Magnesium stearate		
326.09	Coating level[%]		
263.60	20% EtOH solubility[g/L]		
41.27	Stearic acid		
109.88	Copovidone		
15.73	Weight[mg]		

* Ethylcellulose was not eliminated in order, due to the high correlation to Dibutylsebacate. The value reduced after deletion of Dibutylsebacate.

** MCC was not removed, as there was no high correlation with another variable.

7.5 Appendix E – Correlation coefficients for %-release-via-diffusion ratios

Variable	TPD_40_0	TPD_20_0
Calcium stearate	-0.04	-0.06
Carbopol 971 P NF	0.09	0.06
Carbopol 974 P	-0.04	-0.13
Ethylcellulose	-0.12	-0.08
Eudragit RS	-0.06	-0.02
Glycerol Dibehenate	0.25	-0.08
Guar gum	-0.05	-0.07
HPC	-0.03	NaN
HPMC	0.18	0.12
Hydroxypropylstarch	-0.04	NaN
Kollidon SR	-0.01	NaN
Lactose	0.26	-0.04
Mannitol	-0.02	NaN
MCC	0.02	-0.11
PEO	-0.04	NaN
PVA	-0.04	NaN
Povidone	-0.03	NaN
Propylenglycol alginate	-0.06	NaN
Talc	-0.03	-0.03
Titanium dioxide	-0.02	-0.03
Xanthan gum	-0.05	NaN
Size[mm]	0.07	0.17
Solubility dissolution media[g/L]	-0.06	-0.10
log D	0.20	0.10
40% EtOH solubility[g/L]	-0.04	-0.12
Solubility ratio 40	0.49	0.11
Drug loading (%)	-0.12	-0.10
Compression strength [MPa]	0.01	0.43
Breaking Force [N]	0.00	-0.37
Preparation[Melted=1,compressed=0]	-0.17	-0.19
Tablet type[Coated=1;matrix=0]	0.12	0.05
F2 40	-0.05	-0.11
ASD 40	0.05	0.04
F2 20	-0.09	-0.14
ASD 20	0.00	0.04
MDT 40	0.07	0.07
MDT 20	0.19	0.13
MDT 0	0.10	0.05
MDT 40/ratio	-0.03	-0.03
MDT 20/ratio	-0.22	0.05
TPD_40_0	1.00	0.59
TPD_20_0	0.59	1.00