

***In vitro-in vivo* correlation and modelling of drug release for HPMC-based matrix tablets**

Inaugural-Dissertation
to obtain the academic degree
Doctor rerum naturalium (Dr. rer. nat.)

submitted to the Department of Biology, Chemistry and Pharmacy
of Freie Universität Berlin

by
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2017

The enclosed doctoral research work was accomplished from April 2012 until June 2017 under the supervision of Prof. Dr. Roland Bodmeier at the College of Pharmacy, Freie Universität Berlin.

1st Reviewer: Prof. Dr. Roland Bodmeier

2nd Reviewer: Prof. Dr. Philippe Maincent

Date of defense: 14.07.2017

Acknowledgements

First of all, I want to thank my supervisor Prof. Dr. Roland Bodmeier for giving me the opportunity to work and study in his research group and providing me this interesting and challenging research topic. Additionally, I want to thank him for his supervision, scientific guidance, also his financial support in the last stage of my study.

I kindly thank Prof. Dr. Philippe Maincent for his readiness to evaluate my thesis.

I would like to express my gratitude to Dr. Martin Körber, Dr. Andriy Dashevskiy and Dr. Mathias Walther for their support and fruitful discussions throughout my Ph.D. study.

Their scientific input had great impact on my work.

Special thanks also to Eva Ewest, Andreas Krause, Stefan Walther and Gabriela Karsubke for helping me to master the challenges of labwork and paperwork.

I am very thankful to Gaith, Anis, Rebaz, Kathrin, Jia, Rasha and Rick for their kindness, genuine friendship and support at the beginning of my study, so I could adapt myself faster in the new environment. Furthermore, I thank all my colleagues and friends: Marius, Heja, Magda, Coline, Benjamin, Miriam, Marina, Luisa, Fenny, Zoha, Julia, Lisa, Sarah, Marko, Nadeem, Rahul, Prutha, Clara, Agnieszka, Fitsum, Jelena, May, Muhaimin for their support and providing a friendly atmosphere during my stay at the institute. Also, I am sincerely grateful to Amanza Orsini and Benjamin Dohne for their kindness, patience and support.

Finally, I would like to express my deepest gratitude to my parents, my sister and my brother for their love and most sincere encouragement throughout my life.

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1 INTRODUCTION

1.1 Extended release solid oral dosage forms

Due to the difficulty in developing new drugs, more and more attention has been given to developing new drug delivery systems for existing drugs. Extended release (ER) dosage form is one of the drug products categorized under the term modified release dosage forms (FDA, 1997). Extended release (ER) dosage forms release drug slowly, so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time (usually between 8 and 12 hours). Commercial extended release solid oral products are categorized as: matrix, reservoir (or membrane controlled), and osmotic systems.

The matrix system has been most widely utilized to provide extended delivery of drug substances because of its effectiveness and the feasibility for low- and high-loading of drugs with a wide range of physical and chemical properties (Qiu, 2009b). From a product development point of view, it is cost-effective and easy to scale-up and manufacture. In a matrix system, the drug substance is homogeneously mixed into the rate-controlling material(s) and other inactive ingredients as a crystalline, amorphous or, in rare cases, molecular dispersion. Drug release occurs either by drug diffusion and /or erosion of the matrix. Based on the characteristics of the rate-controlling material, the matrix system can be divided into: (a) hydrophilic (water-soluble and /or swellable), and (b) hydrophobic (water-insoluble) systems. Hydrophilic matrix systems are polymer-based drug delivery systems in which two competing mechanisms are involved in the drug release: Fickian diffusional release, and relaxational release. The relative contribution of each component is dependent on the properties of drug and matrix composition. Upon contact with an aqueous solution, hydrophilic tablet starts to swell and consequently a viscous gel layer of hydrated polymer forms around the tablet (Körner et al., 2005) (Fig. 1). In this moment two moving interfaces can be identified, interface between initial dry solid tablet and gel layer, and the interface between gel layer and media (gel-solution interface). In the swelling step, as gel develops, the gel-solution interface moves outward. At the same time, the dry core-gel interface moves inward. With continuous swelling of the matrix tablet and further hydrating of the polymer, the polymer concentration at the gel surface ultimately becomes

lower than “critical polymer concentration” and the outermost layer of polymer chains starts to detach from the gel surface. As the polymer is released from the gel, two scenarios may happen: two interfaces move inward at the same rate which results in a constant gel layer thickness (C), or gel-solution interface continues to move outward while dry core-gel interface moves inward and the gel layer thickness continues to grow. Finally, for products having high gel strength, all of the tablet is consumed and only a gel piece remains to be dissolved in the solvent (e).

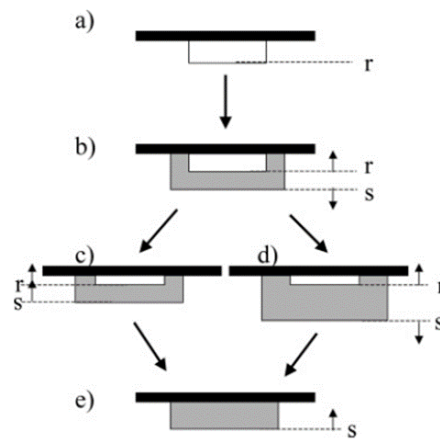


Fig. 1. Schematic representation of the swelling and erosion of a hydrophilic tablet (tablet mounted on a rotating disk), r : dry core-gel interface, s : gel-solution interface; represented from (Körner et al., 2005).

A typical reservoir system consists of a core containing solid drug or highly concentrated drug solution surrounded by a film or membrane of a rate-controlling material. In this design, the only structure effectively limiting the release of the drug is the polymer layer surrounding the reservoir.

The osmotic pump system is similar to a reservoir device, but contains an osmotic agent that acts to imbibe water from the surrounding medium via a semipermeable membrane. The delivery of the active agent from the device is controlled by water influx across the semipermeable membrane. The drug is forced out of an orifice in the device by the osmotic pressure.

1.2 Physiological conditions of gastrointestinal tract in fasted and fed states

The gastrointestinal tract has a dynamic changing environment and the composition of the fluid in the gastrointestinal tract (GIT) varies considerably after food intake. The effect of changing environment on extended release dosage forms is more pronounced given that they are designed to stay in the GIT for a longer period and they pass through variable conditions in the GI tract (Raiwa, 2011; Varum et al., 2013). Food intake is known to have various effects on gastrointestinal luminal conditions in terms of transit times, hydrodynamic forces and/or luminal fluid composition and can therefore affect the dissolution of extended release oral dosage forms. There are extensive literatures available regarding the physiology of GIT in the fasted and fed state (Di Maio and Carrier, 2011; Fleisher. D et al., 1999; Mudie et al., 2010; Varum et al., 2013).

Gastric pH which results from concentration of hydrogen ions is typically 1-2 in the fasted state and ranges from 2.7 to 6.4 in the fed state (Ibekwe et al., 2008). Shortly after ingestion of food, pH of gastric increases dramatically to 6-7, but then it decreases to pH 2.7. Depending on food composition and amount, the gastric pH level declined back to fasted state within 1-4 h after food intake. The alteration of pH in fed state affects the solubility and dissolution rate of pH-dependent drugs and drug release rate from pH-dependent controlled release systems (e.g. enteric coated systems). pH values in the upper small intestine (duodenum and jejunum) is lower in the fed state compared to fasted state. pH level of upper small intestine has been reported as 6.5 and 5 (median value) in the fasted and fed state, respectively (Dressman et al., 1998; Hörter and Dressman, 2001). In the ileum, pH has been shown to range from 6.8 to 8 in the fasted state and 6.8 to 8 in the fed state (Hörter and Dressman, 2001; Ibekwe et al., 2008).

Osmolality is dramatically influenced with food intake. Kalantzi and coworkers reported the gastric osmolarity in the fasted state in the range of 98 mOs/kg (early time points) to 140 mOsm/kg (later times) (Kalantzi et al., 2006a). In the fed state, gastric osmolality increases to 559 mOsm/kg after 30 min and 217 mOsm/kg after 210 min. In the upper small

intestine, osmolality values range from 124 to 278 mOsm/kg in the fasted state (Lindahl et al., 1997) and 250 to 367 in the fed state. Changing osmolality in the fed state influences the drug release from extended release dosage forms (Araya). Drug release rate decreased from Eudrait[®] RL and Eudragit[®] RS with increasing osmolality in the dissolution test medium due to effect of counterions and thus lower degree of polymer hydration (Raiwa, 2011).

Gastric emptying time of a solid dosage form changes dramatically with the effect of food and is largely dependent on meal size and composition (Davis et al., 1984; Dressman, 1986). The gastric emptying rate impacts the rate at which liquids and solids empty from the stomach into the duodenum. It determines the residence time of a drug in the stomach as well as the rate at which the drug is introduced into the small intestine. More prolonged gastric emptying time results in increase the time available for dissolution of drugs and consequently increased bioavailability of poorly soluble drugs. On the other hand, delaying of gastric emptying may result in delaying in drug absorption as drug is available in small intestine later (most drugs are absorbed primarily in the small intestine).

The presence of bile salts and other lipolytic products affect the surface tension of small intestine (Dokoumetzidis and Macheras, 2008). Reducing surface tension in the fed state improves the wetting of the drug or dosage forms. It may increase the solubility of poorly soluble drugs (Ghazal et al., 2009; Kalantzi et al., 2006b). Also, the enhancement of wettability of poly(methyl methacrylate) (PMMA) tablets in presence of bile salt-lipid emulsions was demonstrated (Luner, 2000; Luner and VanDer Kamp, 2001). Gastric surface tension values in the fasted and fed states range from about 41 to 46 and 30 to 31 mN/m, respectively (Kalantzi et al., 2006a). In the upper small intestine, surface tension values range from 28 to 46 mN/m in the fasted state, and 27 to 37 mN/m in the fed state (Persson et al., 2005). A summary of gastrointestinal changes after food intake is shown in (Fig. 2).

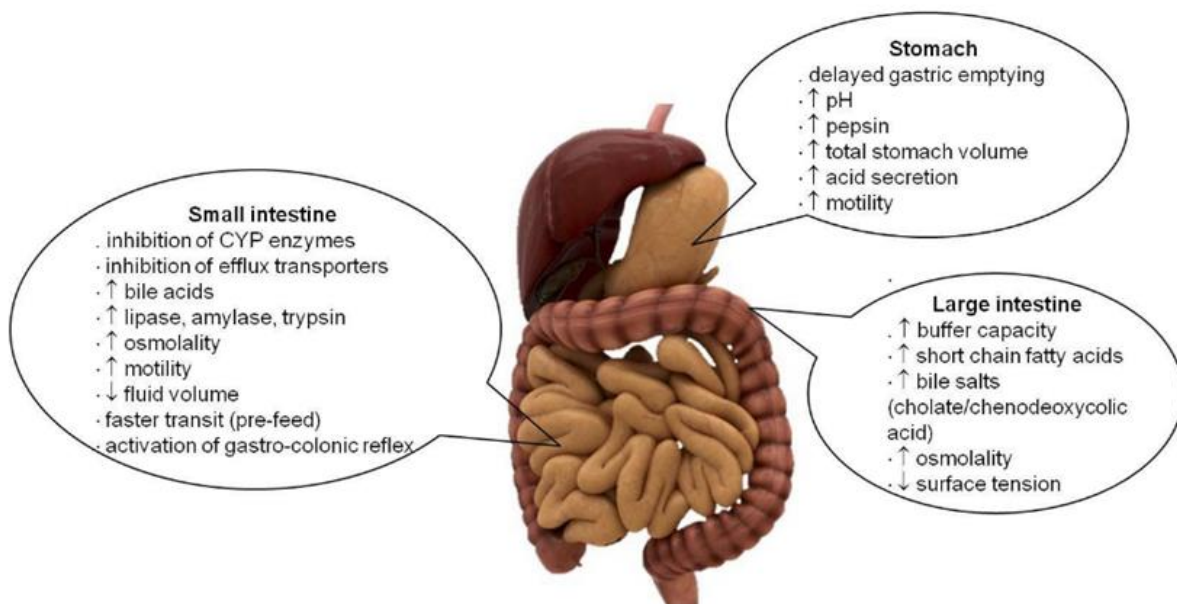


Fig. 2. Summary of gastrointestinal changes in the fed state (compared to fasted state) (Dokoumetzidis and Macheras, 2008)

1.3 Effect of food on drug and solid oral dosage forms

Generally, food intake may influence the drug and dosage forms in different mechanisms in terms of gastric emptying, altering the pH, solubilization effect, permeability of small intestine and intestinal lymphatic transport (Raiwa, 2011).

Low soluble API are more influenced in presence of food compared to highly soluble API due to solubilization effect of bile salt and lipolytic products. Moreover, the increased gastric emptying in the fed state leads to increased residence time of the dosage forms in the stomach (main site for drug solubilization) which consequently results in increased solubility of poorly soluble drug (Fabre and Timmer, 2003). However, highly soluble drugs may be affected in the fed state as well. The time to reach maximum plasma concentration t_{max} of BCS class I drug increases in presence of food due to prolonged gastric emptying. Food-drug interaction was reported for BCS class III drugs which resulted in reduced bioavailability (Fujii et al., 2011; Tanno et al., 2008). In the case of drugs with low

permeability or drugs with narrow window of absorption, food intake can act as a barrier to drug absorption (decreased bioavailability) (Karim et al., 2007).

Generally, multiparticulates are less influenced in the fed state compared to tablets in terms of mechanical stress and gastric emptying (Varum et al., 2013). However, other fed state parameters like effect of bile salt can increase the wettability of multiparticulate extended release dosage forms coated with water insoluble polymer, ethyl cellulose, which results in increased release rate of drug (Hendeles et al., 1985; Hendriks et al., 1998). This effect has been shown for other low permeable polymers like PMMA (Luner, 2000).

Swellable matrix tablets are more susceptible to mechanical stress induced in the fed state. Moreover, high concentration of dietary sugars in the fed state media affects the gel layer formation of HPMC matrix tablets which results in accelerated drug release (Williams et al., 2009). Drug release rate (caffeine) from HPMC matrix tablet decreased in simulated gastric media containing fat emulsion (milk and the parenteral emulsion Intralipid®) due to deposition of a fat layer at the surface of the tablet (Williams et al., 2011).

It is well known that osmotic tablets are more robust in the fed state compared to tablet and multiparticulate dosage forms (Abrahamsson et al., 1998; Lecaillon et al., 1985; Schug et al., 2002). There are extensive literatures available which demonstrate food-independent osmotic tablets. Nifedipine was not affected under fed conditions when administered with osmotic dosage form (Adalat® OROS). However, dose dumping was observed with hydrophilic matrix tablet Coral® in the fed state (Schug et al., 2002). Similarly, robustness of Adalat® OROS was proved at *in vitro* simulated fed state (Garbacz et al., 2009).

1.3.1 Food-independent solid oral dosage forms

The formulation design can significantly reduce the effect of food on the bioavailability of drug. For instance, drug release from diltiazem (or theophylline) pellet dosage forms coated with ethyl cellulose containing small amounts of PVA:PEG graft copolymer (Kollicoat® IR) was not affected in simulated fed state media containing fat, carbohydrate, bile salts and calcium ions (Muschert et al., 2010).

Food effect on trientine (BCS class III) tablet coated with enteric polymer hydroxypropyl methylcellulose acetate succinate (HPMCAS) was significantly lower than trientine oral solution. This was attributed to the delivery of the drug to the middle or lower part of small intestine, resulted in less food (bile salt)-drug interaction. Similarly, the food effect on DX-9065 (a factor Xa inhibitor) was reduced when drug was administered by means of enteric-coated tablet. Some patents have been addressed food-independent solid oral dosage forms. Nifedipine was granulated with hydroxypropyl cellulose and subsequently coated with aqueous dispersions such as ethylcellulose (e.g. Aquacoat[®]) or poly(ethyl acrylate, methyl methacrylate) 2:1 (e.g. Eudragit[®] NE 30 D) (Kanikanti et al., Oct 2004). A sustained release tablet dosage form was developed which was not affected with food intake (Seth, Jan 2002). The tablet comprised of a core containing carbamazepine which was coated with intermediate layer of HPMC and PEG and outer layer of Eudragit[®] RL and silicon dioxide. Extended release matrix tablets comprised of Kollidon[®] SR were not affected with food intake (Grund, 2013; Song et al., 2016).

1.4 In vitro-in vivo correlation (IVIVC)

The FDA describes the *in vitro-in vivo* correlation (IVIVC) as a predictive mathematical model describing the relationship between an *in vitro* property (usually the extent or rate of drug release), and a relevant *in vivo* response (e.g., plasma concentration or amount of drug absorbed) (FDA 1997). IVIVC can be utilized for development, optimization and manufacturing process of solid dosage forms (Qiu, 2009a). However, the major objective of IVIVC is the possibility to use *in vitro* data to predict *in vivo* performance, thus *in vitro* test serves as a surrogate for *in vivo* bioavailability study (Gonzalez-Garcia et al., 2015). IVIVC is categorized by FDA into Level A, Level B, Level C and multiple Level C (FDA 1997). They are different in terms of type of data used to establish the relationship, and the ability to predict the complete plasma profile. Level A is the most informative type of correlation and it represents a point-to-point relationship between *in vitro* and *in vivo*

dissolution, and entire *in vivo* plasma concentration profile can be predicted from an *in vitro* dissolution profile. In the Level B correlation, the mean *in vitro* dissolution time is compared with either the mean *in vivo* dissolution time or mean *in vivo* residence time. Although in the Level B the entire course of *in vitro* and *in vivo* are taken into account, but plasma concentration profile is not predicted based on *in vitro* dissolution data. Level C is the least powerful method and it establishes a single point relationship between a dissolution parameter (e.g. t_{50}) and a pharmacokinetic parameter that characterizes the *in vivo* time course (C_{\max} or AUC). Finally, Multiple Level C correlation relates one or several pharmacokinetic parameters to the amount dissolved at several time points of the dissolution profile.

Generally, IVIVC should be developed using two or more formulations with different release rates (e.g., fast, medium, and slow) and a discriminating *in vitro* test methodology. (only one release rate is sufficient if dissolution is condition-independent) (Uppoor, 2001). The corresponding *in vivo* response can be plasma concentration or the amount of drug released and/or absorbed *in vivo*. When the drug released and/or absorbed *in vivo* used as *in vivo* response, the plasma concentration profile has to be transformed into *in vivo* dissolution profiles by deconvolution method. The *in vivo* dissolution profile (identical to *in vivo* absorption profile) is then used to establish an IVIVC. The classical methods of deconvolution of plasma profiles include Wagner–Nelson (Fig. 3), Loo–Riegelman and numerical deconvolution. The Wagner-Nelson approach is the most frequently used in building IVIVC models which is based on one-compartment model and it has a great advantage of not requiring additional *in vivo* data except oral plasma profile. The Loo–Riegelman method is based on two-compartment model, which requires intravenous dosing data. Model-independent numerical deconvolution requires *in vivo* plasma data from an oral solution or intravenous as impulse function.

The correlation is obtained via comparison of the *in vivo* profile with the scaled *in vitro* dissolution profile by a linear regression, which provides the slope and the intercept as a link function between both profiles (Fig. 3). A slope closer to 1 indicates a 1:1 correlation,

and a negative intercept implies that the *in vivo* process lags behind the *in vitro* dissolution. A positive intercept has no clear physiological meaning.

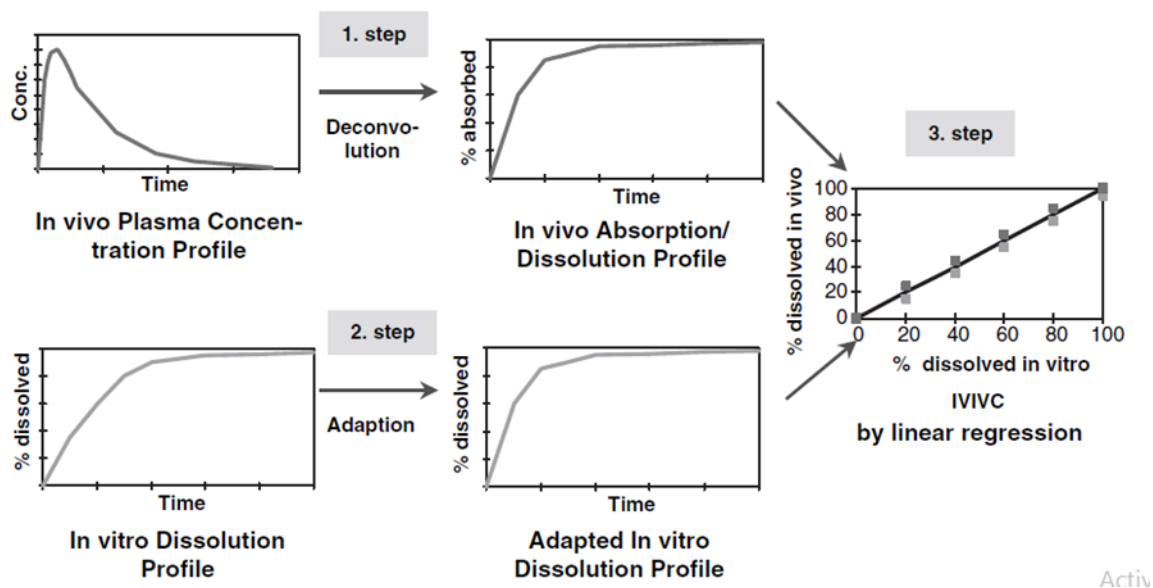


Fig. 3. The classical three steps of deconvolution. (IVIVC, *in vitro*–*in vivo* correlation) (Chilukuri et al., 2007).

1.4.1 Considerations for establishment of IVIVC (in vivo absorption and in vitro test)

Drug absorption from a solid dosage form following oral administration involves mainly three processes: release of the drug from dosage form, dissolution or solubilization of the drug under physiological conditions and permeation of drug across the gastrointestinal tract. Therefore, in developing an IVIVC, the *in vivo* response depends on not only the *in vivo* drug release, but rather on the entire absorption process (final pharmacokinetic profile). The rate and extent of drug absorption *in vivo* after oral administration depends on: 1) physicochemical characteristics of the drug (such as ionization constant, crystal form, solubility, stability, lipophilicity, permeability, surface area, wetting property), 2) dosage form design (dose, release mechanism, composition, type and size of dose unit, sensitivity to shear force, drug release location or duration, etc.), 3) physiological parameters (e.g.

gastrointestinal buffers, pH, ionic strength, bile salt concentration, food effect, residence time, fluid volume and hydrodynamic conditions, enterohepatic recycling, drug permeability through GI membrane, surface area, metabolism, transporters, microflora) (Qiu, 2009a). On the other hand, the *in vitro* parameters for establishing IVIVC are a function of drug and dosage form characteristics and dissolution tests methods.

Ideally, the *in vitro* release profile of oral dosage forms is assumed to match well with corresponding *in vivo* release profile, meaning that to have a good *in vitro-in vivo* correlation. But in fact, there have been many failed attempts in achieving IVIVC which can be attributed to a lack of a predictive *in vitro* test method regarding hydrodynamics, food, bile salts, etc (Dokoumetzidis and Macheras, 2008). Thus, it is crucial to understand the importance of the physicochemical properties of drug, delivery technology, formulation design, *in vitro* test methodology, and their inter-relationship with the gastrointestinal tract (GIT) in developing an IVIVC (Emami, 2006; Gonzalez-Garcia et al., 2015; Humbert et al., 1994; Klancar et al., 2015; Macha et al., 2009; Qiu, 2009a; Royce et al., 2004; Turner et al., 2004). Due to the difficulty of developing a single dissolution system, it would be preferable to know which characteristics of the drug and the dosage form are relevant and then design a relevant dissolution method. Therefore, an IVIVC should be developed on a case-by-case basis.

The *in vitro* test methods carried out for IVIVC are categorized in three types: Conventional dissolution tests (i.e. basket, paddle, reciprocating, flow through cell), Modified standard methods through altering hydrodynamics, mixing, creating shear force, etc. (e.g. USP II with polystyrene beads, USP II with stationary basket, USP II with two-phase, rotating beaker), new models (e.g. TNO; dynamic *in vitro* GI models) (Takeuchi et al., 2014). The new stress test device (Physiostress) was introduced by Garbacz and coworkers to mimic gastric emptying and ileocecal passage. It was successfully utilized to achieve better IVIVC for HPMC matrix tablets containing diclofenac sodium (Voltaren), Quetiapin (Seroquel SR), and nifedipine (Garbacz et al., 2009; Garbacz et al., 2014; Garbacz et al., 2008). Also, USP II, USP III and USP IV demonstrated equally useful in terms of predicting *in vivo* profile. It was shown that hydrodynamics of USP II, III and IV may all be adequate for

generating IVIVC of up to 7 mm monolithic dosage forms with low drug load in the fasted state (Fotaki et al., 2009).

Using biorelevant dissolution tests reflect better *in vivo* conditions in the GI tract, resulting in better prediction of *in vivo* data. Good correlation between *in vitro* drug release (applying USP III and USP IV) and *in vivo* drug absorption in both fasted and fed state of diclofenac coated pellets (ammonio methacrylate copolymer type A) were achieved by using the biorelevant dissolution test methods. Moreover, biorelevant dissolution testing predicted correctly the slower release of diclofenac in the fed state. By using FaSSIFLF (fasted state simulated intestinal fluid without lipid components) employed with paddle, IVIV relationship was obtained for ethylcellulose coated pellets. Using SGF, FaSSIF and FeSSIF demonstrated a good correlation with *in vivo* release data for several immediate release formulations containing poorly soluble drug (Dressman and Reppas, 2000).

During formulation development of extended release divalproex sodium matrix tablet (Depakote[®]) (Qiu et al., 2003a), using conventional *in vitro* dissolution test (USP II, 100 rpm, pH 6.8 phosphate buffer) resulted in slower drug release rate than *in vivo*, also not discrimination between for three different formulations. Based on the investigation the effect of different *in vitro* variables included agitation intensity, pH, apparatus, surfactant and ionic strength of the dissolution medium by means of statistically design experiment, it was demonstrated that higher pH, addition of sodium dodecyl sulfate (SDS) to the dissolution medium, and higher agitation intensity increased the release rate from the matrix tablet. Finally, a new a predictive *in vitro* dissolution method was identified by adding 75mM SDS into 0.05M phosphate buffer and lowering the pH to 5.5. As a result, the drug release rate using this new method was increased and a good correlation between *in vitro* and *in vivo* data was obtained (Qiu et al., 2003b).

1.4.2 IVIVC for immediate release dosage forms

An IVIVC is more challenging to achieve for immediate release dosage forms which are often drug-dependent. *In vitro-in vivo* correlation is normally expected for highly

permeable drugs or drugs under dissolution rate-limiting conditions (Tab. 1). In the case of BCS class II drugs, when dissolution is rate-limiting for drug absorption, and an IVIVC may be possible. For soluble BCS class I drugs, IVIVC is less likely unless drug dissolution is significantly slowed due to formulation design. However, gastric emptying and/or permeability is usually the rate-controlling step in drug absorption for BCS class III drugs, therefore the establishment of IVIVC is rare. However, depending on the drug property and product design, IVIVC may sometimes be found. For example, Opportunity for an IVIVR or IVIVC may sometimes exist for BCS class IV drugs, for which both dissolution and permeability may limit the rate of *in vivo* absorption depending on the relative rate of the two. Various physicochemical, biopharmaceutical, and physiological factors that need to be considered in successful IVIVC of immediate-release oral dosage forms are reviewed by (Li et al., 2005). The physicochemical factors include drug solubility in water and physiologically relevant aqueous media, pK_a and drug ionization characteristics, salt formation, drug diffusion-layer pH, particle size, polymorphism of drug substance. The biopharmaceutical factors that has to be taken into consideration include effects of drug

Class	Solubility	Permeability	Expected IVIVC
I	High	High	Correlation (if dissolution is rate limiting step)
II	Low	High	IVIVC expected
III	High	Low	Little or no IVIVC
IV	Low	Low	Little or no IVIVC

ionization, partition coefficient, polar surface area, absorption potential, and some of the physiological factors are gastrointestinal (GI) content, GI pH, GI transit time.

Table. 1. BCS and expected IVIVC for immediate-release drug products, reproduced from (Sirisuth and Eddington)

1.4.3 IVIVC for extended release dosage forms

For extended release dosage forms, the *in vivo* absorption which is occurred in the small intestine, ascending colon and/or throughout the large intestine is controlled by drug release from dosage form. Therefore, drug dissolution is a rate limiting step for the *in vivo* absorption and it is more likely to achieve IVIVC. The feasibility of an IVIVC depends on drug characteristics, drug delivery technology, and formulation design of the dosage forms. Biopharmaceutical classification system and expected IVIVC for extended release (ER) dosage forms are summarized. Similar to immediate dosage forms, establishing IVIVC for BCS class I and BCS class II is more expected (Tab. 2).

Osmotic systems are not sensitive to *in vitro* and *in vivo* conditions, thus it is more likely to obtain IVIVC. However, it is much more difficult to obtain IVIVC if the *in vitro* test fails to predict drug release *in vivo*. On the other hand, drug release from matrix tablet and pellets are more dependent on drug, formulation and *in vitro* test conditions, so it is more likely to adjust the *in vitro* test condition to achieve IVIVC (Qiu, 2009a) (Tab. 3). For matrix systems, drug release rate and mechanism are also affected by the gel strength of the tablet that often varies with formulation design.

Table 2. BCS and expected IVIVC for extended-release drug products reproduced from (Sirisuth and Eddington)

Class	Solubility	Permeability	Expected IVIVC
Ia	High (site independent)	High (site independent)	Correlation (if dissolution is rate limiting step)
Ib	High (site independent)	Dependent on site and narrow absorption window	IVIVC expected
IIa	Low (site independent)	High (site independent)	Variable
IIb	Low (site independent)	Dependent on site and narrow absorption window	Little or no IVIVC
III	High solubility	Low permeability	Little or no IVIVC
IV	Low solubility	Low permeability	Little or no IVIVC
Va	Variable	Variable	Little or no IVIVC
Vb	Variable	Variable	IVIVC Level A expected

Table. 3. Common extended-release systems and IVIVC, reproduced from (Qiu, 2009a)

ER system	Characteristics
Matrix	<ul style="list-style-type: none">• <i>In vitro</i> release is sensitive to <i>in vitro</i> test conditions• <i>In vivo</i> results depend on individual drugs and formulation design• Hydrophilic matrix: Gel strength and system integrity also affect rate and mechanism of drug release <i>in vivo</i>• Possible to alter <i>in vitro</i> test condition for obtaining IVIVC
Reservoir	<ul style="list-style-type: none">• <i>In vitro</i> release is usually sensitive to <i>in vitro</i> test conditions• <i>In vivo</i> results depend on individual drugs and formulation design• Possible to adjust test condition for obtaining IVIVC
Osmotic pump	<ul style="list-style-type: none">• <i>In vitro</i> release is generally insensitive to test conditions• <i>In vivo</i> results depend on individual drugs• Higher probability of obtaining IVIVC• Lack of flexibility to adjust test condition to match <i>in vivo</i> performance

1.5 Mathematical modelling for predictability of drug release

Mathematical modelling of drug release is utilized for elucidation of underlying drug release mechanisms and simulation of (Siepmann and Siepmann, 2008). Ideally, by means of mathematical modelling, the required composition (type and amount of drug, polymer and additives) and geometry of tablet to achieve a certain drug release profile can be predicted (Siepmann and Peppas, 2012). Different mathematical equation can be applied for different tablets by considering: 1) inner structure of the device (matrix or reservoir), 2) the ratio initial drug concentration and drug solubility (monolithic solution or monolithic dispersion), 3) device geometry (cylinder, sphere, slab) (Siepmann and Siepmann, 2012). Understanding of the involved drug release mechanisms is a prerequisite to predict the drug release from matrix tablets.

Drug release from monolithic dispersions (dissolved and dispersed drug coexist in the wetted areas of the tablet) is described by the Higuchi model which was later extended to the following equation (Higuchi, 1963):

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

Where Q is the release rate per unit surface area, D represents the diffusivity of the drug in the permeating fluid, ε denotes the porosity and τ the tortuosity of the matrix, A is the amount of drug per unit volume, C_s represents the solubility of the drug in the permeating fluid and t is the time.

The mathematical description of drug diffusion from monolithic solution is based on Fick's second law of diffusion (Crank, 1975):

$$\frac{\partial c}{\partial t} = \frac{1}{r} \cdot \left\{ \frac{\partial}{\partial r} \left(rD \frac{\partial c}{\partial r} \right) + \frac{\partial}{\partial \theta} \left(\frac{D}{r} \cdot \frac{\partial c}{\partial \theta} \right) + \frac{\partial}{\partial z} \left(rD \frac{\partial c}{\partial z} \right) \right\}$$

where c is the concentration of the diffusing compound with diffusion coefficient D, t represents the time, and r, θ , and z are the three spatial directions.

In the case of monolithic solution systems, in which either the drug is molecularly dispersed in the matrix carrier or the drug is completely dissolved upon medium imbibition into the system, Fick's second law was solved analytically by Vergnaud (Vergnaud, 1993).

$$\frac{M_t}{M_\infty} = 1 - \frac{32}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{q_n^2} \cdot \exp\left(-\frac{q_n^2}{R^2} \cdot D_{app} t\right) \cdot \sum_{p=0}^{\infty} \frac{1}{(2p+1)^2} \cdot \exp\left(-\frac{(2p+1)^2 \cdot \pi^2}{H^2} \cdot D_{app} t\right)$$

where M_t/M_∞ is the cumulative drug release, n and p are real numbers, q_n are the roots of the Bessel function of the first kind of zero order ($J_0(q_n) = 0$), D is the apparent diffusion coefficient of the drug in the matrix, t is the time, and R and H represent the radius and the height of the tablet, respectively.

The conditions for the application of this equation are:

- Diffusion mass transport of drug is release-rate limiting
- Perfect sink condition during the entire release period
- The diffusion coefficient of diffusing species is constant

- The device is not significantly swelling (or swells very rapidly and then reaches an equilibrium state, e.g. for Kollidon[®] SR matrix tablets)
- Device is not significantly eroding during drug release
- Liquid unstirred boundary layer is generally thin (mass transfer resistance can be neglected).

In this equation, all formulation parameters except for the matrix dimensions (drug solubility, drug loading, tortuosity) merge into apparent diffusion coefficient, D_{app} . Applying D_{app} as fitting parameter and considering the dimensions of the matrix tablet, drug release for matrices with exactly same compositions were predicted (Siepmann et al., 2010). The same model allowed to accurately describe and predict drug release from swellable, non-eroding (Kollidon[®] SR) polymeric matrix tablets for different model drugs (Grund et al., 2013).

Research objectives

- ***In vitro-in vivo* correlation (IVIVC) for hydrophilic matrix tablets with different gel strengths**
 - to characterize the gel strength of swollen matrix tablets by direct and indirect methods
 - to investigate the *in vitro* robustness of hydrophilic matrix tablets
 - to correlate the gel strength of hydrophilic matrix tablets, specifically at the gel-solution interface (erosion front), to the *in vitro* mechanical robustness and IVIVC
 - to suggest predictable *in vitro* methods in order to better resemble the *in vivo* hydrodynamic conditions
- **Predictability of drug release from hydroxypropyl methylcellulose (HPMC) matrix tablets when erosion is the dominant controlling release mechanism**
- **Development of food-independent coated dosage forms**
 - to investigate the effect of media containing surfactant on Aquacoat[®] coated pellets
 - to circumvent the effect of surfactant by two approaches:
 - addition of the surfactant (SDS) inside formulation (i.e. inside drug layer)
 - overcoating the Aquacoat[®] membrane with cationic polymer (e.g. Eudragit[®] RL)

2 MATERIALS AND METHODS

2.1 Materials

2.1.1 Commercial matrix tablets

Six commercial products: Glucophage[®], Alfuzosin[®], Tromphyllin[®], Preductal[®], Quetiapin[®] and Tramabeta[®] formulated as hydrophilic matrix tablets were purchased from retail drug stores in Germany and the USA.

2.1.2 Drugs

Diprophylline, theophylline anhydrous, ibuprofen, carbamazepine (BASF AG, Ludwigshafen, Germany).

2.1.3 Polymers

Hydroxypropyl methylcellulose (Methocel[®] K15M, Colorcon, Dartford Kent, UK), aqueous dispersion of ethyl cellulose (Aquacoat[®] ECD, FMC BioPolymers, Cork, Ireland), ethyl acrylate and methyl methacrylate copolymer with a low content of a methacrylic acid ester with quaternary ammonium groups, granules and aqueous dispersion (Eudragit[®] RS 30 D, Eudragit[®] RL 30 D, Eudragit[®] RS 100) (Evonik Röhm GmbH, Darmstadt, Germany), HPMC E5 (Methocel[®] E5, Colorcon, Dartford Kent, UK), polyvinyl pyrrolidone, PVP (Kollidon[®] 30, BASF SE, Ludwigshafen, Germany), ethylcellulose aqueous dispersion (Aquacoat[®] ECD, FMC BioPolymers, Cork, Ireland).

2.1.4 Others

Triethyl citrate, TEC (Citroflex[®] 2; Morflex, Greensboro, NC, USA); Sucrose nonpareils beads 710-850 μm (NP, Suglets[®], NP Pharm S.A., Bazainville, France); magnesium stearate (Baerlocher GmbH, Unterschleissheim, Germany); sodium dodecyl sulfate, SDS (Carl Roth GmbH, Karlsruhe, Germany).

2.1 Methods

2.1.1 *In vitro-in vivo* correlation of hydrophilic matrix tablets with different gel strengths

2.2.1.1 Tablet characterization

The commercial tablets were characterized with regard to their dimension and hardness using a hardness tester (Multicheck, Erweka GmbH, Heusenstamm, Germany).

2.2.1.2 Determination of HPMC type and content in commercial products

HPMC content was quantified by phenol-sulphuric acid assay (Ghori et al., 2014). Each tablet was dissolved in 50 ml water, and subsequently, the solution was stored in a 4°C refrigerator to ensure complete hydration of HPMC. Afterwards, 3 ml of solution was dialysed with 15000 Da molecular weight cut-off dialysis membrane (Spectra/Por® Biotech) to separate the HPMC content from other components (dialysis solution was changed 2 times after 4 h and 12 h, during the total dialysis process and dialysis was continued for at least 2 h after final change. Dialysed sample (1 ml) was added to 1 ml of 5% phenol in 0.1 M hydrochloric acid, followed by 5 ml of concentrated sulphuric acid. The solution was mixed vigorously for 5 min and placed in a water bath at 25° C for 15 min. Absorbance was measured at maximum wavelength 490 nm and the dissolved HPMC content was calculated from a standard calibration curve.

Different concentrations of varying molecular weight of HPMC type K (i.e. K4M, K15M and K100M) in water were prepared and kinematic viscosity were measured at 25 °C using capillary viscometer (Ubbelohde viscometer types 50113/Ic and 50110/I). There is an approximate relationship between solution viscosity and HPMC concentration based on Philipoff equation (Dow chemicals, 2006).

$$\eta^{1/8} = (KC + 1)$$

where η is viscosity in centistokes (cSt), C is concentration of HPMC in mg/ml and K is constant specific for each molecular weight of HPMC.

The type of HPMC in each product was determined by measuring the kinematic viscosity of dissolved tablet in 50 ml water (using capillary viscometer at 25 °C) and comparing the values with the viscosity of reference polymers.

2.2.1.3 Swelling study and characterization of gel strength of swellable matrix tablets by texture analyzer (direct measurement of gel strength)

For swelling experiment, one planar base of the tablet was coated with impermeable Eudragit® RS (by adding 1-2 droplets of Eudragit® RS solution prepared by dissolving 14 g Eudragit® RS 100 in the mixture of 50 ml acetone and 50 ml isopropanol), and the tablet was subsequently glued from the covered part to the bottom of a small petri-dish. These samples were stirred in 900 ml phosphate buffer pH 6.8 at 50 rpm using the dissolution paddle apparatus. The gel strength of swollen tablets at predetermined time intervals was measured by texture analyzer (TA.XT-plus) equipped with 2 mm in diameter flat-tipped, round steel probe. The test conditions were: pre-test speed 0.2 mm/sec, trigger force 0.1 g, test speed 0.1 mm/sec. Gel strength profile was presented as the first derivative of the force-distance curve which can be expressed by the following equation.

$$\frac{dF(x)}{dx} = rp G(x)$$

x: penetration depth of the probe, F(x): the force measured by texture analyzer, G (x): gel strength at any position x, rp: radius of the probe

The gel strength at the gel-solution interface was considered as the first point after the probe got fully in contact with the gel and the initial noise disappeared (Fig. 4).

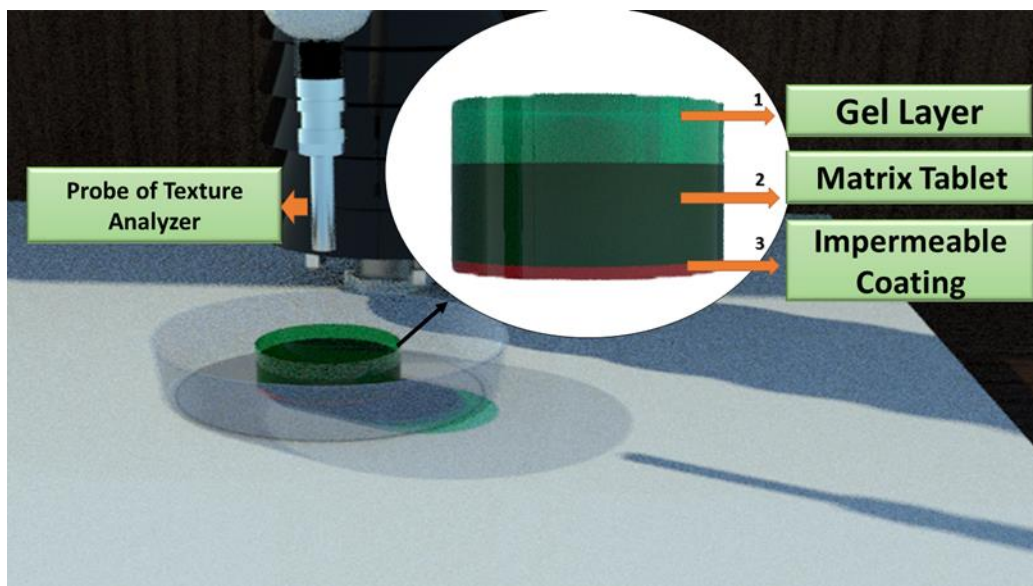


Fig. 4. Schematic representation of texture analysis of the swollen tablet.

2.2.1.4 Rheological investigation of dissolved matrix tablets (indirect or single point measurement of gel strength)

Samples for rheological investigation were prepared by dissolving each tablet in 50 ml water, then keeping solutions overnight in refrigerator in order to ensure complete gel formation of hydrophilic polymers. Rheological properties of tablet's solution were investigated by Modular Compact Rheometer (Anton Paar MCR 302) with double-gap system, using rotation test (controlled shear rate 0.1-1000 1/s,) and oscillatory sweep test (amplitude sweep preset and frequency sweep preset).

2.2.1.5 Water uptake and tablet erosion study

For water uptake and tablet erosion study, tablets were placed in *in vitro* dissolution test (900 ml phosphate buffer pH 6.8 using paddle at 150 rpm), and were withdrawn from dissolution vessels at 1, 2, 4 and 6 h hydration times. The swelling characteristics of tablets were evaluated by measuring tablet dimensions (i.e. diameter, length and width) under microscope and also by calculating percentage tablet weight gain as:

$$\text{weight gain\%} = \frac{(\text{wet weight} - \text{initial weight})}{\text{initial weight}} \times 100$$

Afterwards, the hydrated tablets were put on the petri-dishes and placed in an oven at 105 °C overnight. Dried tablet weight was measured and subsequently corresponding percentage tablet mass loss was calculated as:

$$\text{mass loss\%} = \frac{(\text{initial weight} - \text{dry weight})}{\text{initial weight}} \times 100$$

2.2.1.6 *In vitro* drug release

Dissolution study was conducted in 900 ml phosphate buffer pH 6.8 at 37 °C using USP II paddle apparatus (VK 7000, Vankel Industries, Edison, NJ, USA) with sinkers at 50, 100 and 150 rpm. In addition, to mimic pyloric antrum mechanical forces *in vivo*, modified dissolution tests were performed by applying mechanical loading on tablets at predetermined times. Tablets were placed in dissolution test apparatus (100 rpm in 900 ml phosphate buffer pH 6.8). At 1, 2 and 4 h hydration times, tablets were withdrawn from vessels and placed in petri-dishes (filled with 6 ml of medium), and subjected to predetermined mechanical loading force for 60 s by texture analyzer (TA.XTplus, Stable Micro Systems Ltd., UK, equipped with a 20 mm cylindrical probe). Corresponding force which was applied on the tablets was based on tablet surface area (in order to apply same pressure on all investigated tablets) and it was 2, 3, 4 and 6 N for Alfuzosin[®], Tromphylline[®], Quetiapin[®] and Glucophage[®], respectively. Ultimately, tablets were carefully placed back into the vessel (with medium) and residuals in the petri-dish was rinsed with 5 mL of media (Talukdar et al., 1996). Results of modified dissolution methods were compared to conventional dissolution paddle method at 100 rpm without stress.

2.2.1.7 *In vitro-in vivo* correlation

In vivo plasma concentration profiles, obtained from (Rote Liste, 2015), were deconvoluted by Wagner-Nelson method into *in vivo* absorption profiles used for Level A IVIVC (point-to-point correlation).

2.2.2 Mathematical modeling for predictability of drug release from HPMC matrix tablets

2.2.2.1 Tablet formulation and preparation

For tablet preparation, Methocel® K15M and drug (drug loading 10-95% w/w, diprophylline 212 mg/ml, theophylline 10 mg/ml, ibuprofen 3 mg/ml in pH 6.8) were physically mixed in a mortar with a pestle and finally 1% w/w magnesium stearate was blended to the powder mixtures as lubricant and mixed for further 5 min. Tablets were prepared by compressing the powder mixture with an instrumented 10 mm single punch tableting machine (EK0, Korsch AG, Berlin, Germany) recording compression force during the compaction process (MGCplus, catman, HBM, Darmstadt, Germany). Various initial porosities (5-20 % v/v) for each composition were achieved by increasing compression force. Starting with producing 200 mg tablet and following by increasing tablet weight to 210 mg, 220 mg, 230 mg, 240 mg with keeping the height of tablet constant (i.e. constant geometry) resulted in increasing compression force (5 to 25 KN) and consequently decreasing initial (air) porosity. The tablets were characterized with regard to their dimension and hardness (Multicheck, Erweka GmbH, Heusenstamm, Germany). The porosity was calculated from the ratio of apparent density and true density of the tablets.

2.2.2.1 Drug release

Dissolution study was performed in 900 ml phosphate buffer pH 6.8 at 37 °C using paddle apparatus (with sinker) at 50 rpm. Samples were taken at predetermined time points and analyzed spectrophotometrically (at 230, 272 and 292 nm for ibuprofen, theophylline and diprophylline, respectively).

2.2.2.2 Mass loss and tablet erosion studies

For tablet erosion study, tablets were placed in *in vitro* dissolution test (900 ml phosphate buffer pH 6.8 using paddle at 50 rpm), and were withdrawn from dissolution vessels at 1, 2, 4 and 6 h hydration times and the swelling characteristics of tablets were evaluated by measuring tablet dimensions under light microscope (Inteq® informationtechnik, GmbH,

Berlin, Germany). Afterwards, the hydrated tablets were put on the petri-dishes and placed in oven at 105 °C overnight. The dried tablet weight was measured and subsequently corresponding percentage tablet mass loss was calculated as:

$$\text{mass loss\%} = \frac{(\text{initial weight} - \text{dry weight})}{\text{initial weight}} \times 100$$

2.2.3 Development of food-independent coated dosage forms

2.2.3.1 Drug layering

Theophylline and carbamazepine were layered on sugar pellets using HPMC (Methocel[®] E5) as binder (20% w/w based on drug) in isopropanol/water (88:12 w/w) solution in a fluidized bed coater Glatt GPCG-1 (Glatt GmbH, Binzen, Germany) to achieve 10% and 30% w/w drug content, respectively. In addition, for investigation the effect of surfactant inside formulation (section 3.3.2.2), SDS (1.5-50% w/w based on drug) was layered with drug on sugar pellets as well. The layering conditions were: batch size 400 g, inlet temperature 40 °C, product temperature 35±2 °C, air flow: 60-80 m³/h, nozzle diameter 1.2 mm, spray pressure 1.2 bar, spray rate: 6-10 g/min, final drying at 40 °C for 10 min.

2.2.3.2 Coating of layered pellets

Theophylline (with SDS) layered pellets were coated either with Aquacoat[®] ECD (aqueous dispersion of ethyl cellulose) which was plasticized overnight with TEC (20% w/w based on the polymer content) and adjusted to 15% (w/w) polymer content with purified water, or with an organic ethyl cellulose solution (in 88:12 isopropyl alcohol:water, 7% solid content) in a fluidized bed coater Mini Glatt[®] (Glatt, GmbH, Binzen, Germany). The coating dispersion and solution were sprayed onto theophylline drug pellets until a weight gain of 10% and 20% (based on the drug pellets) was achieved. The process parameters were as follows: inlet temperature 40 °C, spray rate 2-3 g/min, air pressure 0.2 bar, spray pressure 0.9 bar, product temperature 38±2 °C for Aquacoat[®] and 30±2 °C for ethyl cellulose solution, nozzle diameter 0.5 mm. After coating, the pellets were further fluidized for 10

min and subsequently cured for 24 h at 60 °C and ambient relative humidity. Carbamazepine (with and without SDS) layered pellets were coated with blends of Aquacoat[®] and PVP (in ratio of 90:10 and 85:15) in a fluidized bed coater Mini Glatt[®] (Glatt, GmbH, Binzen, Germany). All dispersions were plasticized with TEC (20% w/w based on the ethyl cellulose mass) overnight. The coating dispersions were sprayed onto carbamazepine pellets until a weight gain of 7.5% and 10% w/w (based on the starter core) were achieved. The process parameters were as above. After coating, the pellets were further fluidized for 10 min and subsequently cured for 24 h at 60 °C and ambient relative humidity. Additionally, these Aquacoat[®] coated pellets (7.5 and 10% coating level) were sequentially over coated with Eudragit[®] RS 30 D or Eudragit[®] RL 30 D (plasticized with TEC) to achieve a weight gain of 2.5%, 5%, 7.5% and 10% as top coated pellets (based on the aquacoat[®] coated pellets).

2.2.3.3 Solubility determination

Excess amounts of theophylline or carbamazepine were placed in 20 ml screw cap glass vials with 10.0 g of phosphate buffer solution (PBS) pH 6.8, PBS pH 6.8 with sodium dodecyl sulfate (0.25% w/v) (n=3). The slurries were stirred magnetically at ~200 rpm at 25 °C for 10 min, to insure wetting and dispersion of the drug, and then placed in a horizontal shaker (GFL 3033) (75 rpm, 37 °C) for 48 h. Samples were taken and filtered through a 0.22 µm CME-syringe-filter and analyzed for drug concentration UV-spectrophotometrically (HP 8453, Agilent Technologies Deutschland GmbH, Waldbronn, Germany) ($\lambda = 271$ and 285 nm for theophylline and carbamazepine, respectively) after appropriate dilution. Blanks of drug-free mediums containing different surfactants were treated and measured likewise.

2.2.3.4 Drug release

The drug release study was conducted in 0.1 M HCl, phosphate buffer pH 6.8, phosphate buffer pH 6.8 with 0.25% w/v SDS using paddle method at 50 rpm. At predetermined

times, samples were taken and measured spectrophotometrically ($\lambda = 272$ and 285 nm for theophylline and carbamazepine, respectively).

3 RESULTS AND DISCUSSION

3.1 In vitro-in vivo correlation of hydrophilic matrix tablets with different gel strengths

3.1.1 Introduction

Hydrophilic matrix tablets remain an important approach to achieve controlled oral drug release. They are formulated using non-cross-linked, water swellable polymers (e.g. hydroxypropyl methylcellulose, HPMC), that swell rapidly enough to form a continuous ‘gel layer’ surrounding the dry core which controls the drug release rate during passage of the matrix through the gastrointestinal (GI) tract (Timmins et al., 2014). However, in some cases, the *in vivo* drug release rate is much faster to that determined *in vitro* due to extensive mechanical forces in the GI tract which do not resemble *in vitro* condition (Abrahamsson et al., 1999; Kavanagh and Corrigan, 2004; Klancar et al., 2013). Therefore, the design of a mechanically robust formulation (which can be defined by sufficient gel strength) is key to achieve predictable *in vivo* plasma concentrations, which is consistent with *in vitro* dissolution profile (Timmins et al., 2014).

Upon contact with an aqueous solution, hydrophilic tablets start to swell and consequently a viscous gel layer of hydrated polymer forms around the tablet. With continuous swelling of the matrix tablet and further hydration of the polymer, the polymer concentration at the gel surface ultimately becomes lower than the “critical polymer concentration” and it can not withstand the shear force applied by the surrounding medium. Consequently, the outermost layer of polymer chains starts to detach from the gel surface and slows down further swelling of the tablet (Ju et al., 1995). The critical polymer concentration is constant for each formulation during the entire dissolution process when the shear force environment remains constant (Körner et al., 2005; Körner et al., 2009).

There are three different fronts which were previously distinguished within gelatinous hydrophilic matrix tablets (Colombo et al., 2000). The swelling front between dry glassy core and gel phase, the diffusion front between the dissolved and undissolved drug in the gel layer, and finally the erosion front between the outer surface of tablet and dissolution

medium. The drug release mechanism and therefore drug release rate depend on the movement of different fronts. At early stage of dissolution, the diffusion of dissolved drug through the gel layer governs the release mechanism. At the later stage, when polymer chains start to disentangle from the erosion front, two operating mechanisms drug diffusion through the gel layer and matrix erosion simultaneously play role in release of drug. The contribution of these mechanisms to overall release changes in dependence of the composition of the matrix. The dimensions of the matrix, the solubility of drug and its distribution in the matrix, the content and properties of the matrix former (polymer) are key parameters affecting the processes governing drug release (Maderuelo et al., 2011).

To develop a dissolution test that could better predict *in vivo* performance, the conditions in the gastrointestinal tract (e.g. pH, osmolarity, mechanical forces, surfactants) should be reflected in *in vitro* test successfully. Among these physiological conditions, hydrodynamic (agitation intensity) and mechanical destructive forces within stomach and intestine have a significant impact on drug release from hydrophilic matrix tablets (Klancar et al., 2012). The mechanical forces of the human stomach and small intestine on a tablet as it passes through the GI tract were reported as 2 N and 1.2 N, respectively and they have a significant impact on the integrity of the gel layer (Kamba et al., 2002). In some cases, *in vivo* drug release is very different to that determined *in vitro* due to these mechanical forces (Garbacz et al., 2008). The release of drug by erosional mechanism, which results from disentanglement and dissolution of polymer particles at the surface of the tablet, is accelerated by mechanical forces. Therefore, formulations with sufficient gel strength which perform robustly *in vivo* may deliver the drug to the lower GI-segments. This has two consequences: greater predictability between *in-vitro* and *in vivo*, and less inter-subject variability (Timmins et al., 2014).

It is known that polymer molecular weight and polymer content affect gel strength. However, properties of drug and other excipients should also be taken into account, as they might alter water penetration into the tablet, strength of the gel layer, erosion and consequently the mechanism of drug release (Sako et al., 2002; Turner et al., 2004). The

aim of this study was to correlate the rheological property (i.e. gel strength) of hydrophilic matrix tablets to *in vitro* mechanical robustness and consequently to their IVIVC.

3.1.2 Results

3.1.2.1 Determination of HPMC type and content in commercial products

The amount of HPMC in each commercial product measured by phenol-sulphuric assay is shown in Table. 1.

There is a linear relationship between 8th root of kinematic viscosity and HPMC concentration (based on Philipoff equation, see 2.2.1.2). The linear regression equation for each molecular weight of HPMC was obtained (Fig. 5). The type of HPMC in each product was determined by measuring the kinematic viscosity of dissolved tablet in 50 ml water (using capillary viscometer at 25 °C) and comparing the value with the linear regression equation of reference polymers (Tab. 4).

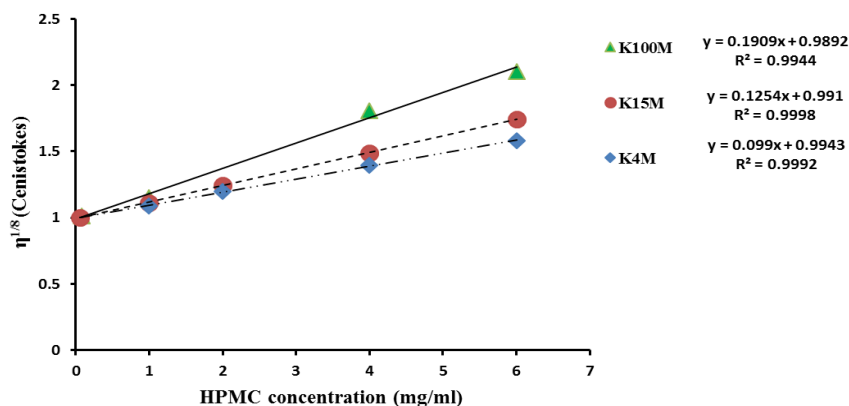


Fig. 5. Viscosity/concentration relationship of different grades of HPMC type K.

Table 4. Commercial hydrophilic matrix tablets (*IV: intrinsic viscosity, MCC: microcrystalline cellulose, NaCMC: sodium carboxymethylcellulose).

Product	API (dose)	HPMC			Other relevant excipients	Weight (mg)	Hardness (N)	Diameter, Length/width (mm)
		%w/w	Type	IV*, dl/g				
Glucophage® XR	Metformin (500 mg)	40	K100M	11.01	MCC, NaCMC	1050	177	19/9 (oval)
Alfuzosin-ratiopharm®	Alfuzosin (10 mg)	>70	K15M	8.98	Lactose, Povidone	308	125	9
Tromphyllin®	Theophylline (300 mg)	20	K15M	8.98		365	94	14/6 (oval)
Preductal®	Trimethizadine (35mg)	37	K4M	7.37	CaHPO ₄ . 2H ₂ O, Povidone	205	129	8
Quetiapin-ratiopharm®	Quetiapine (50 mg)	25	K4M	7.37	MCC, Sodium citrate	519	390	17/7 (oval)
Tramabeta®	Tramadol (100 mg)	HPC			CaHPO ₄ . 2H ₂ O	305	104	9

3.1.2.2 Characterization of gel strength profile of swellable matrix tablets by texture analyzer

The polymer concentration within swollen matrix tablet is not homogeneous, but rather there is a polymer concentration gradient through the gelatinous layer. This polymer concentration gradient renders corresponding gel strength gradient which was previously characterized (Xiao, 2007). It is worth to mention that outer regions within swollen matrix tablet which are more hydrated are characterized by low gel strength and low resistance to penetration of texture analyzer probe, while inner and less hydrated regions have denser gels requiring greater forces for penetration.

A swollen matrix tablet consists of three regions which can be identified by texture analyzer: gel layer, swollen glassy layer, dry core (Fig. 6). Gel layer is distinguished by the first gradual increase of gel strength. A linear gel strength gradient was observed within the gel layer corresponding to linear polymer concentration gradient in this region. The subsequent region after gel layer is partially hydrated swollen glassy layer. Ultimately, dry glassy core, the innermost region, is represented by a plateau next to the swollen glassy layer (Fig. 6).

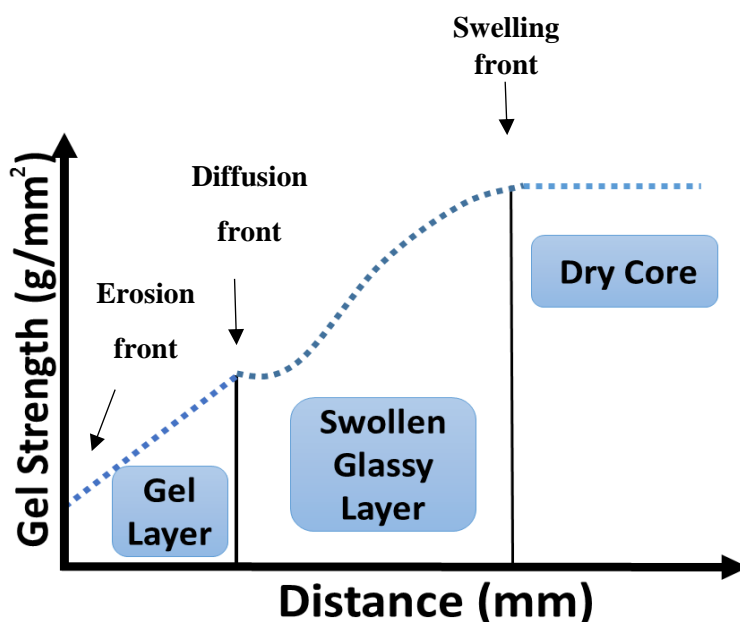


Fig. 6. Schematic representation of gel strength profile within swellable matrix tablet.

For investigated hydrophilic matrix tablets, the similar pattern of gel strength profiles was observed at most of the hydration times, i.e. gel layer, swollen glassy layer, dry glassy core were detected. However, in case of Tromphylline[®] and Tramabeta[®] matrix tablets, a gel strength plateau (instead of linear increase in gel strength profile) was observed at outer gel layer, followed by an increase in gel strength (Fig. 7). For Tramabeta[®] as HPC matrix tablet, this gel strength plateau existed within the majority of swollen matrix tablet until it has reached the core, and ultimately it started to increase sharply. This phenomenon indicates that, for HPC matrix tablet, the interface between gel layer and swollen glassy layer was

not distinguished. For Alfuzosin[®] and Preductal[®] the interface between gel layer and swollen glassy layer became smoother as hydration time progressed, because for low dose and highly soluble drug formulations, diffusion front can move inward as fast as swelling front, thus the thickness between the erosion front and the swelling front controls the drug release.

Understanding gel strength at gel-solution interface (erosion front) and gel strength gradient within gel layer can provide new insight into the robustness of hydrophilic matrix tablets against *in vitro* and *in vivo* hydrodynamics. Formulations having higher gel strength at erosion front during the majority of drug release provide lower critical polymer concentration, and therefore can withstand better against *in-vitro* and *in vivo* hydrodynamics and destructive contraction forces. After 2 h swelling time (using paddle apparatus at 50 rpm), gel strength at gel-solution interface for Glucophage[®], Tromphylline[®], Alfuzosin[®] and Preductal[®] which were formulated with higher viscosity grade of HPMC in sufficient amount (Tab. 4), lies in the range between 5.2 and 8.3 g/mm² (Tab. 5). As swelling time progresses, the matrix tablets are hydrated more; consequently, gel strength decreases for all tablets. Accordingly, gel strength at gel-solution interface after 6 h swelling reached 4.3, 4.5, 5.2, 3 and 2.3 g/mm² for Glucophage[®], Alfuzosin[®], Tromphylline[®], Preductal[®] and Tramabeta[®], respectively (Fig. 8). The slope of gel strength profile within gel layer (first region of gel strength profile) was used as an indication of gel strength gradient. After 6 h swelling, the slope lies in the range of 0.9, 3.8 and 8.7 for Preductal[®], Glucophage[®] and Alfuzosin[®], respectively (Tab. 6). Moreover, the gel layer thickness (obtained from Fig. 7) continues to grow within hydration times for Glucophage[®], Alfuzosin[®] and is almost constant for Tromphyllin[®] (Tab. 7). This clearly indicates that erosion rate in these formulations was slow which resulted in further enhancement of gel layer thickness, indicating predominantly diffusion mechanism of drug release.

In contrast to Glucophage[®], Alfuzosin[®], Tromphyllin[®] and Preductal[®], the gel strength at gel-solution interface for Quetiapin[®] matrix tablet dropped dramatically upon hydration and reached 1.9 g/mm² after 6 h (Fig. 8). In Quetiapine[®], gel layer thickness is similar at 2 h

and 4 h but it could not be detected after 6 h swelling, indicating erosion front moved fast inward and prohibited the further build-up of gel layer thickness (Tab. 7).

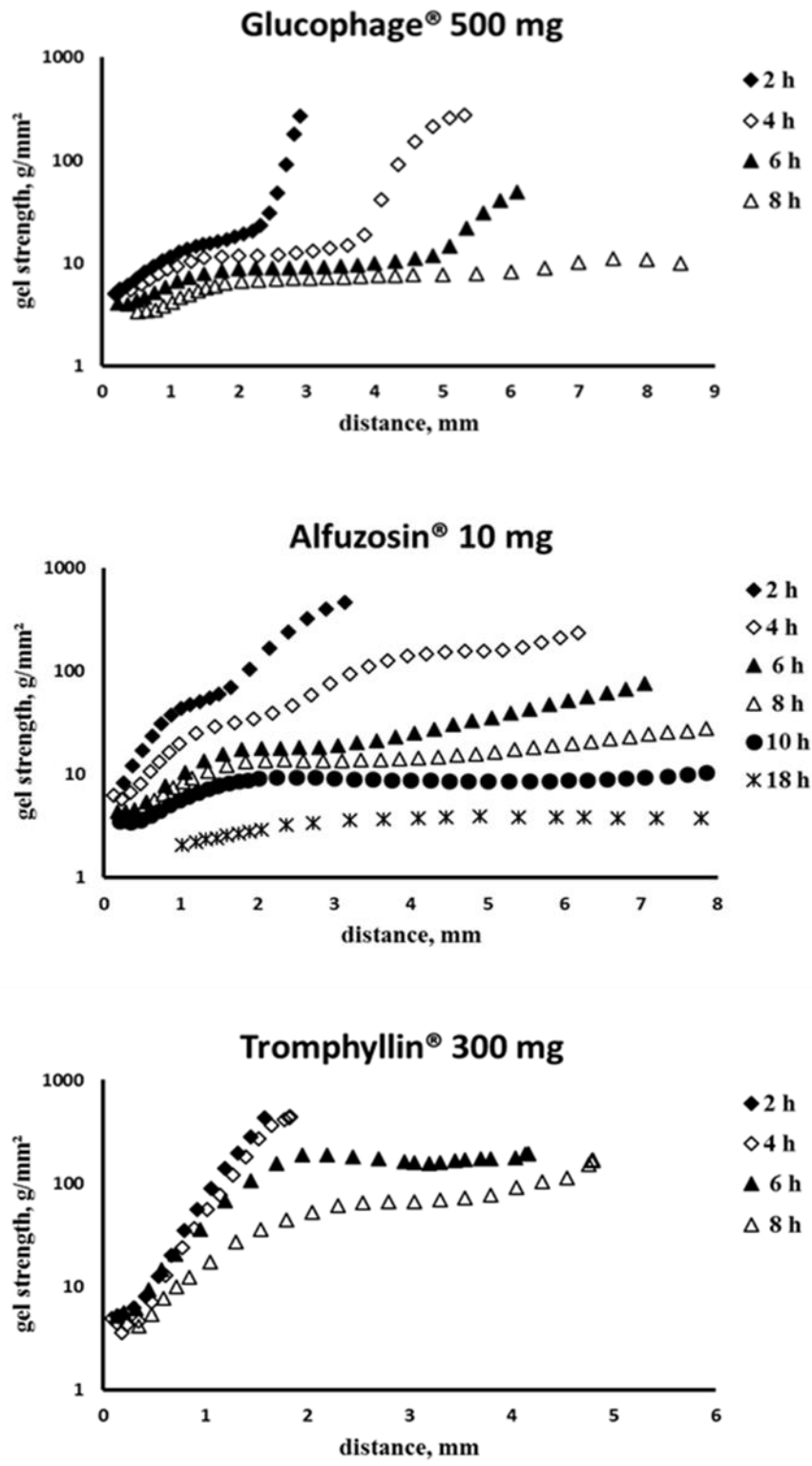


Fig. 7. Gel strength profiles of investigated products by texture analyzer at different swelling time (pH 6.8 using paddle at 50 rpm).

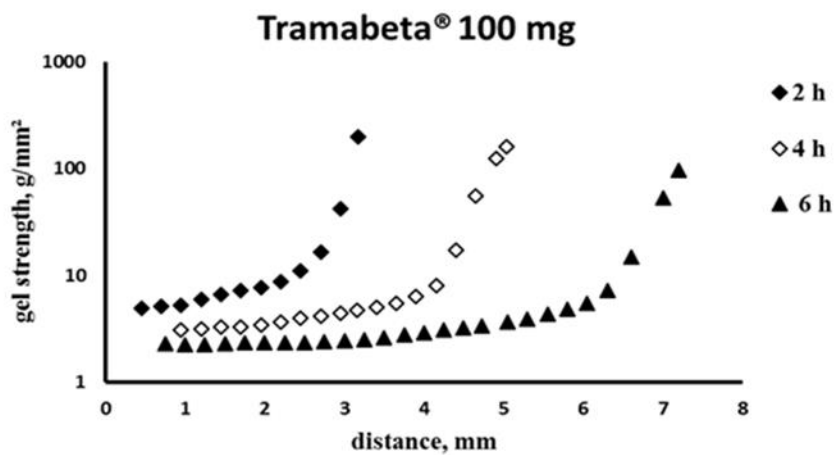
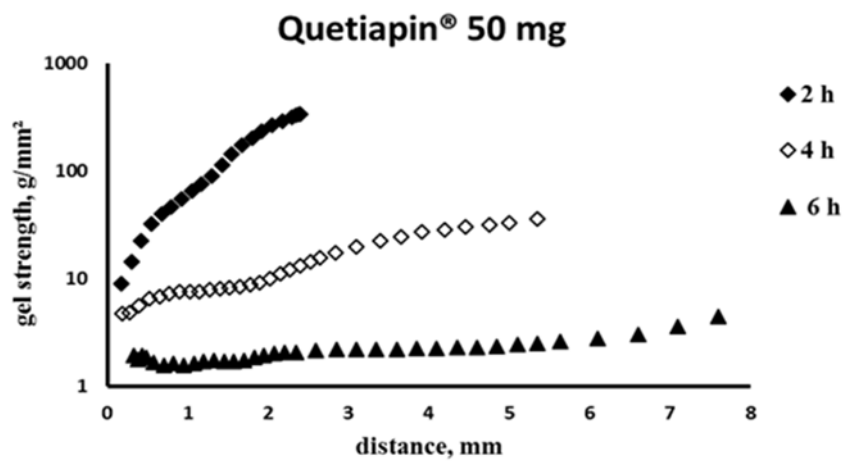
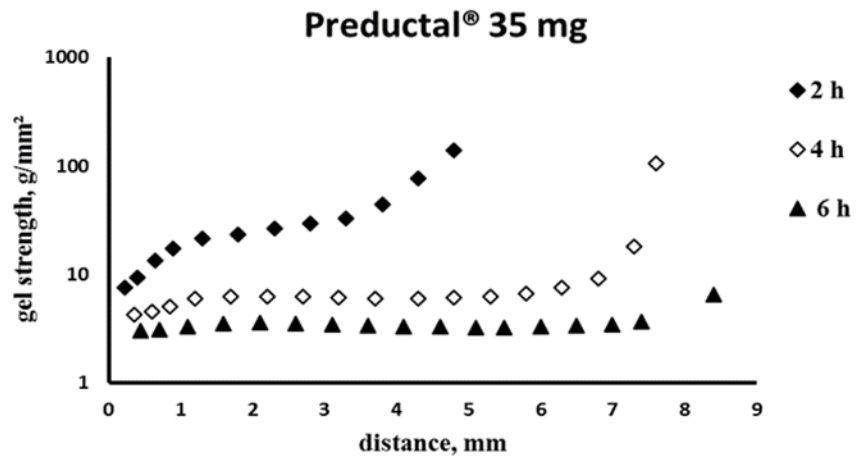


Fig. 7 (continued). Gel strength profiles of investigated products by texture analyzer at different swelling time (pH 6.8 using paddle at 50 rpm).

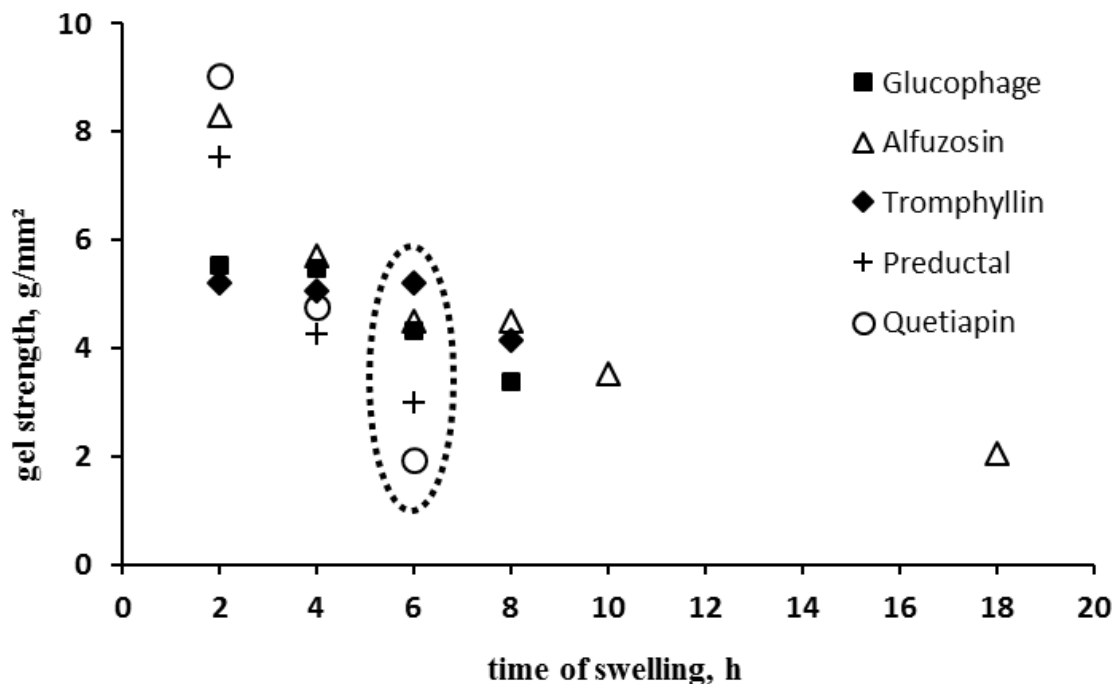


Fig. 8. Gel strength at gel-solution interface (g/mm²) (pH 6.8 using paddle at 50 rpm).

Table 5. Gel strength at gel-solution interface (g/mm²) in different swelling times (pH 6.8 using paddle at 50 rpm) (n.d. = not determined).

Matrix tablet	Swelling time					
	2 h	4 h	6 h	8 h	10 h	18 h
Glucophage [®] 500 mg	5.5	5.4	4.3	3.4	n.d.	n.d.
Alfuzosin [®] 10 mg	8.3	5.7	4.5	4.5	3.5	2.1
Tromphyllin [®] 300 mg	5.2	5	5.2	4.1	n.d.	n.d.
Preductal [®] 35 mg	7.5	4.2	3	n.d.	n.d.	n.d.
Quetiapin [®] 50 mg	9	4.8	1.9	n.d.	n.d.	n.d.
Tramabeta [®] 100 mg	4.9	3.1	2.3	n.d.	n.d.	n.d.

Table 6. Slope at gel layer profile for investigated products in different swelling times (n.d. = not determined).

Matrix tablet	Swelling time					
	2 h	4 h	6 h	8 h	10 h	18 h
Glucophage® 500 mg	8	5.5	3.8	2.9	n.d.	n.d.
Alfuzosin® 10 mg	48.8	16.5	8.7	6.9	4.2	0.8
Tromphyllin® 300 mg	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Preductal® 35 mg	16	2.4	0.9	n.d.	n.d.	n.d.
Quetiapin® 50 mg	63.7	6.6	n.d.	n.d.	n.d.	n.d.

Table 7. Gel layer thickness investigated in different swelling times (n.d. = not determined).

Matrix tablets	Swelling time			
	2 h	4 h	6 h	8 h
Glucophage® 500 mg	1	1.3	1.5	1.5
Alfuzosin® 10 mg	0.7	1.2	1.3	1.6
Tromphyllin® 300 mg	0.3	0.3	0.3	0.3
Preductal® 35 mg	0.9	1.2	n.d.	n.d.
Quetiapin® 50 mg	0.7	0.6	n.d.	n.d.

Comparing gel strength at 50 rpm and 150 rpm clearly demonstrated that the gel strength at gel-solution interface for Quetiapin® was significantly lower at 150 rpm than that at 50 rpm after 4 h swelling (Fig. 9). Ultimately, gel strength could not be detected after 6 h at 150 rpm because the tablet has been hydrated completely. The measured gel strength at gel-solution interface for Quetiapine® using paddle at 50 rpm after 6 h hydration (1.9 g/mm², Fig. 8) was probably below the sufficient gel strength level to withstand the accelerated *in vitro* hydrodynamic condition, resulting in accelerated erosion rate. The gel strength up to 6 h hydration was taken into consideration because it corresponds to the transition time through the upper GI tract in humans in fasted state.

In contrast, for Glucophage®, Alfuzosin® and Preductal®, the gel strength at gel-solution interface within investigated time window at 50 rpm was almost identical to that at 150 rpm (Fig. 9). It can be postulated that for these products drug release mechanism does not change

significantly at accelerated hydrodynamic conditions, and it is governed mainly by swelling/diffusion.

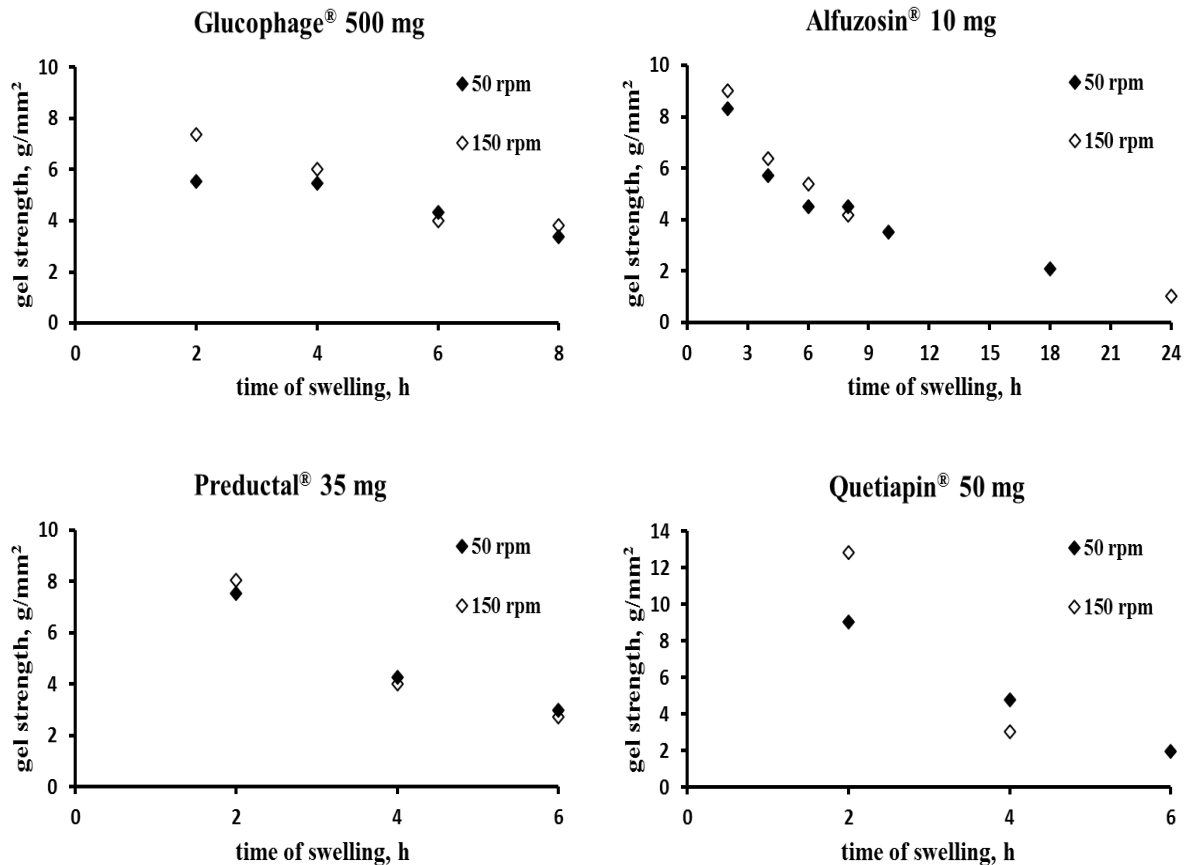


Fig. 9. Effect of stirring speed at 50 rpm vs. 150 rpm on gel strength at gel-solution interface (g/mm²) in different swelling times.

3.1.2.3 Rheological investigation of dissolved matrix tablets (indirect or single point measurement of gel strength)

By dissolving hydrophilic matrices in water, different ingredients of tablet, and specifically polymer molecular weight and content, give a specific viscosity value to the solution which may simulate the outer surface of the hydrated tablet. This rheological property of aqueous

solution determined by steady shear or oscillation tests, may give a better understanding about robustness of matrix tablet prior the dissolution testing.

Regarding steady shear measurement, Glucophage® and Alfuzosin® solutions exhibited non-Newtonian behavior (more gel-like), meaning that they have a plateau constant viscosity within low shear rates and a tendency to shear thinning rheological property at higher shear rates. In contrast, Tramabeta®, Tromphyllin® Preductal® and Quetiapin® solutions behaved as Newtonian solutions; their viscosity was not changed with increased shear rates. Glucophage has the highest zero-shear viscosity (4460.6), followed by Alfuzosin® (283.4) and Tramabeta® (4.1). Zero-shear viscosity (Newtonian viscosity) is the plateau viscosity observed at low shear (Tab. 8 and Fig. 10) and is particularly valuable rheological parameter quantifying the bulk viscosity of a shear-thinning polymer system (Hoare et al., 2010).

Moreover, dynamic moduli of tablet solutions, i.e. storage modulus (G') and loss modulus (G'') using oscillatory stress sweep test have been conducted, since almost all polymer solutions are viscoelastic and they exhibit solid (elastic) and liquid (viscous) properties simultaneously. The linear viscoelastic region (LVR) was first determined by amplitude sweep preset, in order to conduct satisfactory oscillatory test (Akinosho et al., 2013). Only for Glucophage® and Alfuzosin® solutions, storage modulus (G') could be measured within investigated shear stress and their corresponding yield stress value at which G' started to decrease was 4.5 and 0.697, respectively (Tab. 8 and Fig. 7). This indicates a high degree of interparticle interaction in Glucophage solution and thus lower degree of erosion (Asare-Addo et al., 2016).

Conducting frequency sweep present method revealed that for all of the formulations tested, storage modulus (G'') was higher than loss modulus (G'), indicating that all of the tablet solution behaved predominantly as viscous liquids. A higher value of G'' for Glucophage® and Alfuzosin® solutions compared to other products (Tab. 8 and Fig. 10) can be explained by higher entanglement density (Talukdar et al., 1996), reflecting stronger gel will be formed after tablet introduction into dissolution media; consequently, less mechanical susceptibility of tablets. In addition, with a damping factor ($\tan \delta$) value, the

portion of viscous/elastic of the material is characterized, which was lowest for Glucophage[®] and Alfuzosin[®] with values of 1.4 and 3.8, respectively (Tab. 8). It can be concluded that this rheological technique may not be appropriate in terms of differentiating between products showing low viscosity value in 50 ml water (i.e. Tromphyllin[®], Preductal[®], Quetiapin[®]). It may be attributed to collapse of polymer network inside solution by other components, which renders low rheologic parameter value.

Table 8. Rheological parameters measured by steady shear and sweep oscillatory methods.

Matrix tablet	Zero-shear viscosity (mPa.s)	Yield stress (Pa)	G'' at 1 rad/s	Damping factor (tan δ)
Glucophage [®]	4460.6	4.5	3.98	1.4
Alfuzosin [®]	283.4	0.697	0.19	3.8
Tramabeta [®]	4.1	-	0.004	∞
Tromphyllin [®]	3.1	-	0.003	∞
Preductal [®]	2.9	-	0.003	∞
Quetiapine [®]	2.8	-	0.003	∞

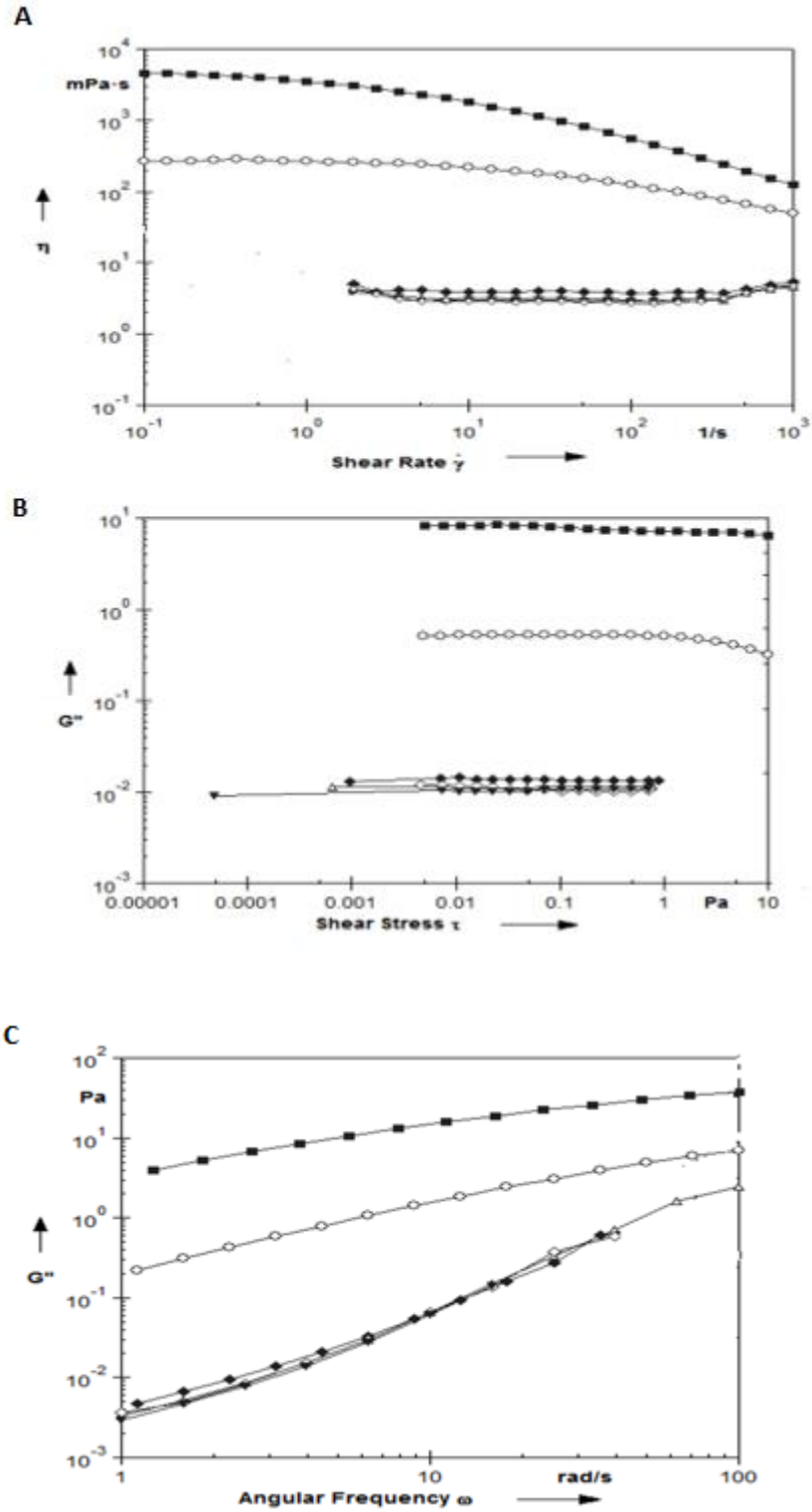


Fig. 10. Steady shear test (A); and oscillatory stress sweep tests by amplitude sweep preset (B) and frequency sweep present (C).

■ Glucophage[®], ○ Alfuzosin[®], ◆ Tramabeta[®], ▼ Tromphyllin[®], △ Preductal[®], ◇ Quetiapin[®]

3.1.2.4 Swelling and erosion study

Swelling (represented by changing weight gain and tablet dimension) and erosion for Alfuzosin[®] and Quetiapin[®] matrix tablets were studied. Alfuzosin[®] weight gain increased gradually and it reached a level of about 250% after 6 h hydration. In contrast, Quetiapin[®] weight gain increased up to 1 h hydration time, after which it decreased significantly because tablet erosion dictates mechanism of drug release and it slowed down further the swelling of the tablet (Fig. 11). Regarding tablet dimension, Alfuzosin[®] diameter was almost constant within hydration times but Quetiapin[®] dimension (which is more evident from its length) dropped markedly after 4 h hydration, indicating fast erosion rate of the tablet (Fig. 11). Moreover, Quetiapin[®] showed a greater mass loss and faster rate of tablet erosion (slope of tablet mass loss percentage within time) compared to Alfuzosin[®] (Fig. 11). Overall, these results were in agreement with findings of previous sections, indicating that mechanically robust products (e.g. Alfuzosin[®]) showed greater swelling and less erosion compared to less robust product (i.e. Quetiapin[®]).

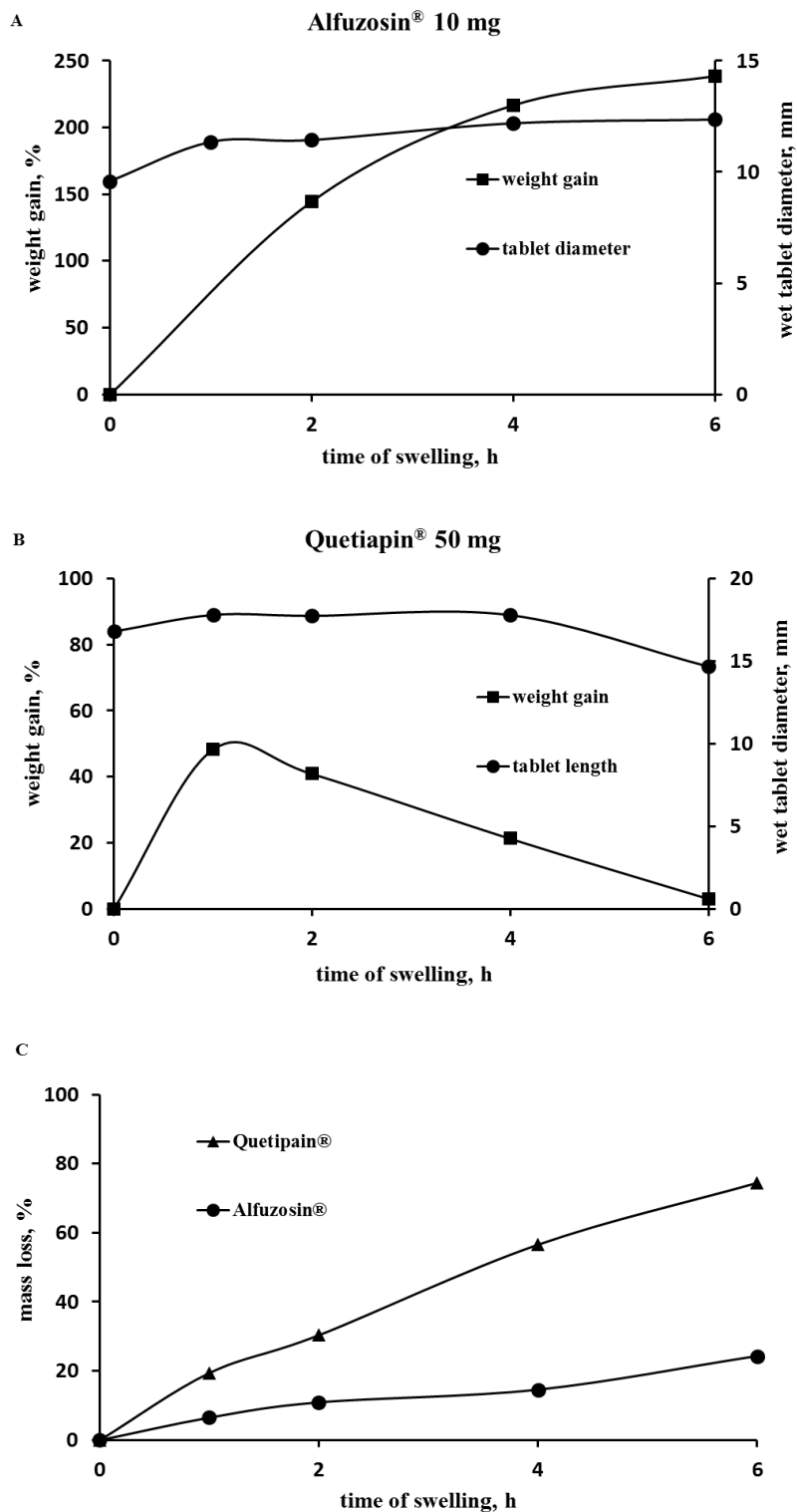


Fig. 11. Changing diameter and wet gain for (A) Alfuzosin® and (B) Quetiapin® and (C) mass loss for Alfuzosin® and Quetiapin® in different swelling times in pH 6.8 using paddle at 150 rpm.

3.1.2.5 *In vitro* drug release robustness

Among the different parameters contributing to the *in vitro* dissolution tests, the hydrodynamic condition (agitation intensity) and mechanical destructive force play a significant role on drug release from hydrophilic matrices. The hydrodynamic, which is described by the rate of fluid movement and shear stress generated within a particular dissolution apparatus, and mechanical destructive force have potential to affect tablet erosion and therefore the rate of drug release from hydrophilic matrix tablets. The influence of hydrodynamics was investigated by changing the shear stress (agitation rate). Moreover, a modified dissolution test (see section 3.1.1.5) was conducted to investigate the influence of contraction forces on hydrophilic tablets.

Drug release from Glucophage[®], Alfuzosin[®], Tromphyllin[®] and Preductal[®] formulated with higher viscosity grade of HPMC in sufficient amount (Table 4) were almost not affected ($f_2 > 50$) by agitation speed between 50 -150 rpm (Fig. 12). In the same manner, the release profiles of Alfuzosin[®], Glucophage[®] and Tromphyllin[®] were almost identical when dissolution tests were conducted by applying loading force at 1, 2 and 4 h hydration times when compared to release profile obtained in non-stress dissolution test (Fig. 13). This can be explained by robustness of their gel layer against *in vitro* agitation rate. This is in agreement with previous studies where the erosion rate *in vitro* and *in vivo* decreases with increasing fraction of a high molecular weight HPMC in tablets above the reported values for polymer percolation threshold (30-35% w/w) (Jain et al., 2014; Yasuji. T et al., 2012). Consequently, these products swell to a large extent, produce a firm gel, and drug release is predominantly governed by swelling/diffusion mechanism, and their drug release rate is not influenced significantly by varying agitation rates. Also, Tramabeta[®] formulated with HPC, exhibited an unchanged drug release at increased agitation speed, indicating robustness of its gel layer which was able to withstand the increased agitation intensities. Complete release was achieved as early as 8 h for Tramabeta and Glucophage under certain condition to 42 h in the case of Alfuzosin (Fig. 12).

It is worth to mention that besides the matrix former, other formulation excipients (e.g. type of filler and drug) are accounted for the formation of a strong gel layer in these formulations. For example, sodium carboxy methylcellulose combined with HPMC (e.g. in Glucophage[®]) has two effects. Firstly, rheological synergism of HPMC and NaCMC result in prolongation of release profile (Palmer et al., 2011), and secondly, complex formation between anionic polymer NaCMC and cationic drug metformine which mitigate rapid initial release of highly soluble drug and retardation of drug release (Feely and Davis, 1988). Regarding the effects of fillers, dicalcium phosphate (e.g. in Tramabeta[®]) and microcrystalline cellulose (in Glucophage[®]) may increase gel strength of HPMC matrix tablets. Using dicalcium phosphate, the slower wetting of the glassy tablet core can enhance mechanical gel strength (Jamzad et al., 2005; Tajarobi et al., 2009). Also, amorphous domains of microcrystalline cellulose remain within the hydrating matrix, which results in weak physical cross-linking between MCC and HPMC and thus increased gel strength (Dürig and Fassihi, 2002).

In contrast to aforementioned tablets, drug release from Quetiapin[®] increased significantly ($f_2 < 50$) with increased agitation speed (Fig. 12). Moreover, drug release profiles from Quetiapin[®] changed markedly with applying loading force during dissolution test of 100 rpm agitation speed (Fig. 13). This is specially more significant when mechanical forces were applied at 2 and 4 h hydration times. At these points, tablets were more hydrated and thus more sensitive to mechanical forces. This can be attributed to lower viscosity grade and lower content of HPMC used in this product (Tab. 4), resulting in less mechanically stable gel layer formed around the tablet. For Quetiapin[®] matrix tablet, in which erosion is the predominant process of release mechanism, increase in stirring rate can facilitate polymer chains detachment from the erosion front of the matrix where polymer concentration has reached the disentanglement threshold. This leads to enhancement of drug release rate. This result is consistent with previous finding, where it was demonstrated that erosion rate is faster in tablets containing HPMC at concentrations below (20 % w/w) the reported values for polymer percolation threshold (Ghimire et al., 2010).

Quetiapine is a weakly basic drug which has a high solubility in the stomach but is poorly soluble at the higher pH of the intestine. Sodium citrate was incorporated in Quetiapin® product in order to achieve pH-independent drug release. However, the effect of sodium citrate on gel layer integrity has to be taken into consideration, as based on a Hofmeister effect, it can reduce HPMC particle swelling and gel layer coalescence, leading to disruption of the establishment of the gel layer barrier (Pygall et al., 2009).

Visual observation of tablets after release with paddle 50 rpm showed that, for Quetiapin® the remaining of the HPMC matrix tablet was a small and soft gel mass and it fell apart when touched, while the Glucophage® (Fig. 14). and Alfuzosin® matrix tablets were intact.

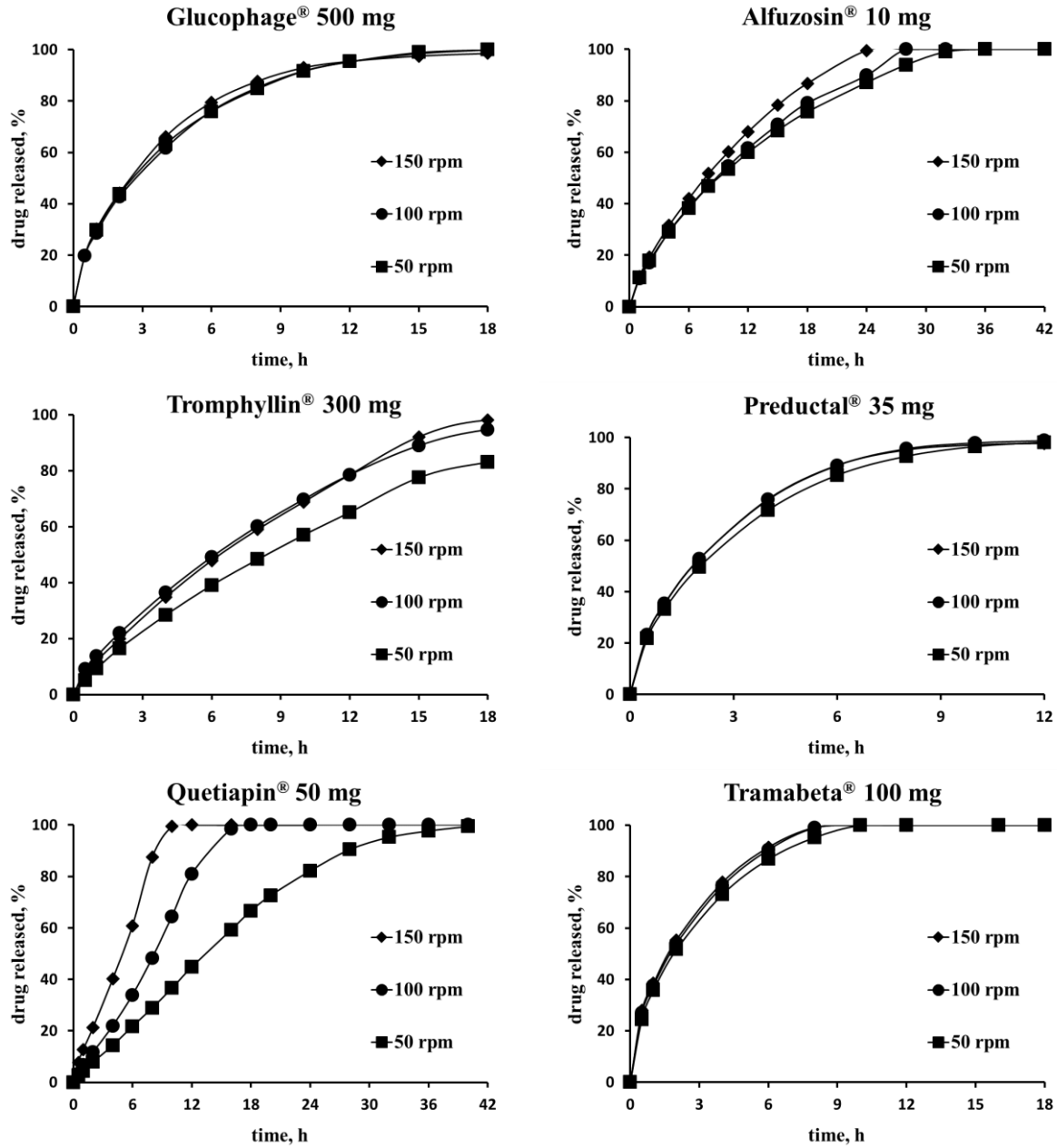


Fig. 12. Effect of different agitation speeds on dissolution profiles of commercial matrix tablets (in pH 6.8, paddle).

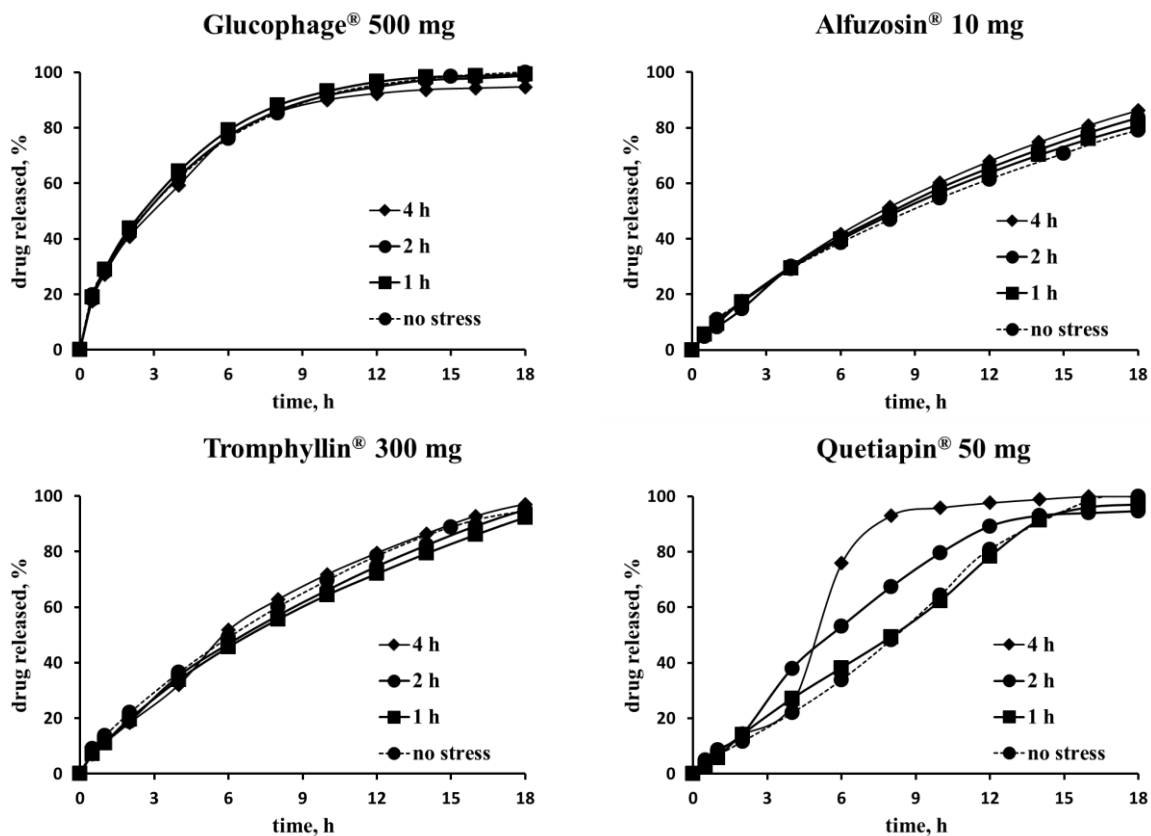


Fig. 13. Effect of applied stress after 1, 2 and 4 h hydration times on the dissolution release profiles of commercial matrix tablets (pH 6.8, paddle 100 rpm).

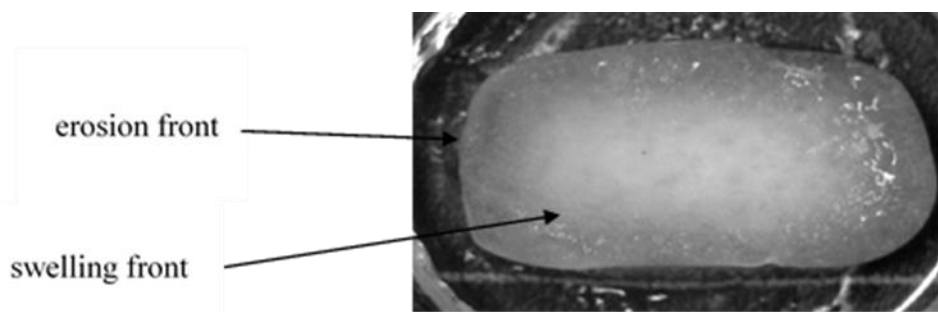


Fig. 14. Photomicrograph of a cross section of Glucophage® tablet after swelling of 24 h in pH 6.8, paddle 100 rpm.

3.1.2.6 *In vitro-in vivo* correlation (IVIVC) of hydrophilic matrix products

It is generally assumed that if the *in vivo* release controlling mechanism also controls the *in vitro* drug release, then it would be possible to establish a Level A IVIVC (Turner et al., 2004). Level A of IVIVC was achieved for Glucophage[®], Alfuzosin[®], Tromphyllin[®] and Preductal[®] matrix tablets when performing *in vitro* dissolution test at the wide range of agitation speeds (50-150 rpm) showing linear correlation coefficient $r^2 > 0.9$ (Fig. 15). Products composed of sufficient amount of higher grade of HPMC, providing high enough gel strength at the gel-solution interface (i.e. lower critical polymer concentration) during release, can withstand the hydrodynamic stress during *in vitro* and *in vivo* release. This resulted in good IVIVC. In contrast, Level A IVIVC for Quetiapin[®] ($r^2 > 0.9$) was established only for agitation speed 150 rpm (Fig. 15). Lower agitation speeds failed to provide predictable *in vitro* dissolution profiles, as they did not represent the *in vivo* accelerated erosion drug release mechanism. Overall, paddle method at 150 rpm in pH 6.8 could be recommended as a method to predict *in vivo* release of hydrophilic matrix tablets in terms of mechanical resistance of the tablets *in vivo*. This is in agreement with findings of Abrahamsson et.al. which demonstrated that human intestinal hydrodynamics were reflected *in vitro* using the paddle method at stirring rate of about 140 rpm (Abrahamsson et al., 1999). Furthermore, using modified *in vitro* dissolution test, Level A IVIVC was achieved for Quetiapin[®] with paddle at 100 rpm agitation speed aligned with applying mechanical loading at 2 h hydration time (Fig. 16).

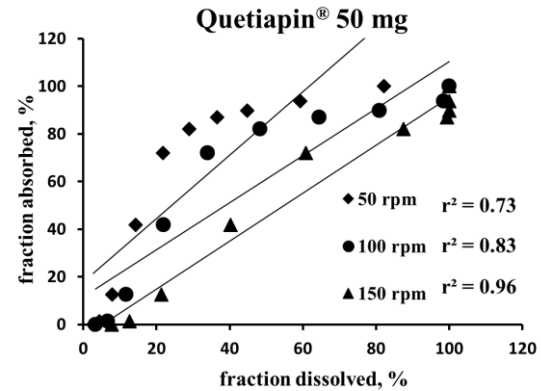
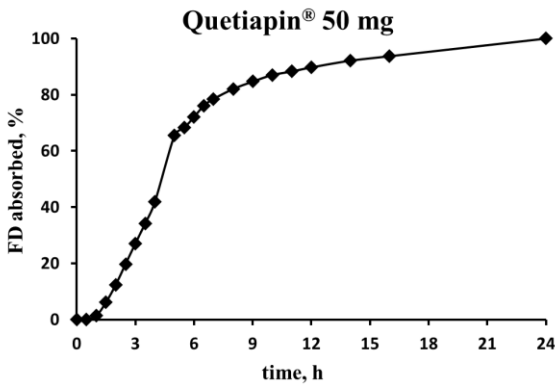
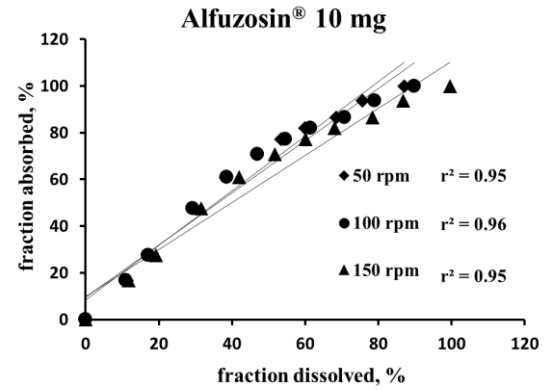
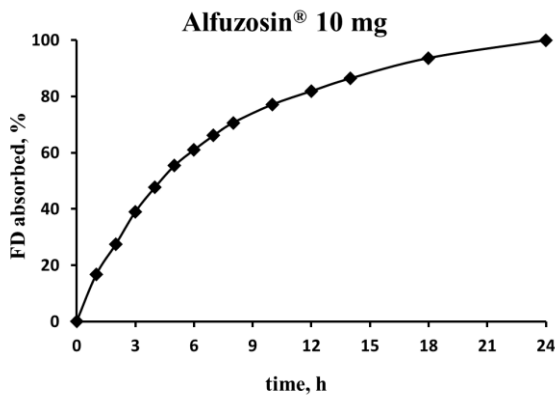
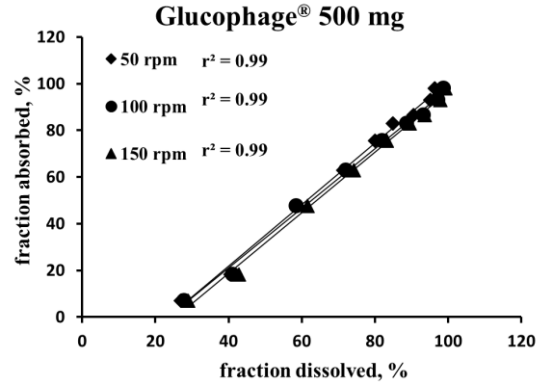
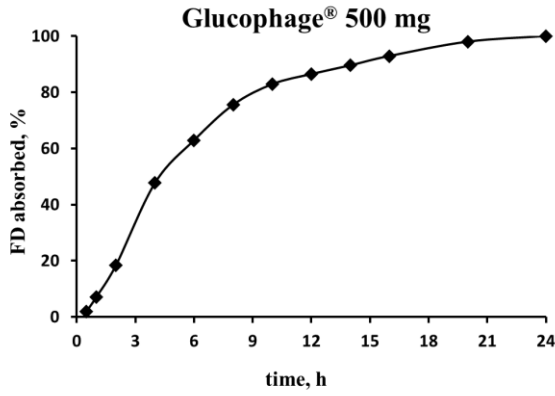


Fig. 15. Fraction drug *in vivo* absorbed vs. time for investigated products after deconvolution of plasma concentration time profiles according to the Wagner-Nelson method and corresponding IVIVC using varying agitation speeds (50-150 rpm).

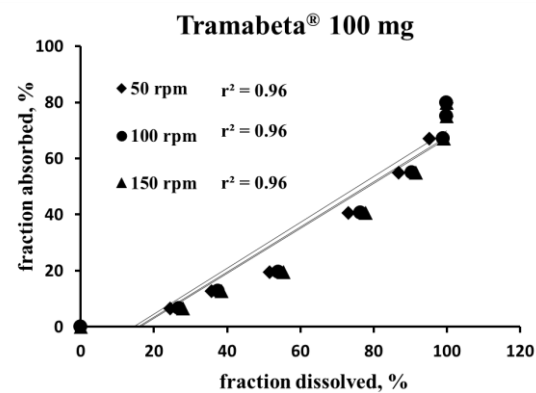
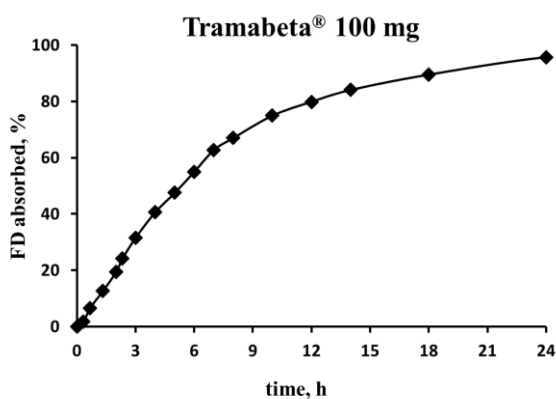
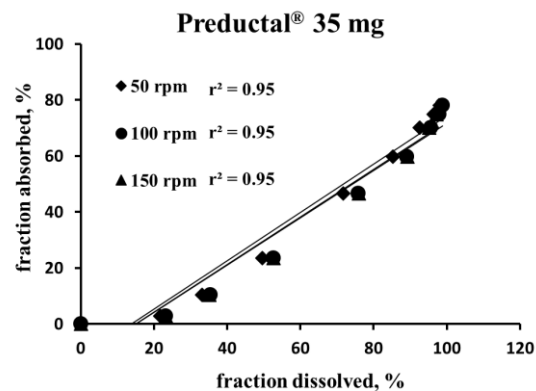
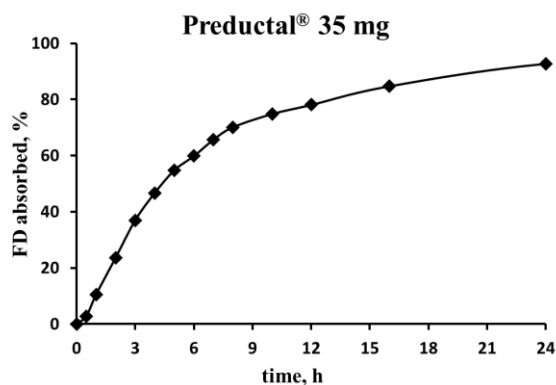
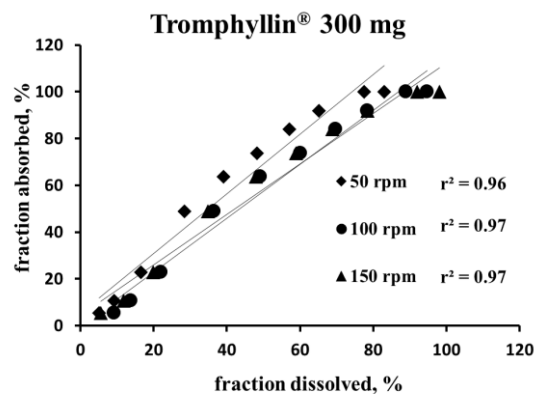
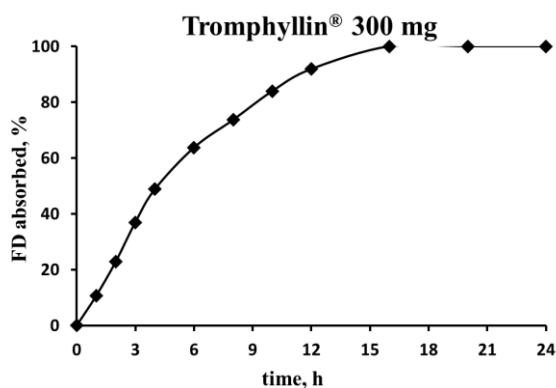


Fig. 15 (continued). Fraction drug *in vivo* absorbed vs. time for investigated products after deconvolution of plasma concentration time profiles according to the Wagner-Nelson method and corresponding IVIVC using varying agitation speeds (50-150 rpm).

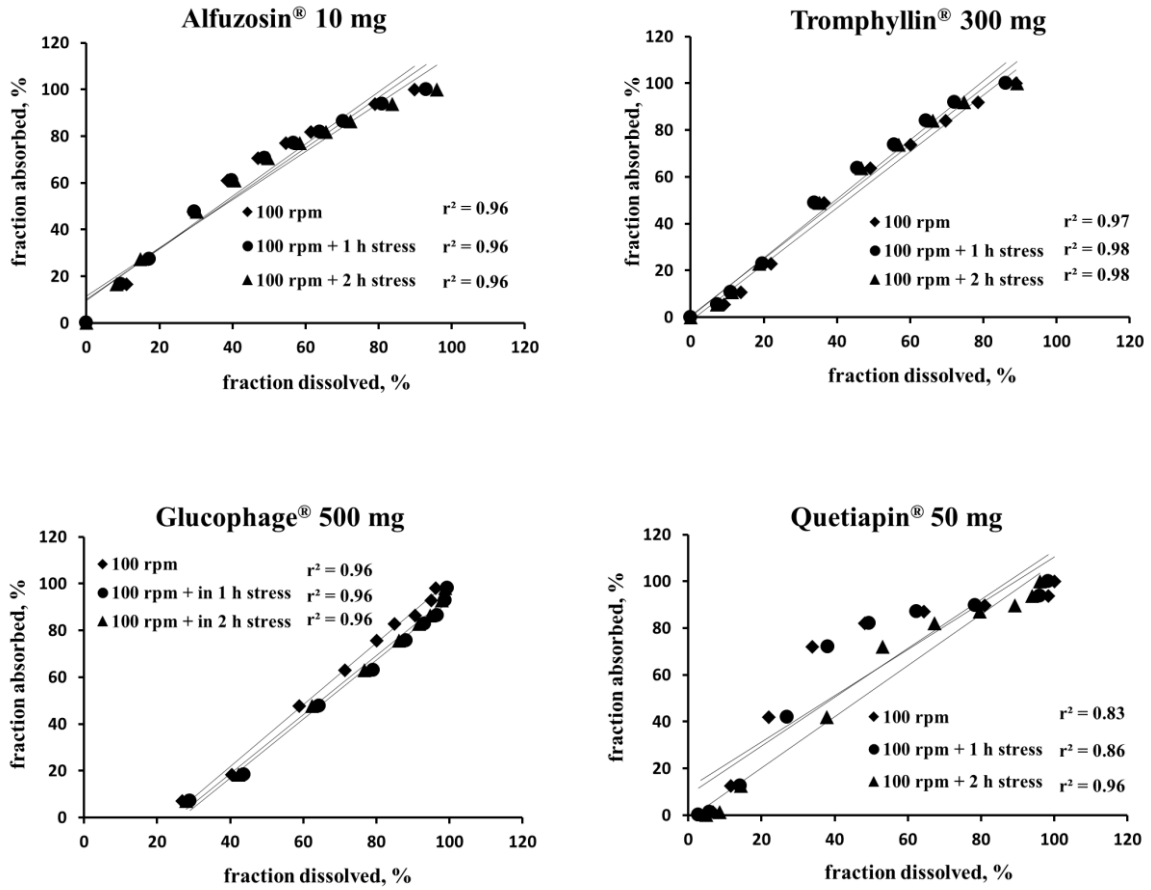


Fig. 16. Fraction drug *in vivo* absorbed vs. time for investigated products after deconvolution of plasma concentration time profiles according to the Wagner-Nelson method and corresponding IVIVC using applying stress at 1 and 2 h swelling time.

3.1.3 Conclusion

Our findings clearly demonstrated that drug release from tablets formulated with higher molecular weight HPMC and with content $\geq 20\%$ w/w was robust against hydrodynamic stress and contraction forces during *in vitro* and *in vivo* release. This could be attributed to sufficient gel strength ≥ 2 g/mm² up to 6 h of hydration and therefore resulted in good IVIVC (Level A) with 50 rpm agitation speed. Moreover, paddle method with 150 rpm, also paddle method with 100 rpm aligned with applying mechanical force at 2 h hydration time, could be recommended as a method to predict *in vivo* release of hydrophilic matrix tablets in terms of mechanical resistance of the tablets *in vivo*. These findings may provide a deeper insight for formulation scientists to select more properly formulation components in order to achieve more robust formulation and therefore stronger IVIVC.

3.2 Mathematical modeling for predictability of drug release from HPMC matrix tablets

3.2.1 Introduction

The mathematical description of the entire drug release process from hydrophilic matrix tablets is rather challenging, due to a number of effects that impact the release kinetics (Frenning, 2011; J. Siepmann et al., 1999; Siepmann and Peppas, 2012). Depending on the composition of the HPMC (hydroxypropyl methylcellulose) matrix tablet and its geometry, drug release is governed by a combination of different mechanisms, namely, drug diffusion through the gel layer, polymer swelling, and polymer erosion. To develop mathematical modelling and predict drug release profile from HPMC matrix tablets, these underlying release mechanisms have to be taken into account.

The mathematical description of drug diffusion from matrix systems is based on Fick's second law of diffusion (Crank, 1975):

$$\frac{\partial c}{\partial t} = \frac{1}{r} \cdot \left\{ \frac{\partial}{\partial r} \left(rD \frac{\partial c}{\partial r} \right) + \frac{\partial}{\partial \theta} \left(\frac{D}{r} \cdot \frac{\partial c}{\partial \theta} \right) + \frac{\partial}{\partial z} \left(rD \frac{\partial c}{\partial z} \right) \right\} \quad (\text{Eq. 1})$$

where c is the concentration of the diffusing compound with diffusion coefficient D , t represents the time, and r , θ , and z are the three spatial directions.

In the case of monolithic solution systems, in which either the drug is molecularly dispersed in the matrix carrier or the drug is completely dissolved upon medium imbibition into the system, Fick's second law was solved analytically by Vergnaud (Vergnaud, 1993).

$$\frac{M_t}{M_\infty} = 1 - \frac{32}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{q_n^2} \cdot \exp \left(-\frac{q_n^2}{R^2} \cdot D_{app} t \right) \cdot \sum_{p=0}^{\infty} \frac{1}{(2p+1)^2} \cdot \exp \left(-\frac{(2p+1)^2 \cdot \pi^2}{H^2} \cdot D_{app} t \right) \quad (\text{Eq. 2})$$

where M_t/M_∞ is the cumulative drug release, n and p are real numbers, q_n are the roots of the Bessel function of the first kind of zero order ($J_0(q_n) = 0$), D is the apparent diffusion coefficient of the drug in the matrix, t is the time, and R and H represent the radius and the

height of the tablet, respectively. The analytical solution of Fick's second law (Eq. 2) was successfully applied to describe the drug release for HPMC matrix tablets, treating the matrix as monolithic solution and considering constant matrix dimensions, perfect sink conditions and constant drug diffusion in axial and radial direction (Siepmann et al., 2013). The same model allowed to accurately describe and predict drug release from swellable, non-eroding (Kollidon® SR) polymeric matrix tablets for different model drugs (Grund et al., 2013). The established model, however, is usually only applied to conditions governing diffusional mass transport under constant matrix dimensions, i.e. not in the range of elevated drug loadings, where matrix erosion occurs (i.e. only diffusional phase, not eroding phase). The aim of this study was to test whether drug release of HPMC tablets formulated with drug loadings provoking matrix erosion could be adequately described based on the established analytical solution of Fick's law by ascribing the corresponding release accelerating effect to an increase of the apparent diffusivity.

3.2.2 Results and discussion

Applying solution of Fick's second law for modelling drug release from HPMC matrix tablets, all formulation parameters, except for the matrix dimensions, merge into the apparent diffusion coefficient of the drug, D_{app} (Eq. 2). Accordingly, any release accelerating effect corresponded to D_{app} , i.e. initial porosity, drug loading, total porosity (sum of initial porosity and porosity resulting from dissolving of drug molecules) and drug solubility.

3.2.2.1 Dynamic changes of HPMC tablet dimensions during drug release

There are some prerequisites for applying solution of Fick's second law for HPMC matrices, i.e. uniform dispersion of drug molecules in the matrix, maintained sink condition and constant diffusivity within the release period. The latter can be met only if the matrix is not significantly swelling and eroding, therefore matrix dimensions remain constant during drug release period.

Based on our preliminary studies on dynamic changes in HPMC matrix tablets' dimensions upon exposure to phosphate buffer pH 6.8, HPMC matrix swelled very rapidly at the beginning. Afterwards, due to the start of tablet erosion which slowed down further swelling of the tablet, tablet dimension reaches an equilibrium state which provide stationary boundary conditions (Fig. 17). That means, although the tablet core reduces during release, but the whole tablet dimensions (tablet and gel layer surrounding the tablet) remains quite constant until all of drug has been released from the matrix. Therefore, the analytical solution of this partial differential equation (Fick's second law) can be applied for HPMC matrix systems. This is consistent with previous findings that water uptake of HPMC/lactose matrix tablets reached plateau values after rapid initial water uptake of tablets (Siepmann et al., 2013).

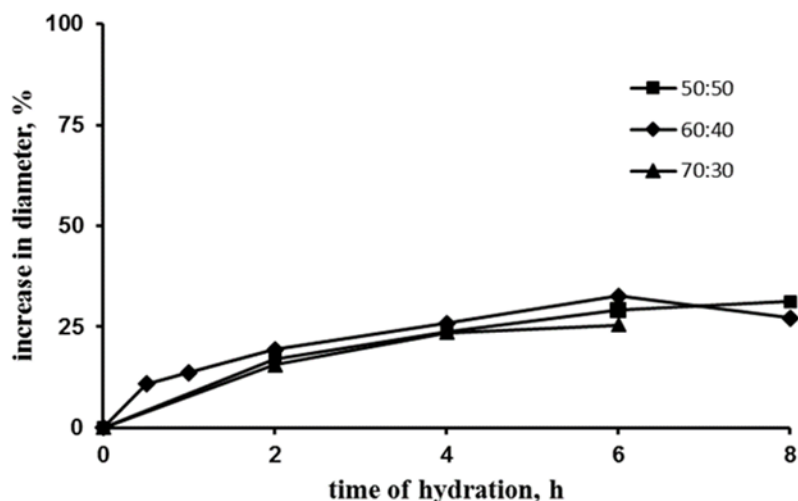


Fig. 17. Changing HPMC matrix tablet dimensions during drug release (legends represent ratio of diprophylline / HPMC K15M).

3.2.2.2 Effect of initial porosity on D_{app}

Different porosities (pore volume in relation to total volume) were achieved by increasing the compression force for each composition, resulting an increase of apparent diffusion coefficient and consequently an increase of drug release (Fig. 18).

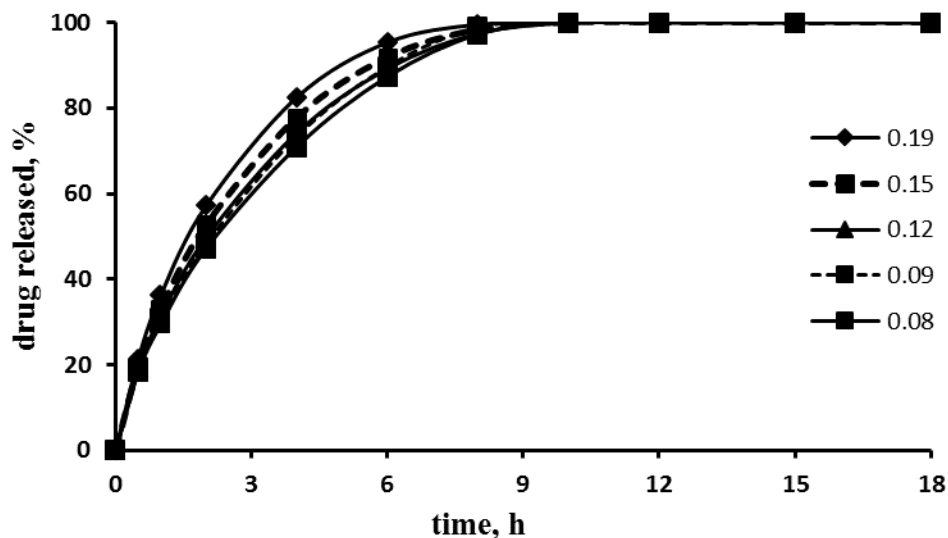


Fig. 18. Effect of initial porosity (v/v) on drug release from diprophylline / HPMC K15M tablets, weight ratio 70:30.

3.2.2.3 Effect of drug loading on D_{app}

Drug release increased with increasing drug loading due to enhancement of porosity, i.e. after dissolving drug particles, pore volume for diffusing molecules increases. This enhancement was more significant from 80% up to 95% w/w, which is attributed to higher apparent diffusion coefficient of higher drug loading (Fig. 19).

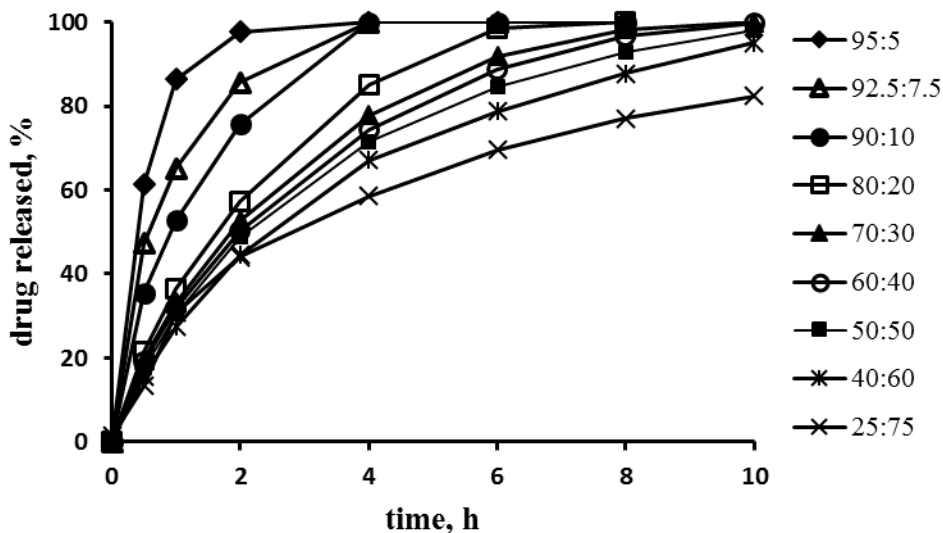


Fig. 19. Effect of drug / polymer weight ratio on diprophylline release from HPMC K15M matrix tablets (14% v/v initial porosity for all formulations).

3.2.2.4 Effect of total porosity on D_{app}

Drug release profiles of HPMC matrix tablets containing model drugs and with various initial porosities (5–20% v/v) were fitted to Equation 2 to obtain the apparent diffusion coefficients (D_{app}) for each composition (Fig. 20). For the highly soluble drug, diprophylline, the correlation of the apparent diffusivity values with the total porosity of the matrix (sum of initial porosity and drug loading) showed a slight increase until about 75% porosity, after which it started to increase markedly due to tablet erosion (Fig. 20). This is in accordance with previous result, meaning that drug release increased significantly with increasing drug loading from 80% up to 95%, which is attributed to higher apparent diffusion coefficient at higher drug loading (Fig. 19).

The change of the apparent diffusion coefficient (D_{app}) in the diffusion phase was best described by a cumulative normal distribution over the range of total porosities (until 75%, Fig. 20), considering ε_{mean1} and σ_1 denoting the mean and standard deviation, and D_{aq1} and D_{p1} the diffusion coefficient of the drug in aqueous pores (polymeric matrix at 75% total porosity) and in the pore-free polymer (10^{-7} cm²/s) respectively (Eq. 3). The apparent diffusivities agreed well with the apparent diffusivities reported previously for the drug loading range up to 60% drug loading (Siepmann et al., 2013).

$$D_{app} = D_{p1} + D_{aq1} \int_0^x \left[\frac{1}{\sigma_1 \sqrt{2\pi}} \cdot \exp\left(-\frac{(\varepsilon - \varepsilon_{mean1})^2}{2\sigma_1^2}\right) \right] d(\varepsilon) \quad (\text{Eq. 3})$$

Importantly, compared to insoluble matrices, which disintegrated at drug loadings exceeding the percolation threshold of the polymer (Grund et al., 2013), HPMC tablets demonstrated a control over D_{app} as the function of tablet porosity / drug loading, applying equation 2 over the entire range of drug loadings. The acceleration of the release at loadings exceeding the polymer percolation threshold (~75%) was approximated by another sigmoidal correlation of D_{app} and the total porosity (Fig. 20). This cumulative normal

distribution can be demonstrated by ε_{mean2} and σ_2 denoting the mean and standard deviation, and D_{p2} and D_{aq2} the diffusion coefficient of the drug in the polymeric matrix at 75% total porosity (3.10^{-7} cm²/s) and in the water, respectively (Eq. 4). D_{app} naturally approximates the diffusivity in water at drug loadings approaching 100%.

$$D_{app} = \begin{cases} D_{p1} + D_{aq1} \int_0^x \left[\frac{1}{\sigma_1 \sqrt{2\pi}} \cdot \exp \left(-\frac{(\varepsilon - \varepsilon_{mean1})^2}{2\sigma_1^2} \right) \right] d(\varepsilon) & x < p \\ D_{p2} + D_{aq2} \int_0^x \left[\frac{1}{\sigma_2 \sqrt{2\pi}} \cdot \exp \left(-\frac{(\varepsilon - \varepsilon_{mean2})^2}{2\sigma_2^2} \right) \right] d(\varepsilon) & x \geq p \end{cases} \quad (\text{Eq. 4})$$

Assuming the first cumulative normal distribution has almost reached its uppermost limit ($x \rightarrow +\infty$) at point p (0.75 porosity), the following function will result:

$$D_{p2} = D_{p1} + D_{aq1} \int_0^{+\infty} \left[\frac{1}{\sigma_1 \sqrt{2\pi}} \cdot \exp \left(-\frac{(\varepsilon - \varepsilon_{mean1})^2}{2\sigma_1^2} \right) \right] d(\varepsilon) = D_{p1} + D_{aq1} \quad (\text{Eq. 5})$$

The first cumulative normal distribution (diffusion part), with mean of 0.45 and standard deviation of 0.1, was continuously joined up with second normal distribution (erosion part), with mean and standard deviation of 0.96 and 0.04, respectively, when release mechanism changed. Similarly, mass loss study revealed that in formulations having a total porosity of more than 0.75, the erosion rate was much more pronounced than with formulations having a total porosity less than 0.75, indicating that erosion mechanism contributing much more in drug release mechanism when the total porosity goes beyond 0.75 (Fig. 21 and Tab. 9).

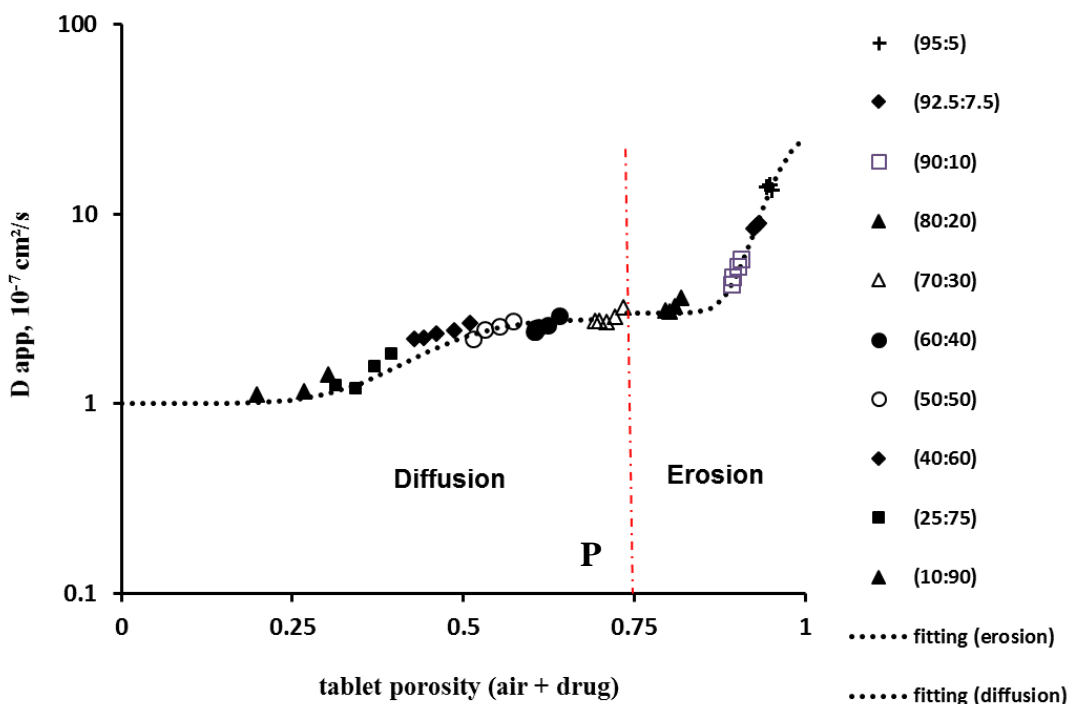


Fig. 20. Apparent diffusion coefficient vs. tablet total porosity for HPMC matrix systems, legends represent diprophylline / HPMC K15M weight rate, tablets disintegrated at > (95:5).

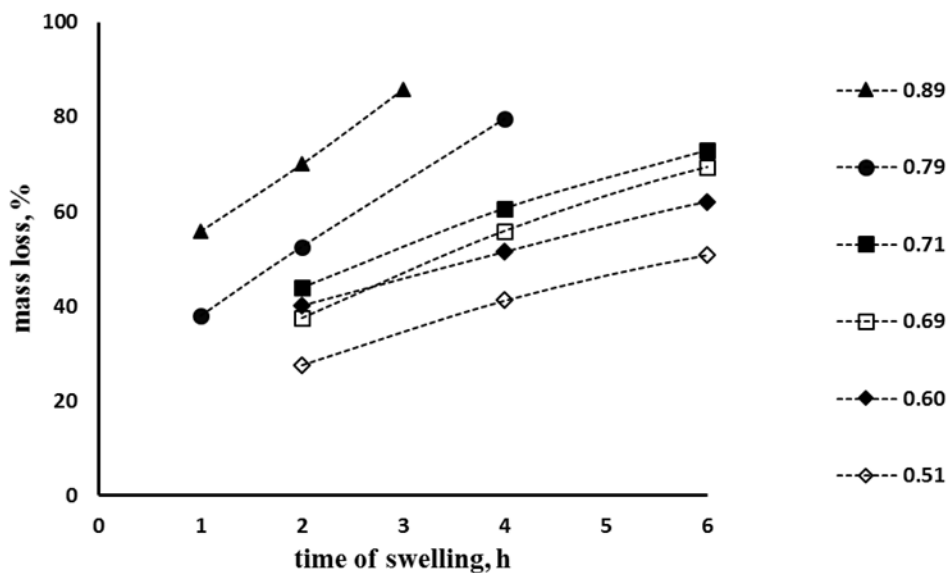


Fig. 21. Effect of total porosity (indicated in the legends) of HPMC K15M matrix tablets on mass loss within different hydration times in phosphate buffer pH 6.8, using paddle method 50 rpm.

Table 9. Erosion rate (calculated from slope of HPMC matrix tablets with different total porosities).

Total Porosity	Erosion rate
0.89	15.0
0.79	13.8
0.71	7.2
0.69	6.6
0.60	4.8
0.51	4.8

3.2.2.5 Effect of drug solubility on D_{app}

Drugs with lower solubility than diprophylline (i.e.theophylline and ibuprofen) resulted in lower D_{app} values (Fig. 22) as seen for insoluble matrices previously (Grund et al., 2013). The correlation of D_{app} and porosity, however, appeared to remain unchanged, making HPMC tablets an ideal candidate for a comprehensive modelling approach.

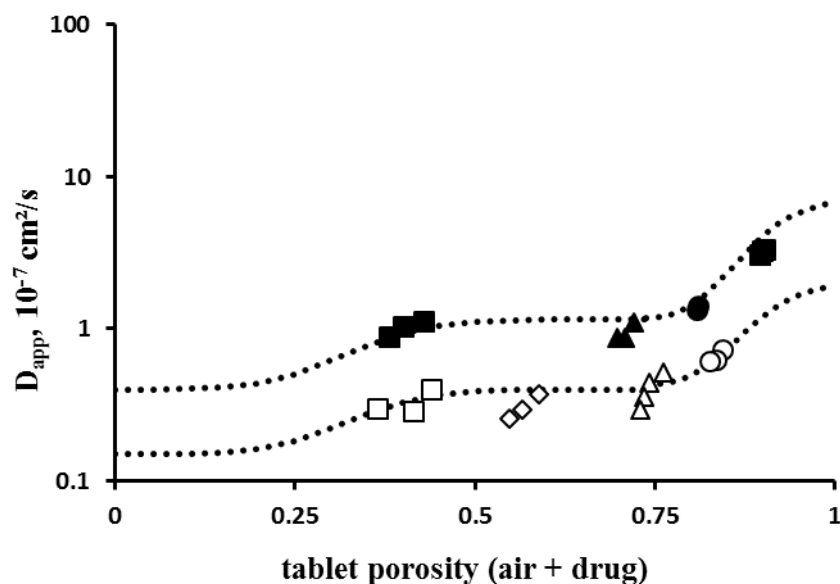


Fig. 22. Apparent diffusion coefficient vs. tablet total porosity (sum of initial porosity and porosity resulting from dissolving drug loading) for HPMC matrix systems, theophylline (filled) and ibuprofen (unfilled).

Furthermore, there is a correlation, in power law, between D_{aq} and drug solubility (Fig. 23). By implementing this relationship into equation 4, it is possible to calculate apparent diffusion coefficients of the HPMC matrix tablets with drugs within range of solubility (Eq. 6).

$$D_{app} = \begin{cases} D_{p1} + 4.08 (Cs)^{0.25} \int_0^x \left[\frac{1}{\sigma_1 \sqrt{2\pi}} \cdot \exp \left(-\frac{(\varepsilon - \varepsilon_{mean1})^2}{2\sigma_1^2} \right) \right] d(\varepsilon) & x < p \\ D_{p2} + 34.6 (Cs)^{0.32} \int_0^x \left[\frac{1}{\sigma_2 \sqrt{2\pi}} \cdot \exp \left(-\frac{(\varepsilon - \varepsilon_{mean2})^2}{2\sigma_2^2} \right) \right] d(\varepsilon) & x \geq p \end{cases} \quad (\text{Eq. 6})$$

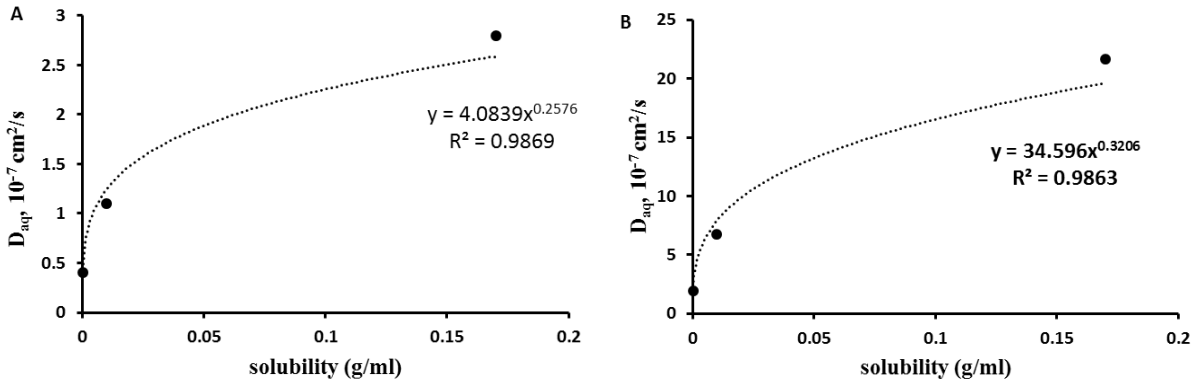


Fig. 23. Plotting A) D_{aq1} vs. solubility of the drug, B) D_{aq2} vs. solubility of the drug

3.2.3 Conclusions

The results indicate that the drug release behavior of HPMC matrix tablets can be mathematically described based on the established analytical solution of Fick's second law even though the tablets contain high drug loadings and start to erode during the dissolution testing.

3.3 Development of food-independent ethyl cellulose coated dosage forms

3.3.1 Introduction

Food intake can significantly influence the gastrointestinal (GI) absorption and therefore bioavailability of orally administered drugs. Fed state may lead to increase, decrease, accelerate, or delay in drug absorption (Fleisher. D et al., 1999; Varum et al., 2013). Food mediated effects are dependent on the physiological environment in the fed state, the physicochemical properties of the drug and drug dosing; however, the formulation is of primary importance.

Generally, extended release multiparticulates are less affected compared to extended release tablets in the fed state. This is related to a lower susceptibility of multiparticulates to changing mechanical stress and gastric emptying in the fed state (Varum et al., 2013). However, other factors, regarding pH change, osmolality, presence of fat, carbohydrates and bile salt (surfactant) may alter drug release from multiparticulates in the fed state.

Previously, it was shown that ethyl cellulose coated pellets containing theophylline or diltiazem showed significant increases in rate and extent of absorption *in vivo* in the presence of food (Hendeles et al., 1985; Hendriks et al., 1998; Jonkman, 1989). Moreover, it is well known that ethyl cellulose coating is not affected by pH change, osmolality and mechanical stress in the fed state; however, enhancement of bile salts (surfactants) in the fed state can increase drug release from aqueous dispersion of ethyl cellulose coated pellets (Raiwa, 2011; Wearley. L et al., 1988). Surfactants can reduce the surface tension of intestinal media in the fed state to 33 mN/m (Pedersen et al., 2000), resulting in improved wettability and water accessibility of ethyl cellulose coating. In addition, surfactants can improve the bioavailability of poorly soluble drugs (e.g. carbamazepine) by micellar solubilization and increased wettability by enhancing the rate of dissolution and/or solubility.

For developing food-independent coated multiparticulate dosage forms, all formulation parameters (i.e. type of drug, core, binder, plasticizer, coating) have to be taken into consideration. Generally, low soluble API are more affected in the fed state due to increasing solubility by micellar solubilization or wettability. Therefore, solubilization technologies (e.g. particle size reduction, amorphous formulations, complexation with cyclodextrins, lipid based formulations) can be employed to reduce food effect. Likewise, some binders (e.g. HPMC) can efficiently improve the wettability and solubility of low soluble API, resulting in more robust systems in the fed state. Lipophilic plasticizers (e.g. DBS) are solubilized and extracted from plasticized films when exposed to lipid content in the fed state. Therefore, hydrophilic plasticizers are preferable.

The aim of this study was firstly, to investigate the effect of surfactant in fed state on Aquacoat[®] coated pellets. The impact of surfactant was resembled *in vitro* in buffer media pH 6.8 containing 0.25% w/v SDS. Secondly, to offset the effect of surfactant in fed state with two approaches: 1. by adding surfactant inside formulation (i.e. inside drug layer and coating) in order to neutralize the effect of surfactant in fed state media. It is assumed that, in this way drug release rate in fasted state (pH 6.8) increases, so drug release profiles in both media (with and without SDS) will be similar 2. by overcoating the ethyl cellulose membrane with cationic polymers like Eudragit[®] RL or Eudragit[®] RS in order to interact with anionic surfactant inside media (i.e. SDS) (Fig. 24).

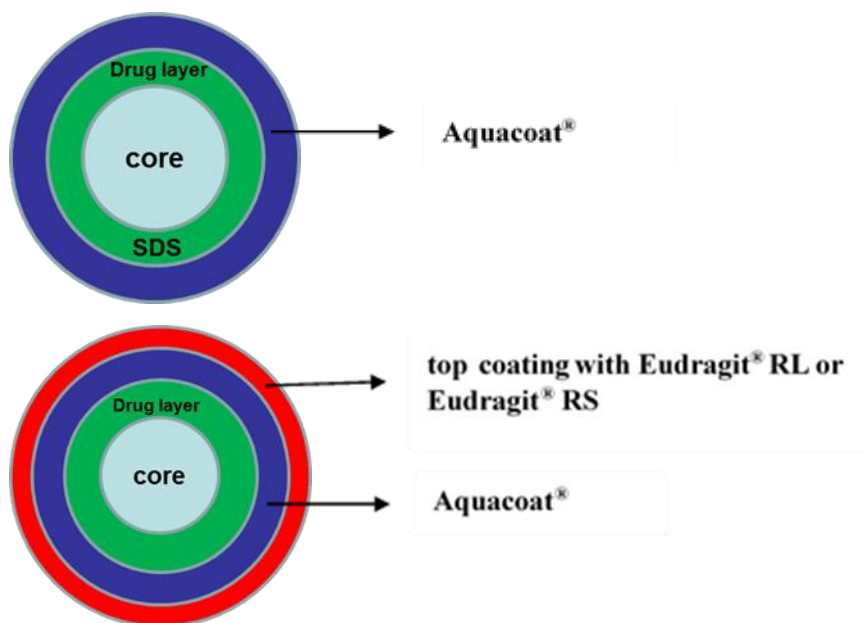


Fig. 24. Schematic representation of two approaches to circumvent the effect of media containing SDS, incorporating SDS inside drug layer and top coating with cationic polymer (Eudragit® RL and Eudragit® RS).

3.3.2 Results and discussion

3.3.2.1 Influence of surfactant on ethyl cellulose coated pellets

The influence of SDS on ethyl cellulose (aqueous dispersion and organic solution) coated pellets, as a factor which may induce increased release rate in fed state *in vivo* were investigated. 0.25% w/v SDS in pH 6.8 was used as a standard concentration, as it can reduce the surface tension of dissolution media to *in vivo* condition in intestine in fed state (33 mN/m) (Raiwa, 2011). Additionally, this amount of SDS increases the solubility of carbamazepine and ensures that sink condition was maintained. Theophylline and carbamazepine were used as slightly soluble and poorly soluble model drugs.

Obviously, drug release from pellets coated with 10% coating level Aquacoat® was faster than 20% coating level, as higher coating level reduces the drug release rate due to longer diffusion pathways (Fig. 25). Moreover, drug release from pellets coated with pure plasticized Aquacoat® ECD (10% or 20% coating level) is faster in pH 6.8 containing 0.25% SDS than in pH 6.8 without SDS and in pH 1 due to improved wettability of coating

(Fig. 22). Besides that, rapid initial drug release was observed from uncured pellets in pH 6.8 (pH-dependent release). Aquacoat[®] contains SDS as stabilizing agent (4% based on total content) which has a complete dissociation in pH 6.8 (pKa 1.9) resulting in better wetting of the uncured pellets (Bodmeier and Paeratakul, 1991; Wesseling and Bodmeier, 1999). Curing step is necessary for complete and homogeneous film formation of Aquacoat[®] pellets in order to obtain pH independent drug release (Wesseling and Bodmeier, 1999).

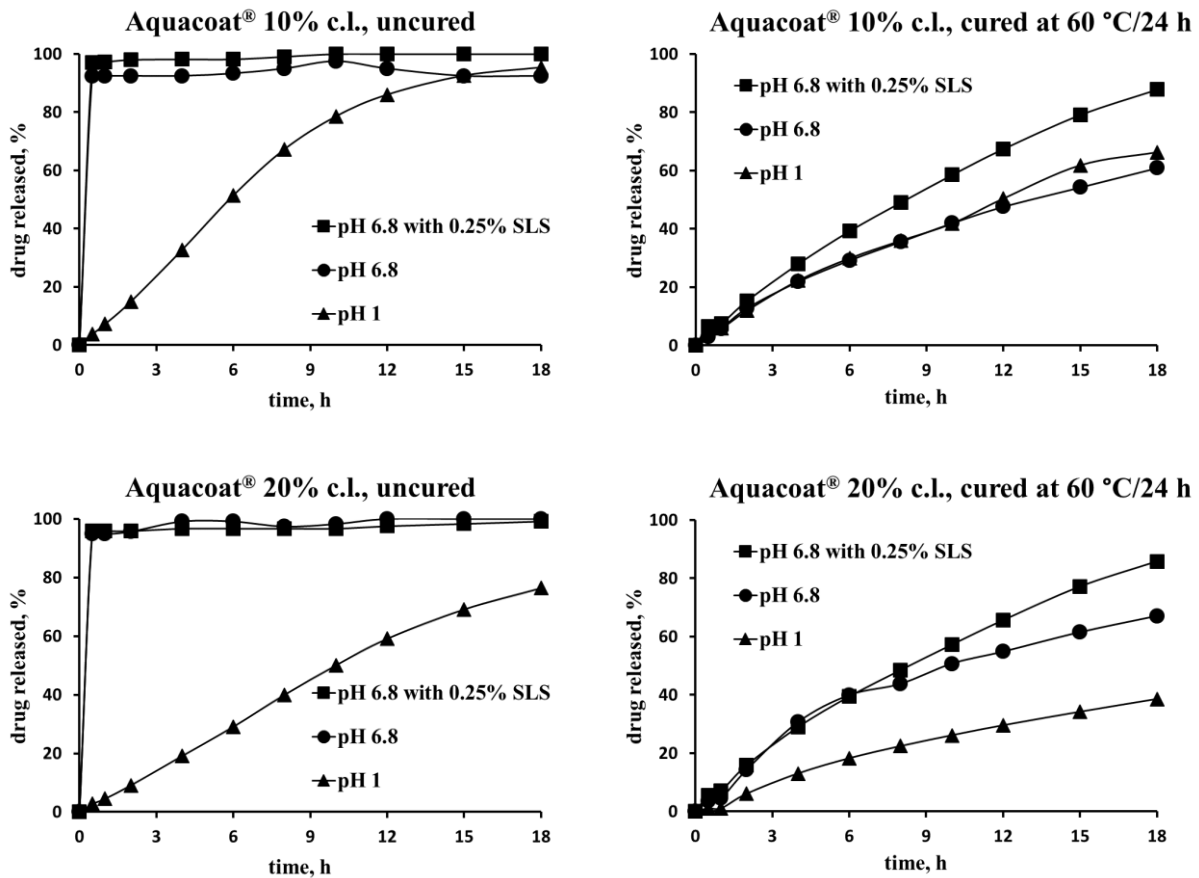


Fig. 25. Effect of curing on theophylline release from Aquacoat[®] coated pellets (10% and 20% coating level) in different media.

Pellets coated with ethyl cellulose organic solution, in contrast to Aquacoat[®] coated pellets, were not affected by the SDS medium (Fig. 26). So, the further investigations regarding effect of surfactant, was conducted on Aquacoat[®] cured pellets.

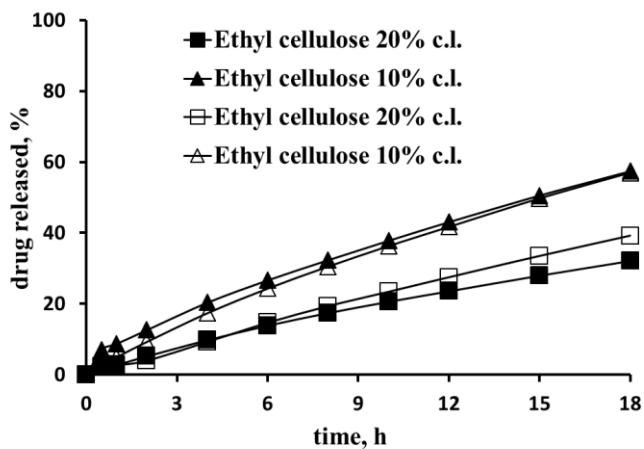


Fig. 26. Effect of medium pH 6.8 containing SDS on theophylline release from ethyl cellulose (organic solution) coated pellets. Open symbols: phosphate buffer pH 6.8, closed symbols: phosphate buffer pH 6.8 with 0.25% w/v SDS.

3.3.2.2 Incorporating surfactant inside theophylline (or carbamazepine) pellets coated with Aquacoat[®]

SDS can increase drug release rate by increasing wettability of the Aquacoat[®] film, so the water penetration through coating layer is faster, therefore, drug release rate increases. In order to achieve food-independent coated dosage form, the first approach was to increase the release rate in media pH 6.8 (by adding surfactant inside the drug layer), so the drug release profile in media pH 6.8 would be identical to that in media pH 6.8 containing SDS (Fig. 24). For this aim, theophylline (or carbamazepine) with SDS were layered onto the core and subsequently coated with 10% and 20% Aquacoat[®].

Addition of surfactant inside drug layer resulted in increased release rate of theophylline from pellets coated with 10% and 20% Aquacoat[®] in pH 6.8; however, drug release increased also in pH 6.8 containing SDS (in a lower extent) (Figs. 27 and 28). This

enhancement of drug release was due to the increased wettability of Aquacoat[®] coating, since the solubility of theophylline was not affected significantly in SDS medium (Tab. 10). For theophylline pellets coated with 10% Aquacoat[®], by adding more than 10% w/w SDS (based on the drug content) SDS inside the drug layer, comparable drug release profiles (based on similarity factor) in pH 6.8 and pH 6.8 with SDS were achieved (Fig. 27). Lower amount of SDS inside drug layer (1.5-5% w/w) was not sufficient to neutralize the effect of SDS inside media (Fig. 27). With 20% Aquacoat[®] coating level, addition of 1.5-10% SDS inside drug layer was not sufficient to increase release profile in pH 6.8 and to achieve similar release profiles in media with and without surfactant (Fig. 28). Overall, by changing wettability and permeability of the Aquacoat[®] film (by adding SDS inside drug layer) and varying coating level, desired release profile (Siepmann et al., 2007), was achievable to obtain surfactant- independent dosage forms.

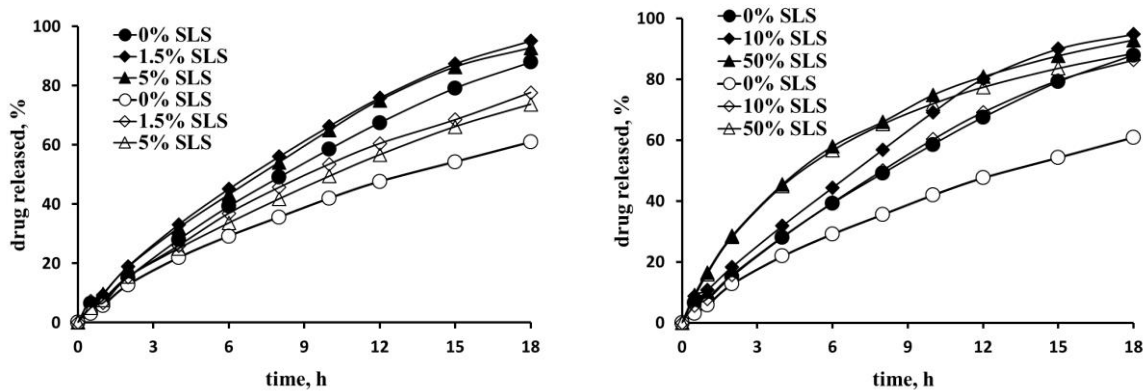


Fig. 27. Theophylline release from pellets coated with 10% Aquacoat[®] ECD and 0, 1.5, 5, 10, 25 or 50% SDS incorporated in the drug layer. Open symbols: phosphate buffer pH 6.8, closed symbols: phosphate buffer pH 6.8 with 0.25% w/v SDS.

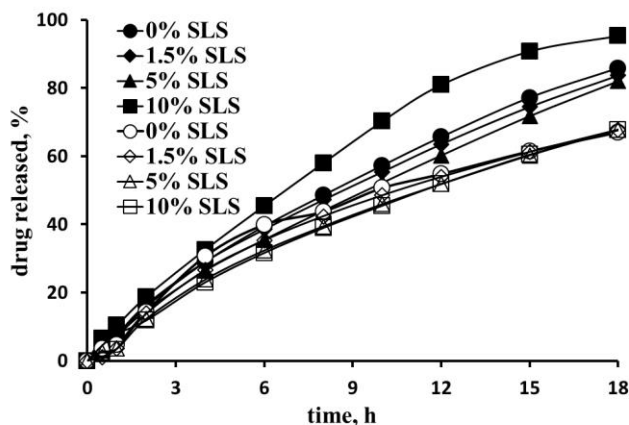


Fig. 28. Theophylline release from pellets coated with 20% Aquacoat[®] ECD and 0, 1.5, 5 or 10% SDS incorporated in the drug layer. Open symbols: phosphate buffer pH 6.8, closed symbols: phosphate buffer pH 6.8 with 0.25% w/v SDS.

Table 10. Solubility of theophylline and carbamazepine in water and in media containing 0.25% w/v at 25°C.

	Solubility in water at 25°C (mg/ml)	Solubility in 0.25% w/v SDS at 25°C (mg/ml)
Theophylline	5.8-8	8.1
Carbamazepine	0.2	0.5

With regard to low soluble drug, carbamazepine, incorporating SDS in the drug layer resulted in rapid release in the first few minutes (Fig. 29). This can be explained by high Log P of carbamazepine (Log P = 1.51), which resulted in significant enhancement of solubility (Tab. 10). Therefore, adding SDS in the drug layer was not an appropriate approach to achieve food-independent release profile for low soluble drug.

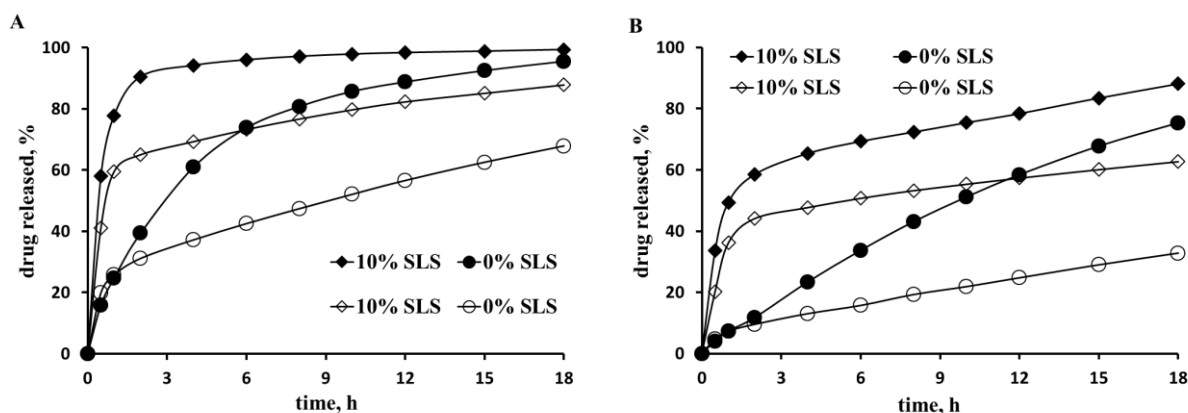


Fig. 29. Carbamazepine release from pellets coated with A)10% and B)20% Aquacoat[®] ECD coating level and 0 or 10% SDS incorporated in the drug layer. Open symbols: phosphate buffer pH 6.8, closed symbols: phosphate buffer pH 6.8 with 0.25% w/v SDS.

Moreover, effect of adding surfactant in the coating was investigated (instead of incorporating inside the drug layer). SDS may interfere with the coalescence during the coating process and resulting in very fast drug release in media pH 6.8 with or without surfactant (Fig. 30).

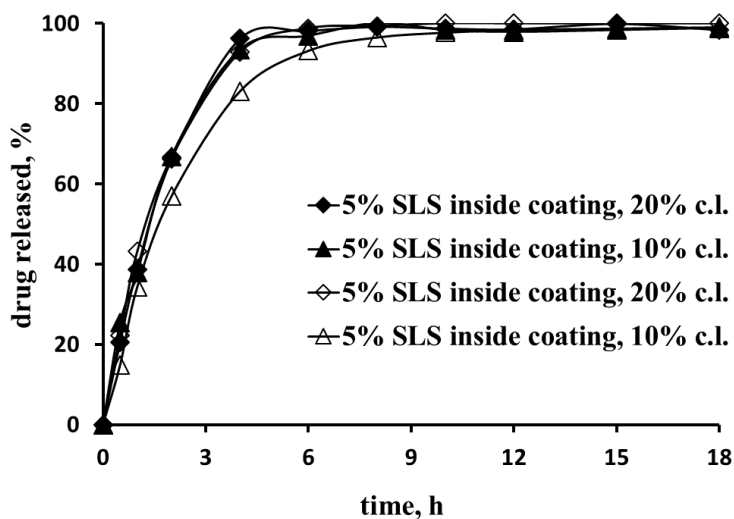


Fig. 30. Effect of adding surfactant (SDS) inside coating. Open symbols: phosphate buffer pH 6.8, closed symbols: phosphate buffer pH 6.8 with 0.25% w/v SDS.

3.3.2.3 Carbamazepine pellets coated with Aquacoat[®] and subsequently top coated with Eudragit[®] RL or Eudragit[®] RS

In the second approach (Fig. 24), the drug-loaded pellets were first coated with Aquacoat[®] followed by top coating with cationic polymers Eudragit[®] RL or Eudragit[®] RS in order to circumvent the effect of anionic surfactant SDS inside media. Carbamazepine-loaded pellets (30% drug content) were first coated with different levels of Aquacoat:PVP (coating levels were 5%, 7.5%, 10% and 12.5% w/w). By simply varying the amount of pore former (PVP), different release profiles in pH 6.8 and pH 6.8 with SDS were achieved (Fig. 31). The formulations which showed significant different release profiles in media with and without surfactant, i.e. Aquacoat[®] /PVP 90:10 with 7.5% or 10% coating level (Fig. 31), were selected for further investigations in order to neutralize the effect of SDS in pH 6.8. For this aim, these Aquacoat[®] coated pellets were top coated with Eudragit[®] RL or Eudragit[®] RS. Eudragit[®] RL and RS (ammonio methacrylate copolymer type A and B) are methacrylate copolymers with cationic quaternary trimethylammonio groups. It is hypothesized that they can offset the effect of anionic surfactant in dissolution media, therefore the drug release from Aquacoat[®] coated pellets are not affected by presence of surfactant.

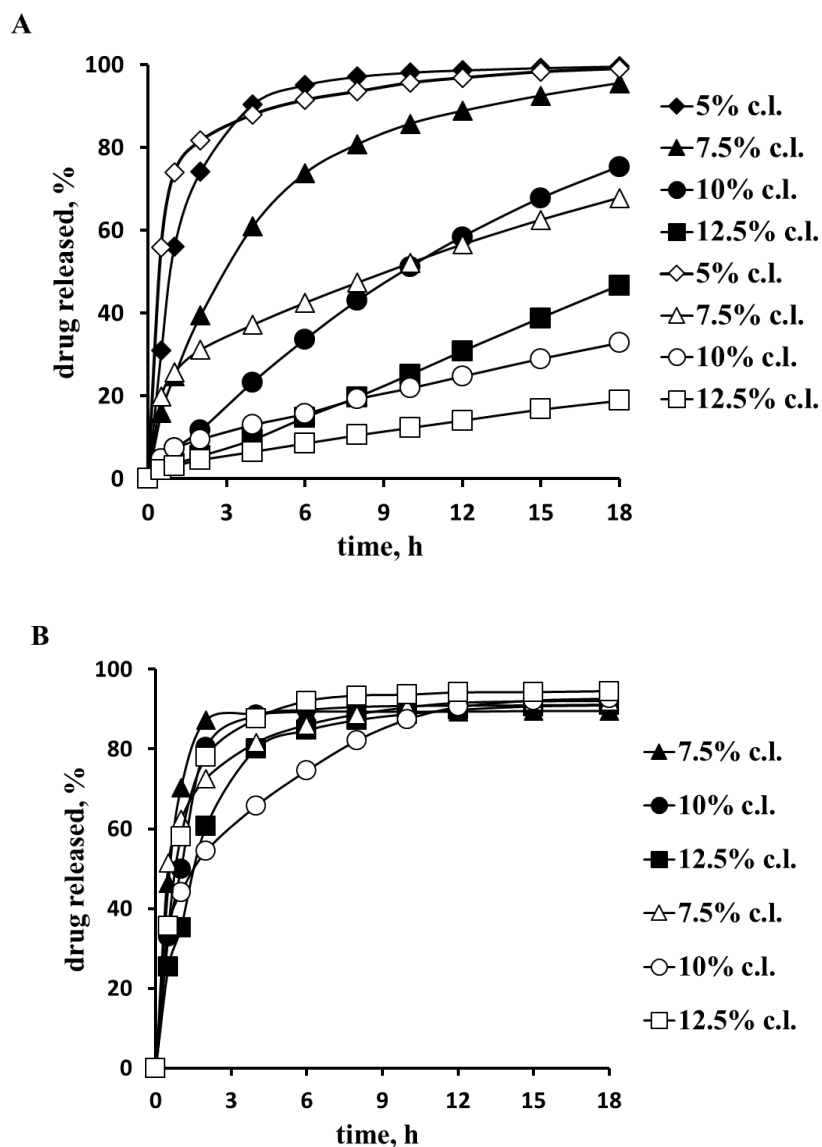


Fig. 31. Effect of varying ratio of Aquacoat:PVP A) 90:10 and B) 85:15 with different coating level (c.l.). Open symbols: phosphate buffer pH 6.8, closed symbols: phosphate buffer pH 6.8 with 0.25% w/v SDS.

Top coating with Eudragit® RS gave S-shaped release profiles in the media containing SDS (Fig. 32). This can be explained by interaction of dissociated SDS with quaternary ammonium groups of the polymer, which leads to dramatic hydration of polymer and producing this unique S-shaped release pattern (Narisawa et al., 1996).

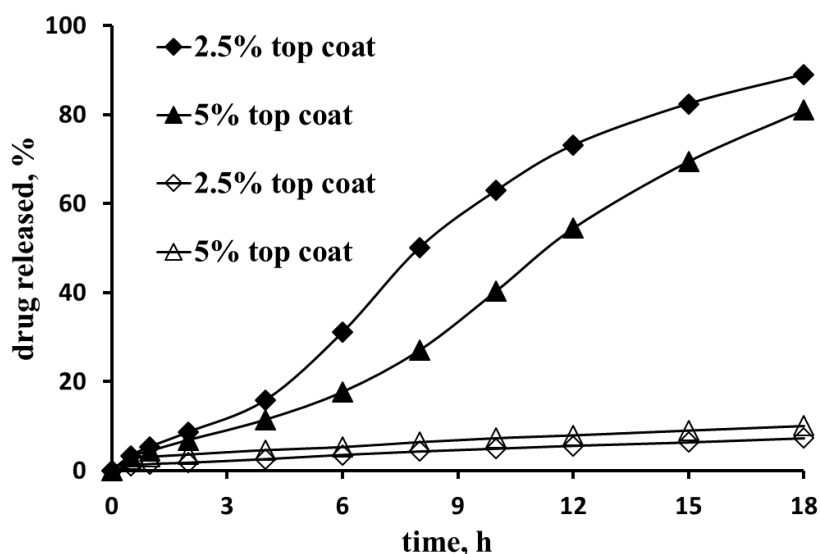


Fig. 32. Effect of applying Eudragit RS as top coating Open symbols: phosphate buffer pH 6.8, closed symbols: phosphate buffer pH 6.8 with 0.25% w/v SDS.

As expected, with applying Eudragit[®] RL on Aquacoat:PVP, drug release decreased significantly in pH 6.8 containing SDS (Fig. 33). More coating level of Eudragit[®] RL resulted in more decrease in drug release rate, due to counteracting with SDS inside the media.

In the same manner, in pH 6.8 without SDS, top coating with Eudragit[®] RL resulted in decreased release profile. However, interestingly, no change in drug release profile was observed when the different level of top coating Eudragit[®] RL (2.5% to 10%) was employed on Aquacoat[®] coated pellets (7.5% or 10% coating level) (Fig. 33). This phenomenon can be postulated by drug-polymer interactions (partitioning of drug into the polymer) which results in a low extent of release. It is possible that carbamazepine (Log P= 1.51) associates with the hydrophobic portions of the polymers and is retained in the membrane during drug release in buffer (Heinicke and Schwartz, 2007). In future approach, SDS can be added to Eudragit[®] RL solution (not dispersion) coating. It is hypothesized that hydrophobic portion

of SDS can be associated with polymer and therefore displace carbamazepine to the aqueous solution.

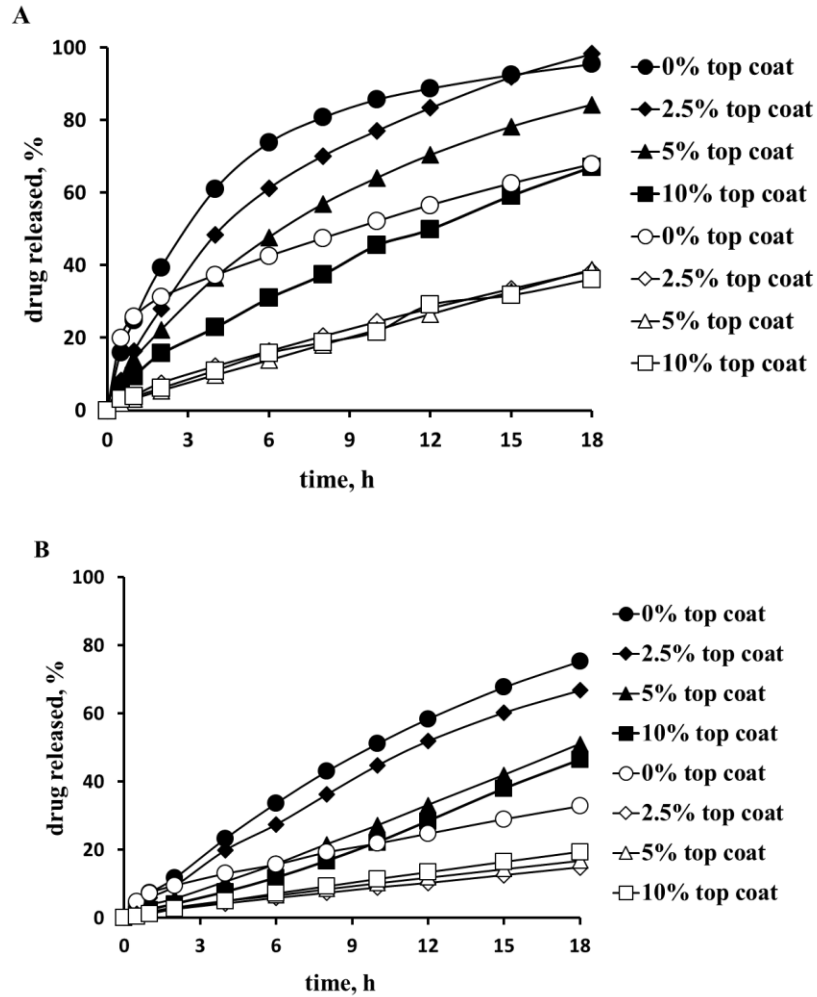


Fig. 33. Effect of adding Eudragit® RL as top coating on Aquacoat:PVP 90:10 A) 7.5% Aquacoat® coating level B) 10% Aquacoat® coating level. Open symbols: phosphate buffer pH 6.8, closed symbols: phosphate buffer pH 6.8 with 0.25% w/v SDS.

3.3.3 Conclusion

Drug release from Aquacoat[®] coated pellets was faster in media pH 6.8 containing 0.25% w/w SDS which was mainly due to better wetting of the coated beads. Effect of surfactant on Aquacoat[®] coated pellets can be reduced by formulation optimization. Desired drug release rate can be obtained by the varying the surfactant content inside the coating layer as well as coating level. For sparingly soluble drug (theophylline) coated pellets with 10% Aquacoat[®], addition of more than 10% w/w SDS (based on drug layer) increased the drug release rate in pH 6.8 sufficiently; therefore, comparable release profiles in pH 6.8 with and without surfactant were achieved. For low soluble drug (carbamazepine), including SDS inside the drug layer resulted in initial burst release in media pH 6.8 with or without surfactant. For low soluble drug, top coating with cationic polymer Eudragit[®] RL was a better approach to offset the effect of surfactant on Aquacoat[®] coated pellets.

4 SUMMARY

***In vitro-in vivo* correlation of hydrophilic matrix tablets with different gel strengths**

The purpose of this study was to correlate the rheological property (i.e. gel strength) of hydrophilic matrix tablets to their *in vitro* robustness against hydrodynamic (agitation intensity) and applied mechanical forces, and consequently to the IVIVC. Six commercial products, i.e. Glucophage[®], Alfuzosin[®], Tromphyllin[®], Preductal[®], Quetiapin[®] formulated as HPMC (i.e. hydroxypropyl methylcellulose) and Tramabeta[®] formulated as HPC were investigated. The gel strength profiles of swollen matrix tablets were characterized, in pH 6.8 using paddle 50 rpm agitation speed, by texture analyzer at varying swelling times. *In vitro* release robustness was investigated under conventional paddle dissolution apparatus under a range of agitation intensities (50-150 rpm). Moreover, to mimic pyloric antrum mechanical forces *in vivo*, modified dissolution method using paddle at 100 rpm aligned with applying mechanical force on tablets at 1, 2 and 4 h hydration times by texture analyzer was performed and results compared with compendial method using paddle at 100 rpm (without stress). Our findings demonstrated that formulations having higher molecular weight HPMC and with content $\geq 20\%$ w/w (i.e. Glucophage[®], Alfuzosin[®], Tromphyllin[®] and Preductal[®]) resulted in robust *in vitro* performance (against both agitation intensities and destruction forces). This could be attributed to their sufficient gel strength at gel-solution interface (erosion front) within majority of release interval. Moreover, good IVIVC (Level A) were obtained for these products in the wide range of agitation speeds (50 - 150 rpm) with linear correlation coefficient ($r^2 > 0.9$). In contrast, Quetiapin[®], in which gel strength dropped below 2 g/mm^2 after 6 h hydration time in pH 6.8 using paddle 50 rpm, was more susceptible against *in vitro* hydrodynamics and mechanical forces. Specifically, *in vitro* release increased significantly when loading forces were applied at 2 and 4 h hydration times. For Quetiapin[®], Level A IVIVC was established only with using higher *in vitro* agitation speed (i.e. paddle at 150 rpm), also when using modified *in vitro* dissolution test (i.e. paddle at 100 rpm aligned with applying mechanical loading at 2 h hydration time).

Overall, the latter two methods were recommended as predictive *in vitro* conditions for hydrophilic matrix tablets.

Mathematical modeling for predictability of drug release from HPMC matrix tablets

Drug release profiles of HPMC matrix tablets containing model drugs (diprophylline, theophylline and ibuprofen, $C_s = 0.3\text{-}170$ mg/ml) with various initial porosities (5–20% v/v) were fitted to the established analytical solution of Fick's second law to obtain the apparent diffusion coefficients for each composition. The correlation of the apparent diffusivity values with the total porosity of the matrix (sum of air porosity and drug loading, i.e. the porosity resulting from the dissolution of drug particles) showed a slight increase until about 75%, after which it started to increase markedly due to the tablet erosion. Similarly, drug release increased significantly with increasing drug loading from 80% up to 95%, which is attributed to higher apparent diffusion coefficient of higher drug loading. The change of the apparent diffusion coefficient was best described by a cumulative normal distribution over the range of total porosities related to the shift of the release mechanism from diffusion to erosion, with ϵ_{mean} and σ denoting the mean and standard deviation, and D_{aq} and D_p representing the diffusion coefficient of the drug in water and in the polymeric matrix at 75% total porosity, respectively. Compared to insoluble matrices, which disintegrated at drug loadings exceeding the percolations threshold of the polymer phase, HPMC tablets indicated a well controllable and predictable behavior in the range of such high drug loadings. Overall, drug release behavior of HPMC matrix tablets was mathematically described based on the established analytical solution of Fick's second law even though the tablets contain high drug loadings and start to erode during the dissolution testing.

Development of food independent ethyl cellulose coated dosage forms

Drug release from Aquacoat[®] coated pellets was faster in media pH 6.8 containing 0.25% w/w SDS (resembling fed state) which was mainly due to better wetting of the coated beads. Effect of surfactant on Aquacoat[®] coated pellets containing model drugs (theophylline or carbamazepine) can be reduced by formulation optimization. Two approaches were utilized to neutralize the effect of surfactant inside media. Firstly, by addition of SDS inside formulation (i.e. inside drug layer) in order to neutralize the effect of surfactant in fed state media. It is assumed that, in this way drug release rate in fasted state (pH 6.8) increases, so drug release profiles in both media (with and without SDS) will be similar. And secondly, by overcoating the ethyl cellulose membrane with cationic polymers like Eudragit[®] RL or Eudragit[®] RS in order to interact with anionic surfactant inside media. For sparingly soluble drug (theophylline) coated pellets with 10% Aquacoat[®], addition of more than 10% w/w SDS (based on drug layer) increased the drug release rate in pH 6.8 sufficiently; therefore, comparable release profiles in pH 6.8 with and without surfactant were achieved. For low soluble drug (carbamazepine), including SDS inside the drug layer resulted in initial burst release in media pH 6.8 with or without surfactant. For low soluble drug, top coating with cationic polymer Eudragit[®] RL was a better approach to offset the effect of surfactant on Aquacoat[®] coated pellets.

Zusammenfassung

***In vitro-in vivo* Korrelation von hydrophilen Matrix Tabletten mit unterschiedlicher Gelfestigkeit**

Das Ziel dieser Studie war eine Korrelation der rheologischen Eigenschaft (z.B. Gelfestigkeit) von hydrophilen Matrixtabletten zu ihrer *in vitro* Robustheit gegen hydrodynamische (Rührintensität) und angewendete mechanische Kräfte, um folglich eine IVIVC zu erhalten. Sechs zugelassene Arzneimittel wurden untersucht, Glucophage[®], Alfuzosin[®], Tromphyllin[®], Preductal[®], Quetiapin[®] sind HPMC (hydroxypropyl methylcellulose) und Tramabeta[®] eine HPC (hydroxypropylcellulose) Formulierung. Die Gelfestigkeitsprofile von gequollenen Matrixtabletten, die bei pH 6,8 in einer Paddle-Apperatur mit 50 U/min gerührt wurden, wurden mit Hilfe eines Texture Analysers bei unterschiedlichen Quellzeiten charakterisiert. Die Robustheit der *in vitro*-Freisetzung wurde mit einer conventionellen Paddle-Apperatur mit 50 – 150 U/min untersucht. Um die mechanischen Kräfte der Pylorismuskulatur am Antrum zu simmulieren, wurde eine modifizierte Freisetzung-Methode mit einer Paddleappatur (100 U/min) und einer mechanischen Kraft, die auf die Tabletten nach 1, 2 und 4 Stunden mit Hilfe eines Texture Analysers ausgeübt wurde, mit der Arzneibuchmethode (ohne mechanischen Stress) verglichen. Unsere Ergebnisse zeigen, dass Formulierungen mit höher molekularem HPMC und einem Gehalt von über 20% (w/w) (z.B. Glucophage[®], Alfuzosin[®], Tromphyllin[®], Preductal[®]) zu robusten *in vitro* Formulierungen führen (bezüglich Rührgeschwindigkeit und Verformungskräften). Dies konnte auf die ausreichende Gel-Festigkeit an der Gel-Lösungs-Schnittstelle (Erosionsfront) während dem größten Teil der Freisetzung zurückgeführt werden. Darüber hinaus wurden für diese Produkte eine gute IVIVC (Level A) mit einem linearen Korrelationskoeffizienten ($r^2 > 0.9$) für Rührgeschwindigkeiten von 50-120 U/min erhalten. Im Gegensatz dazu war Quetiapin[®], bei dem die Gelfestigkeit nach 6 Stunden in pH 6,8 in der Paddle Apparatur (50 U/min) unter $2\text{g}/\text{mm}^2$ fiel, anfällig gegenüber hydrodynamischen und mechanischen Kräften. Die *in vitro* Freisetzung erhöhte

sich signifikant, wenn mechanische Kräfte nach 2 und 4 Stunden nach der Hydratisierung auf die Tablette einwirkten. Für Quetiapin[®] wurde eine Level A IVIVC nur bei schnellen *in vitro* Rührgeschwindigkeiten (150 U/min) erreicht oder wenn die modifizierte Freisetzung (100 U/min und mechanischer Stress nach 2 Stunden) angewendet wurde. Insgesamt wurden die beiden letzten Verfahren als prädiktive Verfahren für *in vitro* Bedingungen für hydrophile Matrix Tabletten empfohlen.

Mathematische Modellierung für die Vorhersagbarkeit der Arzneimittelfreisetzung aus HPMC-Matrix-Tabletten

Wirkstofffreisetzungprofile von HPMC-Matrixtabletten mit den Modellarzneistoffen Diprophyllin, Theophyllin und Ibuprofen ($C_s = 0,3-170 \text{ mg / ml}$) mit verschiedenen Anfangsporositäten (5-20% v/v) wurden an der etablierten analytische Funktion des zweiten Fick'schen Gesetzes angewendet, um die scheinbaren Diffusionskoeffizienten für jede Zusammensetzung zu ermitteln. Die Korrelation der scheinbaren Diffusivitätswerte mit der Gesamtporosität der Matrix (Summe der Luftporosität und der Arzneimittelbeladung, d.h. der Porosität, die sich aus der Herauslösung von Arzneimittelteilchen ergab) zeigte eine leichte Erhöhung bis zu einer Porosität von etwa 75%, danach gab es aufgrund der Erosion der Tablette einen deutlichen Anstieg des D_{app} . In ähnlicher Weise erhöhte sich die Wirkstofffreisetzung signifikant mit einer zunehmenden Wirkstoffbeladung von 80% bis zu 95%, was auf einen höheren scheinbaren Diffusionskoeffizienten bei einer höheren Arzneimittelbeladung zurückzuführen ist. Die Veränderung des scheinbaren Diffusionskoeffizienten wurde am besten durch eine kumulative Normalverteilung über den Bereich der Gesamtporosität im Zusammenhang mit der Verschiebung des Freisetzungsmechanismus von der Diffusion zur Erosion beschrieben, wobei ϵ_{Mittel} und σ die Mittelwert- und Standardabweichung und D_{aq} und D_p die Diffusionskoeffizienten des Arzneistoffes in Wasser und in der Polymermatrix bei 75% Gesamtporosität darstellen. Im Vergleich zu unlöslichen Matrizen, die zerfallen, wenn die Wirkstoffbeladung über der Perkolationsschwelle des Polymers liegt, zeigten HPMC-Tabletten ein gut kontrollierbares und vorhersagbares Verhalten im Bereich dieser höheren Arzneistoffbeladungen.

Insgesamt wurde das Arzneistofffreisetzungsverhalten von HPMC-Matrix-Tabletten mathematisch beschrieben, basierend auf der etablierten analytischen Funktion des zweiten Fick'schen Gesetzes, obwohl die Tabletten hohe Arzneistoffbeladungen enthalten und während der Freisetzung zu erodieren beginnen.

Entwicklung von Nahrungsmittel unabhängigen Ethylcellulose-beschichteten Arzneimittelformulierungen

Die Arzneistofffreisetzung von Aquacoat[®]-überzogenen Pellets war im pH 6,8 Medium mit 0.25% w/w SDS (simuliert Nahrungsmittelleffekte) schneller, was vor allem auf eine bessere Benetzung der beschichteten Pellets zurückzuführen war. Die Wirkung von Tensiden auf die mit Aquacoat[®]-beschichteten Pellets, die Modellarzneimittel (Theophyllin oder Carbamazepin) enthalten, kann durch Formulierungsoptimierung reduziert werden. Zwei Ansätze wurden verwendet, um die Wirkung von Tensiden innerhalb des Mediums zu neutralisieren. Erstens durch Zugabe von SDS innerhalb der Formulierung (d.h. innerhalb des Arzneistoffüberzugs), um die Wirkung von Tensid im zugeführten Medium mit simulierten Nahrungsfetten zu minimieren. Es wird davon ausgegangen, dass auf diese Weise die Arzneimittelfreisetzungsraten im nüchternen Zustand (pH 6,8) zunimmt, so dass Arzneimittelfreisetzungprofile in beiden Medien (mit und ohne SDS) ähnlich sind. Und zweitens durch Überziehen des Ethylcelluloseüberzuges mit kationischen Polymeren wie Eudragit[®] RL oder Eudragit[®] RS, um mit den anionischen Tensiden innerhalb des Mediums in Wechselwirkung zu treten. Für mit schwer löslichem Arzneistoff (Theophyllin) beschichtete Pellets mit 10% Aquacoat[®] erhöhte die Zugabe von mehr als 10% w/w SDS (basierend auf der Arzneimittelschicht) die Arzneistofffreisetzungsraten bei pH 6,8 ausreichend; Daher wurden vergleichbare Freisetzungprofile in pH 6,8 mit und ohne Tensiden erreicht. Bei einem gering löslichen Arzneistoff (Carbamazepin), einschließlich SDS innerhalb der Arzneimittelschicht, trat eine anfängliche schnelle Freisetzung im pH 6,8 Medium sowohl mit und ohne Tensiden auf. Für ein gering löslichen Arzneistoff war

ein Überzug mit kationischem Polymer Eudragit® RL ein besserer Ansatz, um die Wirkung von Tensiden auf Aquacoat®-beschichtete Pellets auszugleichen.

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