Gastroretentive Floating Systems –

Formulation Development and *In Vitro* Evaluation

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Abbreviations and Units

a_N	Isotropic hyperfine splitting constant
API	Active pharmaceutical ingredient
AT	4-Amino-2.2.5.5-tetra-methyl-3-imidazoline-1-oxyl
ATEC	Acetyl triethyl citrate
BCS	Biopharmaceutics classification system
BT	Benchtop
°C	Grad Celsius
cm	Centimetre
DMSO-D6	Deuterated dimethyl sulfoxide
DSC	Differential scanning calorimetry
DST	Dissolution stress test
EPR	Electron paramagnetic resonance
ESR	Electron spin resonance
FD	Floating duration
FDDS	Floating drug delivery systems
FLT	Floating lag time
GIT	Gastrointestinal tract
GRDDS	Gastroretentive drug delivery system
GRT	Gastric retention time
h	Hour
HBS	Hydrodynamically balanced systems
HCl	Hydrochloric acid
HPMC	Hydroxypropyl methylcellulose
IBS	Internal buffer system
KSR	Kollidon® SR
MCC	Microcrystalline cellulose
mg	Milligram
min	Minute
mm	Millimetre
MMC	Migrating motor complexes
MPVA	Macrogol poly(vinyl alcohol) grafted copolymer
MRI	Magnetic resonance imaging
MSFI	Multispectral fluorescence imaging
MUMS	Multi unit minitablet systems
N	Newton
NMR	Nuclear magnetic resonance
OSRDF	Oral sustained release dosage forms
Pa	Pascal
PEG	Poly(ethylene glycol)
Ph. Eur.	European Pharmacopoeia 7.8
pH_M	Microenvironmental pH
PVA	Poly(vinyl alcohol)
PVAc	Poly(vinyl acetate)
PVP	Poly(vinyl pyrrolidone)
r.H.	Relative humidity
rpm	Rotations per minute
s	Second
SGF	Simulated gastric fluid without enzymes USP
SNARF	Seminaphtarhodafluor
TEC	Triethyl citrate
USP	United States Pharmacopoeia
UV	Ultra violet wavelength

1 Introduction

1.1 Oral sustained release dosage forms

The oral route is the most frequently used and preferred way to deliver drugs systemically to the human body (Pawar et al., 2011). This way of drug application offers many advantages for health personnel as well as for patients. It enables an easy, unassisted administration by patients without the need of trained personnel. Time controlled release of active ingredients was a further progress in administration of drug delivery systems by the oral route. These oral sustained release dosage forms (OSRDF) minimize fluctuations in drug concentration within the plasma and at the side of action over prolonged periods of time. This leads to optimized therapeutic effectiveness and reduces side effects of active ingredients which need to have constant plasma levels (e.g. antihypertensive drugs, analgesics for chronic diseases). Therefore, the total dose of active ingredients can be reduced as well as the administration frequency. Both parameters can strongly enhance patient compliance (Streubel et al., 2006). However, the development of OSRDF is not an easy task and researchers were faced to challenges like the impossibility of the dosage forms to remain near the absorption site within the gastrointestinal tract until complete release (Prinderre et al., 2011). Once OSRDF are emptied from the stomach, the passage through the upper intestine is rather rapid which often leads to an incomplete dug absorption, especially for drugs showing so called “absorption windows” in the duodenum or upper jejunum (Streubel et al., 2006). Therefore, the gastric retention time (GRT) of OSRDF is an important factor for their efficacy, as it affects the drug bioavailability of many drugs (Bardonnet et al., 2006).

1.2 Physiology of ingestion

The GRT of oral dosage forms is highly variable, lasting from a few minutes to more than 12 hours (Singh and Kim, 2000). This variability attributes to unpredictable bioavailability of active ingredients of many OSRDF and thereby diminished efficacy of the administered drug dose (Adibkia et al., 2011). The human stomach is anatomically divided into the fundus, the body and the antrum. The last-mentioned is responsible for mixing motion and acts as pump for gastric emptying (Waugh and Grant, 2010). The filling state of the stomach is an important factor affecting the GRT because it induces different patterns of gastrointestinal motility (Chawla et al., 2003).

The motility of the stomach in the fasted state is characterized by inter-digestive myoelectric cycles or so called “migrating motor complexes” (MMC) which are series of electrical events including 4 phases (Streubel et al., 2006b). The first phase (basal phase) with rare contractions lasts 45-60 minutes. The second or preburst phase shows intermittent action potential and

contractions for 30-45 minutes. These contractions are gradually increasing in intensity and frequency over time, leading to the third phase. The third phase (burst phase) is characterized by intense and regular contractions with a duration of 5-15 minutes. These so called “housekeeper waves” make sure that indigestible solids, such as insoluble monolithic tablets, are removed from the stomach. The fourth phase is a short transitory period of time (0-5 minutes) between burst and basal phase where the contractions decrease in intensity and frequency.

The gastric motility during the fed state is characterized by a period of irregular contractile activity over 3 to 4 hours. Therefore, ingestion induces a lag time prior to the onset of gastric emptying (Desai and Bolton, 1993). GRT of single unit dosage forms in the fasted state is normally below 1 hour while it may increase to values up to 10 hours in the fed state depending from the caloric content of meals (Talukder and Fassihi, 2004). There are many parameters which possibly prolong the GRT like high acidity and osmolality of the stomach ingredients, stress, female gender and advanced age. Reduced GRT were reported for patients suffering from depression and after the administration of prokinetic agents (Arora et al., 2005). The body posture may have an influence on the GRT as well as the density of OSRDF. Nevertheless, the most important parameters which influence the GRT of OSRDF are the feeding state and the size of the dosage form (Talukder and Fassihi, 2004). The size of the pylorus, which is open during fasting state, is 12 ± 7 mm. The first mouthful usually goes direct to the duodenum and leads to a closure of the pyloric sphincter. Indigestible materials like OSRDF are definitely evacuated during ingestion by interdigestive MMC peristaltic waves if their size is below 7 mm while a size of more than 15 mm is said to be necessary to prolong the GRT especially in the fasted state (Bardonnet et al., 2006).

1.3 Gastroretentive drug delivery systems

1.3.1 Applications of gastroretentive drug delivery systems

Gastroretentive drug delivery systems (GRDDS) are a topic of interest within pharmaceutical formulation development for more than 40 years (Singh and Kim, 2000). GRDDS are drug delivery systems which are retained in the stomach for a sufficient time interval against physiological barriers (gastric motility), releasing the drug in a controlled manner (Pawar et al., 2011). A prolonged GRT of OSRDF shows different advantages compared to common ones. Most important is the enhanced bioavailability of drugs having their major absorption zone in the stomach or in the upper part of the intestine (drugs with a so called absorption window, e.g. riboflavin and levodopa) or showing a higher solubility, stability or absorption at acidic pH (e.g. ranitidine HCl and metronidazole). An improved bioavailability of these drugs leads to an improvement in therapeutic efficacy and a decrease of the necessary dose (Jiménez-Martínez et al., 2008; Kavimandan et al., 2009). These optimized OSRDF are advantageous for drugs which

are locally active in the gastric mucosa like antibiotics for helicobacter pyloric eradication (Bardonnet et al., 2006) or for peptic ulcer and gastritis treatment (Jang et al., 2008) as well because of its site-specific drug delivery. Furthermore, high fluctuations in GRT of OSRDF may lead to fluctuations of plasma drug concentration which could be reduced using systems with a defined gastric retention. In addition, it is possible to reduce side effects by prolonging the retention time in the stomach for drugs which are disturbing normal colonic bacteria (e.g. amoxicillin trihydrate) (Dehghan and Khan, 2009).

1.3.2 Approaches to gastric retention

A huge number of different formulation approaches with the goal of gastric retention have been reported in literature. These formulation technologies were periodically reviewed in detail (Deshpande et al., 1996; Singh and Kim, 2000; Arora et al., 2005; Garg and Gupta, 2008; Dehghan and Khan, 2009; Pawar et al., 2012) and will therefore be introduced only briefly within this chapter with special attention to advantages and disadvantages of the most important technologies.

Mucoadhesive or bioadhesive systems should adhere to the stomach wall and therefore resist the emptying process (Pund et al., 2011). The main difficulty of these systems is the high turnover rate of the mucus which decreases the efficiency. Another disadvantage of mucoadhesive technology is the possibility of binding to other mucosal lining like the oesophagus with a potential danger for the patient (Pawar et al., 2012).

High density systems showing a density > 2.4 – 2.8 g/cm^3 are another topic of interest. These systems should be retained in the lower part of the stomach and therefore show increased GRTs (Simoni et al., 1995). Until now, no such system is available on the market. One reason might be the restricted amount of drug which is possible within these systems due to technical problems to achieve sufficient high densities (Pawar et al., 2012).

Another exceptional technique to prolong gastric retention is the use of magnetic systems. These systems consist of a small internal magnet and an extra corporal magnet which should control gastrointestinal transit (Gröning et al., 1998). Drawbacks of these systems are the high manufacturing costs, the difficulties in manufacture and the patient compliance.

The most important technologies regarding quantity of published scientific work and output of marketed products are expandable and floating systems. Expandable systems should increase in size very fast when introduced into the gastric fluid, preventing its passage through the pyloric sphincter (Klausner et al., 2003). A lot of different shapes and materials were analysed for their ability to prolong gastric retention, e.g. Accordion pill^{TM} and superporous hydrogels. An advantage of expandable systems is the independence of performance on the filling state of the stomach. Drawbacks are storage troubles due to the use of hydrolysable, biodegradable

polymers, short-lived mechanical shape memory and difficulties in economical manufacturing and scale up (Pawar et al., 2012). The expandable systems need to increase in size very fast to prevent the premature passage through the pyloric sphincter. On the other hand, they need a sufficient resistance as well to withstand mechanical contractions within the stomach (Streubel et al., 2006). Furthermore, there is the hazard of permanent retention of expandable systems inside the stomach with the risk of life threatening effects upon multiple administrations and the possibility of occlusion of the oesophagus or pylorus (Kagan and Hoffman, 2008).

Floating systems possess a density lower than the gastric fluid which causes them to float on the stomach contents (Arora et al., 2005). Therefore, these systems are said to be preserved of gastric emptying process as long as there are sufficient stomach contents to float on. The low density, which enables the floating process, can be achieved in different ways. First way is the development of inherent low density systems by entrapment of air, e.g. hollow chambers (Krögel and Bodmeier, 1999b) or hollow microspheres/ microballons (Kawashima et al., 1991) or an additional incorporation of low density material like fatty substances/ oils (Sriamornsak et al., 2005) or foam powder (Streubel et al., 2003). Another principle of floating devices are hydrodynamically balanced systems (HBS) which generate low densities upon hydration due to swelling (Sheth and Tossounian, 1984; Streubel et al., 2006b). These systems normally consist of gel-forming or highly swellable cellulose-type hydrocolloids (Singh and Kim, 2000). Another common principle to achieve low densities are gas-generating/ effervescent systems. These systems are usually matrices which are prepared using swellable polymers and effervescent components (e.g. sodium hydrogencarbonate) (Ingani et al., 1987). The effervescent components are forming carbon dioxide upon hydration, which is entrapped by the swellable polymers within the matrices and therefore decreases the density of these systems. Drug delivery devices, containing chambers of liquids which gasify at body temperature, were described within literature as well (Michaels, 1974). Another particular principle of gas-generating floating devices are raft forming systems (Washington, 1990). These systems usually contain a gel forming agent (e.g. alginic acid), effervescent agents and acid neutralizing agents, which form a sodium alginate gel (raft) with incorporated carbon dioxide when in contact with gastric fluids. The raft floats on gastric contents and prevents the reflux of these (i.e. gastric acid) by acting as a barrier between stomach and oesophagus.

Floating systems are quite popular because they show no adverse effects on the gastrointestinal motility (Singh and Kim, 2000). Nevertheless, the efficacy of floating systems highly depends on the filling state of the stomach. Food intake is the main determinant of gastric emptying. Gastric retention is said to be depending on caloric content of the food rather than on specific gravity (Waterman, 2007). Especially in the fasted state, no beneficial effect of floating devices on gastric retention was found compared to a similar non-floating formulation (Müller-Lissner and Blum, 1981). Therefore, floating drug delivery systems (FDDS) should be administered

after meal. For the fed state, a prolongation of GRT of floating devices has been demonstrated (Agyilirah et al., 1991), especially for smaller FDDS (Timmermans and Moës, 1994). The difference between floating and non-floating devices was more distinguished with drug delivery systems with diameters below 10 mm. There was almost no difference between devices having a diameter of more than 14 mm whereby the size and not the density seemed to be responsible for the gastroretention time. A high level of fluid within the stomach is required to effectively separate the dosage form from the pyloric region (Whitehead et al., 1998). This issue led to the recommendation of the frequent drinking of water during therapy with FDDS (Hwang et al., 1998). The position of patients was found to have an influence on the performance of floating systems as well. Bennett et al. (1984) observed shorter GRT for subjects laying on their left side or on their backs compared to subjects laying on their right side. The reason for this behaviour is the anatomy of the human stomach where the floating devices were presented to the pylorus even ahead of the meal when the subjects were lying on their left side. Furthermore, most floating systems possess floating lag times prior to the floating process with the risk of premature emptying.

Floating HBS or effervescent matrix systems are the most commonly approach for FDDS. They have the advantage of an easy and fast production and can be used for drugs with different solubility characteristics. A drawback for most matrix systems is the sensitivity of the drug release on pH/ agitation / ionic strength of the surroundings and the batch-to-batch variation of many polymers which are used for matrix formations (Dahl et al., 1990; Garbacz et al., 2008; Peppas et al., 2000; Sahoo et al., 2008; Viridén et al., 2009). Drug release of matrix formulations commonly follows first order kinetics and is caused by diffusion, swelling and/ or erosion (Siepmann and Peppas, 2001) depending on the used polymer and composition. The floating strength of floating matrix systems was found to be low in general. Either the density is similar to 1 (HBS systems), or only small amounts of carbon dioxide, which is formed by effervescent reaction, can be incorporated in matrix systems without causing matrix disintegration. On the other hand, high floating strength values were observed for coated, gas-generating FDDS (Strübing et al., 2008a/ 2008c). The membrane enabled the retention of high amounts of carbon dioxide leading to balloon-like structures. Coated systems show a higher robustness to agitation variation in general which enables a stable dissolution process despite changing mechanical stress during the GIT passage (Garbacz et al., 2008). Controlled drug release through a polymer membrane has different characteristics as well. The drug release is more linear in general and is caused mainly by diffusion mechanism (Källstrand and Ekman, 1983). Nevertheless, the systems show the risk of dose dumping if the membrane is damaged which can lead to an overdosage of the patient. Furthermore, the production of coated systems is more time and cost consuming when compared to matrix systems. Only drugs which are able to diffuse through polymer membranes can be used for this formulation approach.

Table 1 Marked products using gastroretentive technologies (adopted from Pawar et al., 2012).

Product	**API**	**Company**	**Technology**
Xifaxan	Rifaximin	Lupin, India	Bioadhesive tablets
Gabapentin GR	Gabapentin	Depomed, USA	Polymer based swelling technology (AcuForm™)
ProQuin XR	Ciprofloxacin		
Glumetza	Metformin-HCl		
Cipro XP	Ciprofloxacin HCl + betaine	Bayer, USA	Erodible matrix based system
Meformin Hydrochloride	Metformin-HCl	Galenix, France	Minextab Floating system®
Cafeclor LP	Cefaclor		
Tramadol LP	Tramadol		
Madopar	Levodopa + benserazide	Roche, UK	HBS system
Valrelease	Diazepam		
Cytotec	Misoprostol	Pharmacia Limited, UK	Bilayer floating capsule
Zanocin OD	Ofloxacin	Ranbaxy, India	Effervescent floating system
Riomet OD	Metformin-HCl		
Cifran OD	Ciprofloxacin		
Conviron	Ferrous Sulphate	Ranbaxy, India	Colloidal gel forming floating system
Inon Ace Tablets	Simethicone	Sato Pharma, Japan	Foam based floating system
Liquid Gaviscon	Alginic acid + potassium bicarbonate	GlaxoSmithKline, USA	Raft forming system
Topalkan	Aluminium magnesium antacid	Pierre Fabre, France	Raft forming system
Prazopress XL	Prazosin-HCl	Sun Pharma, Japan	Effervescent and swelling based floating system
Baclofen GRS	Baclofen	Sun Pharma, India	GRID (coated multi-layer floating and swelling system
Coreg CR	Carvedilol	GlaxoSmithKline, USA	Micropump

Each gastroretentive system, which was shortly introduced here, shows advantages and disadvantage regarding efficacy and safety. For this reason, dual working systems are within current focus of scientific work and pharmaceutical companies to enhance the efficacy and safety of GRDDS (Pawar et al., 2012). Principles, which are often combined, are floatation and mucoadhesion or floatation and swelling. Table 1 shows products, which are already marketed as gastroretentive drug delivery systems. Most of them are using the floating principle to prolong gastric retention and duration of action. Nevertheless, there are few human *in vivo* data publicly available to demonstrate the success of gastroretention of these products (Gusler et al., 2001; Klausner et al., 2003/2003b; Sheth et al., 1984). In addition, Waterman (2007) remarks the often missing or improper control dosage forms and the disregard of the caloric content of meals during analysis. Furthermore, the number of investigated patients is usually too low to allow statistical analysis and most studies are using pharmacokinetics instead of imaging techniques to prove gastroretentive properties. Further studies are necessary, which prove and

compare the different principles of gastroretention using standardized study protocols, to allow more definite conclusions about the efficacy of these systems *in vivo*.

1.3.3 *In vitro* und *in vivo* techniques for analysis of floating drug delivery systems

Analytical parameters, which are specified in most scientific work about FDDS, are floating lag time (FLT) and floating duration (FD). FLT means the time which is required by floating systems to emerge on the surface of the dissolution medium (Rahman et al., 2006). Simulated gastric fluid without enzymes (SGF, pH 1.2) or 0.1 N hydrochloric acid is commonly used as test medium as it mimics *in vivo* conditions of the fasted stomach. Until now, no medium was defined for the fed state although FDDS are recommended to be administered after meal (Parikh and Amin, 2008). Nevertheless, the FLT is an important parameter for batch-to-batch comparison and it is essential especially for gas generating systems. Gas generating systems show often longer FLTs due to the reaction time of a sufficient generation of carbon dioxide. However, reasonable short FLTs are necessary to minimise the risk of passing the pylorus prior to buoyancy.

The FD is defined as total time period which a FDDS remains floating. A USP dissolution apparatus with 900 ml SGF is normally used for determination of FD (Parikh and Amin, 2008). Other authors tried to additional simulate the gastric motility to achieve better *in vitro/ in vivo* correlation of the floating behaviour (El-Gibaly, 2002; Ichikawa et al., 1991).

For the development of FDDS, not only start and duration of the floating process are important. FDDS have to be able to ascend through highly viscous media of the fed stomach as well. Therefore, Timmermans and Moes (1990, 1991) developed an apparatus to determine the *in vitro* floating force over time of buffer contact. This apparatus enables the measurement of the force equivalent to the resultant weight which is required to maintain a floating object totally submerged in a fluid (Parikh and Amin, 2008). The resulting floating strength is specified as resultant weight versus time curves and gives information about stability and durability of the floating process. The floating strength of a FDDS is an important factor to better understand the possible *in vivo* floating behaviour through highly viscous media. *In vitro/ in vivo* correlation of the floating strength of a floating system versus the *in vivo* efficiency of its floating behaviour would be a very helpful tool for formulation development as well. It would be a great progress for the development of FDDS if it would be possible to connect a specified floating strength profile with the success of gastric retention *in vivo*.

Another important parameter to characterise FDDS as well as other sustained release formulations is the *in vitro* drug release. Commonly used procedures for dissolution studies face some challenges caused by floating of the systems. In literature, dissolution studies are normally carried out in SGF or other acidic media to simulate a release in gastric fluid using a USP

dissolution apparatus I or II. The usage of paddles leads to incomplete exposure of the FDDS to the dissolution medium due to the floating process, which is similar to *in vivo* conditions. If the paddle speed is to slow, it might be that the FDDS are not rotating on the surface of the medium which may lead to concentration differences within the medium with following release determination errors. Therefore, some researchers started to modify the dissolution apparatus for the special requirements of FDDS (Burns et al., 1995; Burns et al., 1998; Dürig and Fassihi, 2000; Nakagawa et al., 2006; Pillay and Fassihi, 1998) or tried to mimic the *in vivo* conditions of the human stomach (Bajpai and Dubey, 2007; Gohel et al., 2004; Gohel and Sarvaiya, 2007). Another approach to mimic conditions of the fasted human stomach is the dissolution stress test apparatus of Garbacz et al. (2008/ 2010). Nevertheless, *in vivo* conditions combine high viscous media with changing pH and regular occurrence of pressure waves which are hard to completely meet *in vitro*. All proposed tests for FDDS gain information about floating behaviour and drug release which give helpful information in formulation development. But the success of these systems in a safe prolongation of gastric retention can only be proven by human *in vivo* studies. Animal models can not give a secure reflection of *in vivo* conditions in humans due to anatomical and physiological differences (Kagan and Hoffman, 2008; Waterman, 2007). Different analytical techniques are used to follow the way of solid, oral formulations within the human body (Parikh and Amin, 2008) and to determine the GRT of these formulations like x-ray (Machida et al., 1989), γ-scintigraphy (Ali et al., 2007; Sato et al., 2004), gastroscopy (Klausner et al., 2003b), magnetic marker monitoring (Weitschies et al., 1997), ultrasonography (Shalaby et al., 1992), ^{13}C octanoic acid breath test (Torrado et al., 2004) and magnetic resonance imaging (MRI) (Steingötter et al., 2003/2003b). Especially MRI has shown to be a useful technique for this purpose which combines safety for the volunteers as well as an easy tracking of delivery devices, even of single pellets, within the human stomach using a low dose of black iron oxide as contrast agent (Knörgen et al., 2010).

1.4 Microenvironmental pH

The variability of physiological conditions within the human gastrointestinal tract (e.g. pH, gastric residence time, intestinal motility, food intake) can be a serious challenge for a predictable release and pharmacological effect of oral drug delivery systems (Grundy and Foster, 1996). Especially the variability of the gastrointestinal pH has shown to be an important parameter for drugs with ionisable functional groups such as weak acids and bases. In most cases, the unionized form shows a low aqueous solubility leading to changed solubility under acidic (stomach) and neutral (intestine) conditions. The dissolution rate of a drug with diffusion-controlled release behaviour is dependent on the solubility of the drug in the diffusion layer

(Gibaldi, 1984). Thus, pH-dependent solubility may lead to incomplete drug release and remarkable intra- and inter-individual variability of emerging drug plasma levels.

The concept of microenvironmental pH (pH_M) is often used in conjunction with solid formulations characterising the pH, which is generated within the formulation during hydration by surrounding media or humidity (Siepe, 2006; Badaway and Hussain, 2007). The pH_M has shown to affect drug stability inside solid formulations as well as dissolution behaviour, both influencing the bioavailability of an active compound (Badaway and Hussain, 2007). For this reason, several attempts have been published with the intention to modify and measure the pH_M within solid dosage forms to achieve pH-independent release or enhance storage stability of weakly acidic and basic drugs. One strategy is the incorporation of enteric polymers into hydrogel matrix devices. These polymers show a pH dependent solubility and are supposed to act as pore formers (Akiyama et al., 1994; Streubel et al., 2000) and pH modulators (Tatavarti et al., 2004) for weakly basic drugs. Another attempt is to influence the pH_M by incorporation of pH modifying substances. Organic acids, showing different solubility and acid strength, were used to enhance the release of weakly basic drugs (Thoma and Zimmer, 1990; Streubel et al., 2000; Varma et al., 2005; Siepe et al., 2006; Tatarvati et al., 2006; Gutsche et al., 2008). On the other hand, basic salts were reported to improve the release of weak acids (Doherty and York, 1989; Riis et al., 2007; Tran et al., 2008).

Many factors influence the pH_M of OSRDF including excipients, active compounds, amount of water penetration, diffusion processes and pH of surrounding media. Therefore, a certain prediction is rather difficult. There is an urgent need to monitor the local pH within solid formulations to optimise the pH_M regarding drug stability and requested drug release. Although the pH of solutions is easy to determine potentiometrically, it is much more challenging to analyse the pH_M of solid or nearly solid formulations. Several techniques were used to gain information on the pH_M, however, there are no well-established methods available which can be used for all purposes. Diffuse reflectance spectroscopy was used to determine the pH_M of dry tablets (Glombitza et al., 1994/1995; Scheef et al., 1998; Zinchuck et al., 2005, Pudipeddi et al., 2008). However, only the surface pH could be determined and possible interactions between the pH sensitive dye and excipients should be kept in mind. Incorporation of pH indicator dyes and following examination of occurring colours over time of hydration was also reported (Streubel et al., 2000; Varma et al., 2005; Adhikary and Vavia, 2008; Ching et al., 2008). This dye method was easy to apply but only a rough, imprecise estimation could be obtained. To achieve information concerning pH_M within the tablet core during contact with buffer, tablets had to be cross-sectioned. Another attempt was the usage of surface pH electrodes to analyse the surface pH_M of solid dispersions (Tran et al., 2008) as well as the pH_M of cryosections of hydrated tablets (Gutsche et al., 2008). Again, to gain insight on the pH_M of the inner regions, tablets had to be cut in pieces. Confocal laser scanning microscopy was used to non-invasively image pH

sensitive fluorescent dyes, giving a spatial resolution of pH_M (Cope et al., 2002; Li and Schwendeman, 2005). One restriction of this technique is the limited object size, thus, only eroding microspheres were analysed.

Multispectral fluorescence imaging (MSFI) is a well-established technique that is suitable for the separation and quantification of multiple fluorescence emissions from imaging probes in preclinical animal studies (Manning et al., 2009; Schädlich et al., 2011/2012). pH-sensitive dyes such as members of the seminaphthorhodafluor (SNARF) family can be excited at a single wavelength and the emission can be collected at multiple wavelengths corresponding to the discrete spectra of protonated (HA) and deprotonated (A^-) species in solution. MSFI paired with these pH-sensitive fluorochromes was found to be feasible for pH measurements in solution and/or in tissue (Hight et al., 2011). MSFI systems suitable for use in preclinical animal studies are now readily available and relatively inexpensive.

Electron paramagnetic resonance (EPR; electron spin resonance, ESR) spectroscopy allows the non-invasive detection of paramagnetic compounds. The majority of drug delivery devices are not directly detectable by EPR because of the absence of naturally occurring radicals. Thus, it is necessary to incorporate paramagnetic substances e.g. stable nitroxide radicals within the objects of interest. Depending on the used substance (so called spin probe), information about microviscosity, micropolarity and pH_M inside drug delivery systems can be obtained based on the spectral sensitivity of the nitroxides to their environment (Mäder et al., 1997; Brunner et al., 1999; Lurie and Mäder, 2005; Kempe et al., 2010). EPR imaging now combines spectral information with the spatial distribution of a spin probe. Therefore, EPR imaging can be used as continuous, non-invasive technique for the spatial determination of pH_M within hydrated devices.

1.5 Research objectives

Gastroretentive systems are a topic of interest within pharmaceutical formulation development for more than 40 years due to several advantages compared to common OSRDF as described in previous sections. The aim of this work was the development and optimisation of coated, gas-generating FDDS as gastroretentive systems. The floating principle was found to be the most often used and safest formulation approach for gastric retention within literature and pharmaceutical industry. Floating HBS or effervescent matrix systems are the most commonly approach for FDDS. Drawbacks of these systems are the often low floating strengths values and the sensitivity of the drug release of most systems on pH/ agitation/ ionic strength of the surroundings. Because of many advantages, coated, gas-generating FDDS showing high floating strength values and stable, linear drug release rates were the main focus of this work.

There are only few data available in literature dealing with coated floating systems. Ammonio methacrylate copolymer, type A Ph. Eur. (Eudragit® RL 30 D, named Eudragit RL) and poly(vinyl acetate) Ph. Eur. (Kollicoat® SR 30 D, named Kollicoat SR) were found to be the most frequently used polymers for gas-entrapping membranes due to their high flexibility. Both polymers should be evaluated with respect to robustness, control of drug release, pH dependence and floating characteristics for comparison purposes.

Eudragit RL is a copolymer of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups. Eudragit RL is water insoluble but highly permeable. It is used as film former (as aqueous dispersion, Eudragit RL 30 D) for functional pharmaceutical coatings as well as as matrix former (Eudragit® RL 100) (Evonik 2011). This polymer was found to be feasible as gas-entrapping membrane for floating tablets, pellets and minitablets before (El Samaligy, 2010; Goole et al., 2008/b; Krögel and Bodmeier, 1999).

Kollicoat SR 30 D is a poly (vinyl acetate) dispersion (27 %) which is stabilized with povidone (2.7 %) and sodium lauryl sulphate (0.3 %). Polyvinyl acetate is water insoluble. Kollicoat SR shows a low minimum film forming temperature of 18°C and high tensile strength (BASF AG). Water soluble povidone leaches out leaving pores for drug diffusion when in contact with dissolution medium. Kollicoat SR is registered in the European Pharmacopoeia (Eur. Ph.) since 2004. It was used for controlled drug dissolution as well as for FDDS before (Sawicki and Łunio, 2005; Strübing et al., 2008a/ 2008c).

Kollicoat® IR (named Kollicoat IR) was added to the Kollicoat SR coating dispersion to adjust floating and drug release characteristics of the coated tablets (Strübing, 2008c). Kollicoat IR consists of a spray dried powder of poly(ethylene glycol)(=PEG)-poly(vinyl alcohol) (=PVA) graft copolymer. PEG units and PVA units are related to each other as 25 %:75 % ratio, forming a comb-like structure. Kollicoat IR shows high water solubility and dissolution rate. The low viscosity of coating solutions causes a fast and simple processibility. PEG/ PVA grafted copolymer forms highly flexible films, as the plasticizer (PEG) is covalently bonded to the polymer (BASF AG). Kollicoat IR is mainly used as fast dissolving film former for taste masking or protection against humidity and light. In membrane controlled drug delivery systems, PEG-PVA grafted copolymer acts as a pore forming agent, whereas drug release rates can be adjusted by a change in Kollicoat IR concentration (Strübing, 2008c). Kollicoat IR is monographed in the Eur. Ph. since 2010.

To reduce the risk of dose dumping, tablet cores of coated FDDS should consist of a matrix forming drug layer and a floating layer. Kollidon® SR (named Kollidon SR) be preferably used as matrix forming excipient because it was found to be suitable for floating devices itself (Steenpaß et al., 2004). Kollidon SR consists of a physical mixture of 8 parts of poly (vinyl acetate) (PVAc) and 2 parts of poly (vinyl pyrrolidone) (PVP). It is a free flowing powder

which can be used for direct compression. Kollidon SR deforms plastically. Resulting tablets show a high compactibility and low friability (Hauschild and Picker-Freyer, 2006). Because of its aqueous solubility, PVP acts as pore former after contact with water and therefore facilitates drug diffusion. Sponge-like matrices can be observed after 12 hours of buffer contact.

FDDS for two active pharmaceutical ingredients (API's), having pharmaceutical relevance for gastric retention and differing in its solubility profile, should be developed. Metformin-HCl is an oral antidiabetic drug of the biguanide class (see Figure 1). It improves the glucose tolerance in type II diabetes by supressing the glucose production by the liver, increasing the insulin sensitivity and decreasing the glucose absorption from the GIT. Therefore, it is used especially for overweight patients because it is not causing additional weight gain. Possible side effects are gastrointestinal disorder (diarrhoea, cramps, nausea, vomiting) and lactic acidosis. Metformin-HCl is freely water-soluble (Basak et al., 2007) and a strong base which is protonated at physiologic pH. Nevertheless, it shows some pharmacological challenges which are important for formulation development as a short biological half-life (1.5 – 3h), a high dose (0.5 – 3.0 g/ day) and a low bioavailability (50 – 60 % under fasting conditions) (Nayak et al., 2011). Therefore, Metformin-HCl is stated within the biopharmaceutics classification system (BCS) as a class III drug (high solubility and low permeability) (Cheng et al., 2004). The main area of absorptions was found to be the proximal part of the small intestine (Gusler et al., 2001; Stepinsky et al., 2002). Metformin-HCl as small polar molecule is to hydrophilic to go through membranes. Therefore, the main route of absorption is the paracellular route (approx. 90 %; Proctor et al., 2008). The pore size of epithelial junctions decreases aboral in the intestine which leads to a higher permeability in the upper GIT. Therefore, normal OSRDF show a decreased bioavailability (Kagan and Hoffman, 2008). Furthermore, Metformin-HCl shows a dose-dependent, thereby saturable, absorption (Proctor et al., 2008). Marathe et al. found that the extent of metformin absorption was improved when the gastrointestinal motility of the patients was slowed down with metoclopramide. Therefore, Metformin-HCl is a suitable candidate for GRDDS and was used as easily soluble model drug for formulation establishment.

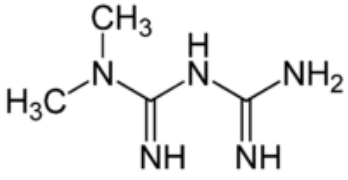


Figure 1: Structure of Metformin

A coated, balloon-like FDDS should be developed as once-a-day formulation showing high floating strength, short, pH independent FLT and a stable drug release independently from surrounding pH, ionic strength or buffer agitation. Industrial feasibility should be analysed by scale up trials in a GMP-conform environment. These tablets were intended to be used for

clinical study supply for *in vivo* studies as well. The preparation of a pilot human *in vivo* study is part of this work.

There are already Metformin-HCl containing formulations on the market which claim a prolonged GRT. One example are Glumetza™ 500 mg tablets from Depomed which shall enlarge up to 3 times its original size upon hydration. The swelling process should lead to a prolonged GRT (8 h with low-fat meal, 13 h with high-fat meal) due to prevention of pyloric sphincter passage (Berner and Cowles, 2006). The matrix tablets consist of higher molecular weight hydrophilic polymer (poly (ethylene oxide)). Glumetza™ 500 mg tablets should be compared with coated, balloon-like FDDS regarding robustness and *in vitro* drug release.

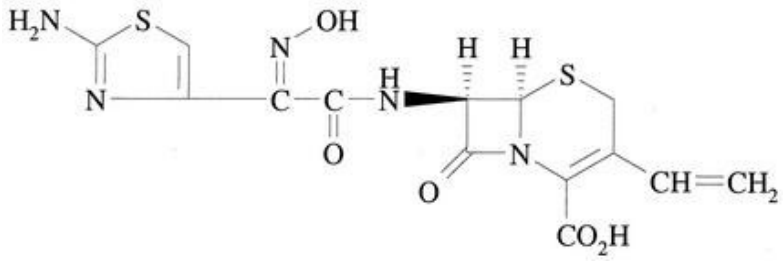


Figure 2: Structure of Cefdinir

The second drug, Cefdinir, is an oral third generation cephalosporin with an expanded antibiotic spectrum (see Figure 2). It is used for the treatment of acute bronchitis, rhino-sinusitis, pharyngitis, otitis media and pneumonia. As for other cephalosporin antibiotics, bactericidal activity of Cefdinir results from inhibition of cell wall synthesis by acting on penicillin binding proteins. Cefdinir was the highest-selling cephalosporin antibiotic in the United States in 2008. Possible side effects of Cefdinir therapy are diarrhoea, vaginal infections/ inflammation, nausea, headache and abdominal pain. Drawbacks are a short biological half-life (around 1.5 h) and a low absolute bioavailability (21 % after administration of a 300 mg capsule, 16 % after administration of a 600 mg capsule). Furthermore, Cefdinir shows a low and pH dependent solubility (slightly soluble in 0.1 M HCl (1.56 mg/ml), sparingly soluble in phosphate buffer pH 7.4 (21 mg/ml), insoluble in acetate buffer pH 4.0 (0.72 mg/ml)) (Omnicef® 300 mg capsule, technical information). It is stated as BCS class IV drug (low permeability, low solubility). Cefdinir is said to show no significant food effect. The therapeutic dose is 600 mg/day (300 mg every 12 h/ 600 mg every 24 h) without regards to food. A nonlinear relationship between the dose and the maximal plasma concentration was found, which indicates a limited absorption process (Richer et al., 1995). The initial uptake is pH-dependent, with an increased uptake at acidic pH. Cefdinir is transported across brush-border membranes by dipeptide and monocarboxylic acid carriers (saturable, carrier-mediated absorption) (Tsuji et al., 1993). The dipeptide transporter PEPT1 is present almost exclusively in the small intestine (Kagan and Hoffman, 2008). Therefore, Cefdinir is best absorbed from the duodenum and jejunum, to a

lesser extent from the ileum, but not from the colon (Zhu et al., 2006). Because of its increased uptake at acid pH and its enhanced absorption from the proximal GIT as well as its saturable absorption mechanism, Cefdinir is a suitable candidate for GRDDS to enhance its low bioavailability.

Because of its pH dependent solubility, the release of Cefdinir out of OSRDF is strongly dependent on the pH of surrounding medium. The aim of the Cefdinir formulation study was the development of FDDSs with optimised characteristics for a drug with low and pH dependent solubility. Therefore, the influence of pH-modifiers, solubilizers, filling materials, disintegrants and tablet core preparation on drug release of Cefdinir should be analysed. The aspired FDDS should enable short FLT, high floating strength values, long floating duration and a stable, pH independent release of Cefdinir. Furthermore, the microenvironmental pH within multi-layer tablets should be monitored to enable the development of formulations with suitable microacidity for a pH independent release of Cefdinir. Therefore, analytical methods for the determination of microacidity had to be established. For this purpose, a suitable pH indicator dye, fluorescence imaging and EPR imaging should be analysed for their potential to gain information on microenvironmental pH during dissolution of tablet preparations (see 1.4).

Summary of research objectives:

- Development of coated, balloon-like FDDS as once-a-day formulation.
- Optimisation of developed FDDS regarding floating characteristics, safety and robust and constant release.
- Comparison of coating polymers, which were used for formation of gas-entrapping membranes, regarding robustness, control of drug release, pH dependence and floating characteristics of resulting formulations.
- Formulation development of FDDS using Metformin-HCl as freely soluble model drug with the goal of high floating strength values, short FLT, long floating duration and robust and safe release characteristics (no dose dumping).
- Comparison of the optimised FDDS with Metformin-HCl containing commercial product, which is claimed to be gastroretentive (Glumetza™ 500).
- Preparation of a human clinical study to analyse the effectivity of developed floating systems to prolong the gastric retention in comparison to similar non-floating formulations.
- Formulation development of FDDS for Cefdinir, a drug showing low, pH dependent solubility, with the goal of high floating strength values, short FLT, long floating duration and a stable, pH-independent drug release.
- Analysis of microacidity within hydrated multi-layer tablets including analytical method establishment (pH indicator dye, fluorescence and EPR imaging).

2 Materials and Methods

2.1 Materials

Materials which were used for tablet preparation, coating and buffer preparation are listed in Table 2 together with corresponding manufacturers and applications of the materials.

Table 2 Materials, manufacturers and application of materials.

Material	**Manufacturer**	**Application within formulation**
Metformin hydrochloride	Biotrend Chemicals AG, Wangen, Switzerland	API
Ketoprofen	Sigma-Aldrich Chemie GmbH, Steinheim, Germany	API
Cefdinir	Biotrend Chemicals AG, Wangen, Switzerland	API
Carboxy SNARF®-1	Invitrogen GmbH, Darmstadt, Germany	Fluorescence dye
Bromcresol purple	Merck KGaA, Darmstadt, Germany	pH indicator dye
4-Amino-2,2,5,5-tetra-methyl-3-imidazoline-1-oxyl (AT)	N.N. Vorozhtsov Institute of Organic Chemistry, Novosibirsk, Russia	EPR spin probe
Sicovit Black 85 (Magnetite /black iron oxide, E172)	BASF, Ludwigshafen, Germany)	Contrast agent MRI
Sodium bicarbonate (grinded in mortar, passed through a 250 µm sieve)	Caesar &Loretz GmbH, Hilden, Germany	Carbon dioxid formation
Citric acid (grinded in mortar, passed through a 250 µm sieve)	Carl Roth GmbH & Co KG, Karlsruhe, Germany	Adjuvant for carbon dioxid formation
Sodium chloride	Sigma-Aldrich Chemie GmbH, Steinheim, Germany	Enhancement of ionic strength
Tri-calcium phosphate	Carl Roth GmbH & Co KG, Karlsruhe, Germany	pH modifier
Calcium hydroxide	Carl Roth GmbH & Co KG, Karlsruhe, Germany	pH modifier
Di-sodium hydrogen phosphate dihydrate	Carl Roth GmbH & Co KG, Karlsruhe, Germany	pH modifier
Eudragit® EPO (Basic Butylated Methacrylate Copolymer Ph.Eur.)	Evonik Industries AG, Essen, Germany	pH modifier, matrix former
Brij® O10 (Polyoxyethylene (10) oleyl ether)	Sigma-Aldrich Chemie GmbH, Steinheim, Germany	Solubilizer
Sepitrap™ 4000 (Polyoxyl 40 hydrogenated castor oil)	SEPPIC GmbH, Köln, Germany	Solubilizer
Sepitrap™ 80 (Polysorbate 80)	SEPPIC GmbH, Köln, Germany	Solubilizer
Lutrol® F68 (Poloxamer 188)	BASF, Ludwigshafen, Germany	Solubilizer
Ryoto® sugar ester S1670	Mitsubishi-Kagaku Foods Corporation, Japan	Solubilizer
Avicel® PH 102 (MCC 102)	FMC Biopolymer, Philadelphia, USA	Filling material
Avicel® PH 200 (MCC 200)	FMC Biopolymer, Philadelphia, USA	Filling material
Emcompress® (Calcium hydrogen phosphate dihydrate)	J. Rettenmaier & Söhne GmbH & Co. KG, Rosenberg, Germany	Filling material
D-Mannitol	Sigma-Aldrich Chemie GmbH, Steinheim, Germany	Filling material
PEG 800	Sigma-Aldrich Chemie GmbH, Steinheim, Germany	Filling material

Material	Manufacturer	Application within formulation
Fujicalin® (type S6)	Fuji Chemical Industry Co., Ltd., Toyama-Pref., Japan	Filling material
Kollidon® CL (polyvinyl pyrrolidone, cross-linked)	BASF, Ludwigshafen, Germany	Disintegrant
Kollidon® SR (8 parts of polyvinylacetate and 2 parts of polyvinyl pyrrolidone)	BASF, Ludwigshafen, Germany	Matrix former
Methocel K15M Premium (HPMC 15.000 mPa*s)	Colorcon GmbH, Idstein, Germany	Matrix former
Methocel K100 CR	Colorcon GmbH, Idstein, Germany	Matrix former
Aerosil® (Colloidal Silicon dioxide)	Evonik Industries AG, Essen, Germany	Glidant
Magnesium stearate	Magnesia GmbH, Lüneburg, Germany	Lubricant
Kollicoat® SR 30D (Poly (Vinyl Acetate) Dispersion 30 % Ph. Eur.)	BASF, Ludwigshafen, Germany	Coating polymer
Kollicoat® IR (polyvinyl alcohol-polyethylene glycol graft copolymer)	BASF, Ludwigshafen, Germany	Coating polymer
Eudragit® RL 30 D (Ammonio Methacrylate Copolymer, Type A Ph.Eur.)	Evonik Industries AG, Essen, Germany	Coating polymer
Kollidon® 30 (Polyvinyl pyrrolidone)	BASF, Ludwigshafen, Germany	Pore former
Lactose-monohydrate	Euro OTC Pharma GmbH, Bönen, Germany.	Pore former
Acetyl triethyl citrate (ATEC)	Sigma-Aldrich Chemie GmbH, Steinheim, Germany	Plasticizer
Glycerin triacetate (Triacetin)	Sigma-Aldrich Chemie GmbH, Steinheim, Germany	Plasticizer
Titanium dioxide	Sigma-Aldrich Chemie GmbH, Steinheim, Germany	Pigment
Syloid® 244 FP (colloidal silicon dioxid)	Grace GmbH & Co KG, Worms, Germany	Anti-tacking agent
Salzsäure 37%	Grüssing GmbH, Filsum, Germany	Buffer preparation
Tween® 80 (Polysorbat 80)	Carl Roth GmbH & Co KG, Karlsruhe, Germany	Surfactant
Glumetza™ 500 mg	Depomed, Inc, Menlo Park, United Sates	Marked gastroretentive tablet for comparison purposes

2.2 Preparation of tablet cores

2.2.1 Metformin-HCl containing tablet cores

The powder mixtures for the manufacturing of Metformin containing tablets were prepared according to compositions shown in Table 3 by blending all ingredients, except magnesium stearate, in a cube mixer (Erweka AR 400, Erweka GmbH, Heusenstamm, Germany) or with pistil and mortar (small batches) for 10 minutes. After adding magnesium stearate, the mixture was blended for another 2 minutes. Compositions of tablet cores B-J are shown in Table 4. Powder blend of 1-layer matrix tablets K (tablet mass of 450 mg) were prepared by mixing 27.8 % of Metformin-HCl, 1.0 % magnesium stearate and 71.2 % of Kollidon® SR. Biconvex

tablets measuring 11 mm in diameter were prepared by direct compression using a single punch tableting machine (Korsch EK0, Korsch Pressen GmbH; Berlin, Germany). For preparation of 2- and 3- layer tablets, weighed amounts of the different layers were fed successively into the die of the tablet press and compacted using a tableting speed of 10 cycles per minute. Multiple unit minitablet systems (MUMS) were produced by first preparing minitablets of the drug layer (2 mm in diameter), mixing the amount of minitablets, which contained the requested amount of Metformin-HCl, with the blend of the floating layer and filling the mixture into the die of the tablet press. Oblong 2-layer tablets (21 mm length, 9.6 mm width) containing 500 mg of Metformin-HCl were prepared by direct compression using a rotary tableting machine (Fette P1 F, Schwarzenbek, Germany).

Table 3 Composition of powder mixtures of tablet cores A-J.

Components [%]	**1-layer tablets A (350 mg/ tablet)**	**2-/3- layer tablets**							
		DL1	**DL2**	**DL3**	**DL4**	**FL1**	**FL2**	**FL3**	**FL4**
Kollidon SR	42.8	50.4	32.4	22.4	40.4	41.4	-	-	-
Metformin-HCl	35.7	48.1	48.1	48.1	48.1	-	-	-	-
$NaHCO_3$	14.3	-	5.0	5.0	-	40.7	20.0	25.0	20.0
Citric acid	5.7	-	3.0	3.0	10.0	16.4	8.0	10.0	15.0
Mg-stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Aerosil	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
MCC 102	-	-	-	-	-	-	70.5	-	-
MCC 200	-	-	-	-	-	-	-	63.5	63.5
HPMC 15.000	-	-	10.0	20.0	-	-	-	-	-

Table 4 Composition of tablet cores B – J; 125 mg Metformin HCl per tablet if not stated otherwise.

Formulation	**Drug layer**	**Floating layer**
2-layer tablet B	DL1 (260 mg)	FL1 (1 x 140 mg)
2-layer tablet C	DL1 (260 mg)	FL2 (1 x 140 mg)
3-layer tablet D	DL1 (260 mg)	FL2 (2 x 70 mg)
2-layer tablet E	DL1 (260 mg)	FL3 (1 x 140 mg)
2-layer tablet F	DL1 (260 mg)	FL4 (1 x 140 mg)
2-layer tablet G	DL2 (260 mg)	FL3 (1 x 140 mg)
2-layer tablet H	DL3 (260 mg)	FL3 (1 x 140 mg)
2-layer tablet I	DL4 (260 mg)	FL3 (1 x 140 mg)
2-layer tablet J (500 mg MF)	DL3 (1040 mg)	FL3 (1x 210 mg)
MUMS tablet L	DL1 (260 mg mini tablets)	FL2 (190 mg)

The compression force for all formulations was adjusted to receive tablets with a crushing force of 75 N after compression. Tablets were subjected to curing conditions of 50°C in a drying oven (Memmert GmbH & Co KG, Schwabach, Germany) for 2 h. Radial crushing forces were determined as an average of 10 tablets using the crushing force tester TBH 30 (Erweka GmbH, Heusenstamm, Germany) after curing and were found to be between 100-140 N. The friability of tablet cores was determined as an average of 20 tablets being weighed before and after 100 rotations of the friability tester (Abriebtester, VEB Arzneimittelwerk Dresden, Germany) according to the Ph. Eur. and was found to be below 0,05%.

2.2.2 Preparation of floating and non-floating coated 2-layer placebo tablets (Scale-up)

Floating and non-floating coated 2- layer placebo-tablets were prepared by Piramal (Piramal Pharmaceutical Development Services, Ahmedabad, India) as feasibility study/scale up under GMP conditions. The scale-up tablets were produced on a running bilayer rotary tableting machine (CIP Machinery, India) while the previous batches (see 2.2.1) were produced utilizing the inching process (hand compression). The formulation of both tablet cores can be seen in Table 5.

Table 5 Formulation of floating and non-floating 2-layer placebo tablets. Floating tablet: Placebo layer A/ Floating layer; Non-floating tablet: Placebo layer B/ Non-floating layer.

Components [%]	Placebo layer A (260 mg)	Floating layer (140 mg)	Placebo layer B (260 mg)	Non-floating layer (140 mg)
Kollidon SR	97.5	-	-	-
Sodium bicarbonate	-	25.0	-	-
Citric acid	-	10.0	-	-
MCC 200	-	63.5	-	98.5
Emcompress	-	-	97.5	-
Aerosil	0.5	0.5	0.5	0.5
Magnesium stearate	1.0	1.0	1.0	1.0
Sicovit Black 85	1.0	-	1.0	-

2.2.3 Tablet cores for microacidity measurements

The powder mixtures for the manufacturing of tablets, which were used for microacidity experiments (see 3.2), were prepared according to compositions shown in Table 6 by blending all ingredients except magnesium stearate with pestle and mortar for 10 minutes. After adding magnesium stearate, the mixtures were blended for another 2 minutes. For preparation of 2- and 3- layer Placebo tablets, weighed amounts of the different layers were fed successively into the die of the tablet press and precompacted manually. The final compression force was adjusted to receive tablets with a crushing force of 75 N after compression. Biconvex 2-layer tablets consisting of 200 mg of KSR-P or KSR layer and 100 mg of HPMC-P or HPMC layer were

prepared by direct compression using a rotary tablet press (RL 12, Kilian GmbH & Co KG, Germany). Resulting 2-layer tablets had a weight of 300 mg and a diameter of 9 mm. In addition, 3-layer tablets with an additional inter layer of 50 mg of glycerol monostearate were produced. The inter layer should achieve a better adhesiveness of both layers and decrease diffusion processes between the layers. All analysed tablet preparations are illustrated in Figure 3.

Table 6 Composition of powder mixtures for tablet preparation (Metformin-HCl (MF) and Ketoprofen (Keto) were used as model drugs).

Components [%]	KSR layer	KSR-P layer	HPMC layer	HPMC-P layer	KSR drug layer	KSR-P drug layer
Kollidon SR	70.0	70.0	-	-	70.0	70.0
Lactose	28.5	17.4	43.5	32.4	11.1	-
Methocel K100	-	-	55.0	55.0	-	-
Na_2HPO_4 x $2H_2O$	-	9.9	-	9.9	-	9.9
Citric acid x H_2O	-	1.2	-	1.2	-	1.2
Drug (MF/ Keto)	-	-	-	-	17.4	17.4
Aerosil	0.5	0.5	0.5	0.5	0.5	0.5
Mg-stearate	1.0	1.0	1.0	1.0	1.0	1.0

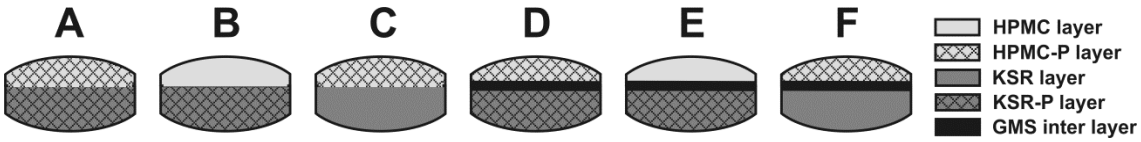


*Figure 3 Tablet compositions of tablets **A-F**, each tablet consisted of 200 mg KSR/-P layer and 100 mg of HPMC/-P layer, an additional inter layer of glycerol monostearate (GMS, 50 mg) was included in 3-layer tablets **D-F** .*

2.2.4 Cefdinir containing tablet cores

The powder mixtures for the manufacturing of Cefdinir containing tablets were prepared according to compositions shown in Table 7 - Table 14 by blending all ingredients, except the magnesium stearate, with pestle and mortar for 10 minutes. After adding magnesium stearate the mixtures were blended for another 2 minutes. Biconvex tablets measuring 11 mm in diameter were prepared by direct compression using a single punch tableting machine (Korsch EK0, Korsch Pressen GmbH; Berlin, Germany). The shape of the Cefdinir matrix tablets (I1-I6) was flat faced. For preparation of 2-layer tablets (tablets B-D), weighed amounts of the two layers were fed successively into the die of the tableting machine and pre-compacted manually. For preparation of the press-coated tablets (tablets E1-E5), tablet cores measuring 9 mm in diameter were prepared on a rotary tablet press (RL 12, Kilian GmbH & Co KG, Germany). Press coated tablets were prepared afterwards by filling a weighted amount

of the floating layer formulation into the die of the single punch tableting machine, adding the tablet core centrically and covering the core with the remaining dry powder coating formulation. The final compression force for all tablets was adjusted to 7±1 kN.

Table 7 Formulations of 1-layer tablet cores A1-A3 (350 mg/tablet).

Components [%]	**A1**	**A2**	**A3**
Kollidon SR	42.8	42.8	42.8
Metformin-HCl	35.7	-	-
Cefdinir	-	35.7	35.7
Sodium hydrogencarbonate	14.3	14.3	-
Citric acid	5.7	5.7	-
Kollidon 30	-	-	20
Magnesium stearate	1.0	1.0	1.0
Aerosil	0.5	0.5	0.5

Table 8 Formulations of 2-layer tablet cores B1-B6.

Components [%]	**Floating layer (150 mg)**	**Drug layer 300 mg)**					
		B1	**B2**	**B3**	**B4**	**B5**	**B6**
$NaHCO_3$	20.0	-	-	-	-	-	-
Citric acid	8.0	-	-	-	-	-	-
MCC 102	70.5	-	-	-	-	-	-
Cefdinir	-	44.6	43.1	41.7	40.3	39.1	37.9
NaCl	-	-	10.0	-	-	-	-
Na_2HPO_4	-	-	-	10.0	-	-	-
$Ca(OH)_2$	-	-	-	-	10.0	-	40.1
$Ca_3(PO_4)_2$	-	-	-	-	-	10.0	-
Kollidon 30	-	20.0	20.0	20.0	20.0	20.0	20.0
Emcompress	-	33.4	24.9	26.3	27.7	28.9	-
Magnesium stearate	1.0	1.5	1.5	1.5	1.5	1.5	1.5
Aerosil	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Mass of drug layer [mg]		**280**	**290**	**300**	**310**	**320**	**330**

Table 9 Formulations of 2-layer tablet cores C1-C3.

Components [%]	**Floating layer (150 mg)**	**Drug layer (300 mg)**		
		C1	**C2**	**C3**
$NaHCO_3$	20.0	-	5.0	5.0
Citric acid	8.0	-	-	-
MCC 102	70.5	-	-	-
Cefdinir	-	41.7	41.7	41.7
Na_2HPO_4	-	-	15.0	-
Sepitrap 4000	-	15.0	15.0	15.0
Eudragit E	-	-	-	15.0
MCC 200	-	41.8	21.8	21.8
Magnesium stearate	1.0	1.0	1.0	1.0
Aerosil	0.5	0.5	0.5	0.5

Table 10 Formulations of 2-layer tablet cores D1-D4.

Components [%]	**Floating layer (140 mg-160 mg)**	**Drug layer (330 mg)**			
		D1	**D2**	**D3**	**D4**
$NaHCO_3$	20.0	-	-	-	-
Citric acid	8.0	-	-	-	-
MCC 102	70.5	-	-	-	-
Cefdinir	-	37.9	37.9	37.9	37.9
Na_2HPO_4	-	10.0	10.0	10.0	10.0
Sepitrap 80	-	10.0	-	-	-
Sepitrap 4000	-	-	10.0	-	-
Eudragit E	-	10.0	10.0	10.0	15.0
KollidonCl	-	5.0	5.0	5.0	5.0
Mannitol	-	25.6	25.6	35.6	-
MCC 200	-	-	-	-	35.6
Magnesium stearate	1.0	1.0	1.0	1.0	1.0
Aerosil	0.5	0.5	0.5	0.5	0.5

Table 11 Formulations of press-coated tablet cores E1-E5.

Components [%]	**Floating layer (200 mg-240 mg)**	**Tablet core (300 mg)**				
		E1	**E2**	**E3**	**E4**	**E5**
$NaHCO_3$	25.0	5.0	5.0	5.0	5.0	5.0
Citric acid	10.0	-	-	-	-	-
MCC 200	63.5	41.8	26.8	26.8	26.8	36.8
Cefdinir	-	41.7	41.7	41.7	41.7	41.7
Na_2HPO_4	-	10.0	10.0	10.0	10.0	-
Sepitrap 4000	-	-	15.0	-	-	-
Sepitrap 80	-	-	-	15.0	-	-
Lutrol F68	-	-	-	-	15.0	-
Eudragit E	-	-	-	-	-	15.0
Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0
Aerosil	0.5	0.5	0.5	0.5	0.5	0.5

Table 12 Formulations of 1-layer tablet cores G1-G6 (350 mg).

Components [%]	**G1**	**G2**	**G3**	**G4**	**G5**	**G6**
Cefdinir	35.7	35.7	-	35.7	35.7	-
$NaHCO_3$	14.3	14.3	14.3	14.3	14.3	14.3
Citric acid	5.7	5.7	5.7	5.7	5.7	5.7
MCC 200	42.8	32.8	42.8	32.8	-	-
Na_2HPO_4	-	-	-	10.0	-	-
Eudragit E		10.0	-	-	-	-
Cefdinir granulated with Sepitrap 80	-	-	35.7	-	-	35.7
Kollidon Cl	-	-	-	-	10.0	10.0
Fujicalin	-	-	-	-	32.8	32.8
Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0
Aerosil	0.5	0.5	0.5	0.5	0.5	0.5

Table 13 Formulations of 1-layer tablet cores H1-H3 (350 mg).

Components [%]	**H1**	**H2**	**H3**
Cefdinir granulated with Ryoto® sugar ester S1670	35.7	-	-
Cefdinir granulated with Sepitrap 80		35.7	35.7
$NaHCO_3$	14.3	14.3	14.3
Citric acid	5.7	5.7	5.7
MCC 200	32.8	32.8	-
Eudragit E	10.0	10.0	10.0
Fujicalin	-	-	32.8
Magnesium stearate	1.0	1.0	1.0
Aerosil	0.5	0.5	0.5

Table 14 Formulations of matrix tablets I1-I7 (300 mg); Tablets I7: 2-layer tablets consisting of 379 mg matrix layer I1 and 100 mg floating layer (see Table 8), coated with Eudragit RL coating.

Components [%]	**I1**	**I2**	**I3**	**I4**	**I5**	**I6**
Cefdinir	33.0	33.0	33.0	33.0	33.0	-
Cefdinir granulated with Ryoto® sugar ester S1670	-	-	-	-	-	33.0
$NaHCO_3$	5.0	5.0	5.0	5.0	5.0	5.0
Citric acid	1.0	1.0	1.0	1.0	1.0	1.0
HPMC 15.000	30.0	30.0	30.0	30.0	30.0	30.0
MCC 200	-	8.5	10.0	10.0	20.0	-
Na_2HPO_4	10.0	10.0	-	10.0	-	10.0
Eudragit E	10.0	10.0	10.0	-	-	10.0
Sepitrap 80	8.5	-	8.5	8.5	8.5	8.5
Magnesium stearate	2.0	2.0	2.0	2.0	2.0	2.0
Aerosil	0.5	0.5	0.5	0.5	0.5	0.5

2.3 Coating of tablet cores

Coating dispersions 1-4 were prepared according to compositions shown in Table 15 and containing coating polymers in a 85%/15% Kollicoat® SR/IR rate (Coating 1-3) or 80%/20% Kollicoat® SR/IR rate (Coating 4), related to each other as dry mass. Kollicoat® IR was dissolved in distilled water. Triacetin, Kollidon® 30, titanium dioxide and talc/ Syloid® 244 FP were added and dispersed for 3 min using an Ultra Turrax (Ultra-Turrax® T25 basic, IK-Werk GmbH & Co KG, Staufen, Germany) at 12.000 rpm. The achieved suspension was incorporated into the Kollicoat® SR 30 D suspension and whole dispersion was stirred using a blade stirrer (MR 25, VEB MLW Prüfgeräte-Werk, Medingen, Germany) at 100 rpm during the whole coating run to prevent settling.

Table 15 Composition of coating dispersions of Kollicoat SR/IR (poly(vinyl acetate)).

Components [g]	Coating 1	Coating 2	Coating 3	Coating 4
Kollicoat® SR 30 D	248.0	248.0	248.0	211.0
Kollicoat® IR	11.2	11.2	11.2	14.2
Triacetin	3.5	10.0	-	10.0
ATEC	-	-	17.0	-
Kollidon® 30	2.5	2.5	2.5	2.5
Titanium dioxide	2.5	2.5	2.5	2.5
Syloid®	8.0	8.0	17.0	8.0
Purified water	224.5	217.8	201.8	254.3

Coating dispersions 5 and 6 were prepared according to compositions shown in Table 16 and contained coating polymers Eudragit® RL (Coating 5) or Eudragit® RL/RS in a 80%/20% ratio, related to each other in dry mass (Coating 6). Lactose monohydrate was dissolved in purified water. Triethyl O-acetylcitrate and Syloid® were added and dispersed for 3 min using an Ultra Turrax (Ultra-Turrax® T25 basic, IK-Werk GmbH & Co KG, Staufen, Germany) at 12.000 rpm. This suspension was incorporated into the Eudragit® RL 30 D (/Eudragit® RS 30 D) suspension and whole dispersion was stirred using a blade stirrer (MR 25, VEB MLW Prüfgeräte-Werk, Medingen, Germany) at 100 rpm during the whole coating run to prevent settling.

Table 16 Composition of coating dispersion of Eudragit RL (ammonio methacrylate copolymer, type A (Ph. Eur.)).

Components [g]	Coating 5	Coating 6
Eudragit RL 30D	336.0	268.8
Eudragit RS 30D	-	67.2
ATEC	20.4	20.4
Lactose	9.0	9.0
Syloid	9.6	9.6
Purified water	225.0	225.0

The coating process was carried out in a drum coater (Lab-Coater GC 300, Glatt Maschinen- und Apparatebau AG, Pratteln, Switzerland). To reduce the amount of tablet cores needed and to prevent sticking, 20-50 g of prepared tablet cores were mixed with 700-800 g of biconvex MCC tablets with a diameter of 9 mm. Process parameters for the coating of the tablet cores are shown in Table 17. Tablet samples were taken at different coating levels for further analysis.

The coating process was carried out for about 1 hour to achieve a coating thickness of 8-10 mg/cm^2. Tablets were dried for 5 minutes with a pan speed of 3 rpm afterwards. Coated Metformin-HCl containing tablets were subjected to curing conditions of 50°C in a drying oven (Memmert GmbH & Co KG, Schwabach, Germany) for 24 h. Storing conditions for coated tablets were 20°C and 40 % relative humidity.

Table 17 Coating process parameters.

Coating parameters	Adjustment
Inlet temperature	50 °C
Outlet temperature	30-33°C
Process air	100 m^3/h
Atomizing air pressure	2 bar
Spray rate	7 g/min
Pan speed	7 rpm

Floating and non-floating coated 2- layer placebo-tablets were coated by Piramal using a drum coater (GAC 250, Gansons limited, Thane, India) under similar conditions.
Metformin-HCl and Cefdinir containing tablet cores were coated with Coating 2 unless stated otherwise.

2.4 Stability studies

Metformin-HCl containing tablets were stored under constant conditions in a climatized room (20°C/ 40 % relative humidity). Drug release as well as floating lag time and floating duration of tablet samples was analysed at predetermined time intervals over 12 months. To analyse the effect of relative humidity on drug release and floating behaviour, coated 2-layer tablets were stored at 20°C/ 75 % relative humidity using an desiccator with an oversaturated suspension of sodium chloride.

2.5 Determination of dissolved drug amount

2.5.1 Dissolution of Metformin-HCl containing balloon-like floating devices

Dissolution studies were carried out using an automatic dissolution tester (PTWS 310, Pharmatest Apparatebau, Hainburg, Germany) in accordance with the Ph. Eur. apparatus 2 (paddle apparatus). The method of stirring mechanism (paddle or basket) showed to have no influence on the drug release. Therefore, paddles were used because it enabled a floating behaviour similar to *in vivo* conditions (tablets floating on the surface of release medium). Tablet samples were analysed in 900 ml of simulated gastric fluid USP (SGF, pH 1.2) of 37 °C with a rotation speed of 50 rpm unless stated otherwise. The pH 1.2 of the surrounding buffer was used as typical pH of the fasted human stomach which is usually used for characterisation of gastroretentive dosage forms (Talukder and Fassihi, 2004; Jantratid et al., 2008). Release of Metformin-HCl was determined by measuring the UV absorption at 239 nm (250 nm for tablets with 500 mg Metformin-HCl) and calculated using calibration curves of the drug. Dissolution experiments were carried out over 24 hours and performed in triplicate. Results are specified as

mean values. Relative standard deviation was below 5 % of the total Metformin HCl content if not stated otherwise.

2.5.2 Dissolution stress test apparatus

Different Metformin-HCl containing tablets were analysed using a dissolution stress test apparatus (Garbacz et al., 2008) to get an impression of their possible *in vivo* behaviour under the occurrence of house keeper waves within the human stomach. Therefore, phases of mechanic stress caused by pressure waves were applied at different time intervals of dissolution testing by three symmetric pressure waves of 6 seconds duration and a magnitude of 100 or 300 mbar as described before (Garbacz et al., 2008). Tablets were analysed over 12 hours of buffer contact using SGF or phosphate buffer pH 4.5 at 37°C. The release of Metformin-HCl was measured by UV absorption at 240 nm (250 nm for Glumetza 500 mg tablets). The floating behaviour of tablets after occurrence of pressure waves was analysed by observation. Dissolution studies were carried out on 6 tablets for each formulation and condition.

2.5.3 Drug release of Metformin-HCl and Ketoprofen containing matrix tablets

Dissolution studies were performed to investigate if different pH_M within a tablet could influence the drug release (see Table 6). Metformin-HCl and Ketoprofen were used as model drugs. Drug containing matrix tablets were prepared by incorporating 17.4 % of drug instead of lactose into the Kollidon SR layer giving a drug content of 34.8 mg per tablet (see Table 6). The drug release was determined from 2-layer tablets **B** and **C** and 3-layer tablets **E** and **F**. Dissolution studies were carried out with an automatic dissolution tester (PTWS 310, Pharmatest Apparatebau, Hainburg, Germany) in 900 ml of buffer pH 3 (citric acid/ phosphate buffer consisting of 0.01 M citric acid solution and 0.02 M disodium hydrogenphosphate solution in a ratio of 4:1 with a resulting pH of 3) at 37 °C and 50 rpm.. The pH 3 of the surrounding buffer was used as typical pH of the late phase of the fed stomach (Jantratid et al., 2008) which is important especially for gastroretentive systems. The drug release was analysed by measuring UV absorbance at 233 nm for Metformin-HCl, and 275 nm for Ketoprofen and calculated by using calibration curves. Dissolution experiments were carried out over 12 hours and performed in triplicate. Results are specified as mean values.

2.5.4 Dissolution studies of Cefdinir containing tablets

Dissolution studies were carried out using an automatic dissolution tester (PTWS 310, Pharmatest Apparatebau, Hainburg, Germany) in accordance with the Ph. Eur. apparatus 2 (paddle apparatus). Tablet samples were analysed in 900 ml of simulated gastric fluid (SGF, pH 1.2) of 37 °C with a rotation speed of 50 rpm unless stated otherwise. Released Cefdinir

amounts were determined by measuring the UV absorption at 318 nm and calculated using calibration curves of the drug. Dissolution experiments were carried out over 24 hours and performed in triplicate. Results are specified as mean values. Relative standard deviation was below 5 % of the total Cefdinir content if not stated otherwise.

Total Cefdinir recovery after 24 hours of buffer contact was determined by drying the hydrated tablet for 12 hours at room temperature, mortar the dried tablet and dissolve the resulting powder in 100 ml of phosphate buffer solution pH 6.0 R2. Ph. Eur. Cefdinir content of the tablet residues was determined by measuring UV absorption of the dissolved sample as described above. Cefdinir recovery was calculated by adding the amount of Cefdinir, which was released after 24 hours of dissolution test, to the amount of Cefdinir which was detected in the tablet residues. Cefdinir recovery was expressed as percentage of the initial Cefdinir content per tablet.

2.6 Monitoring of floating strength

To analyse the floating strength of tablets, an experimental setup using an apparatus simplified according to Timmermans and Moës (1990) was used. This apparatus measures the force which is required to maintain a sample totally submerged into the dissolution medium (Figure 4).

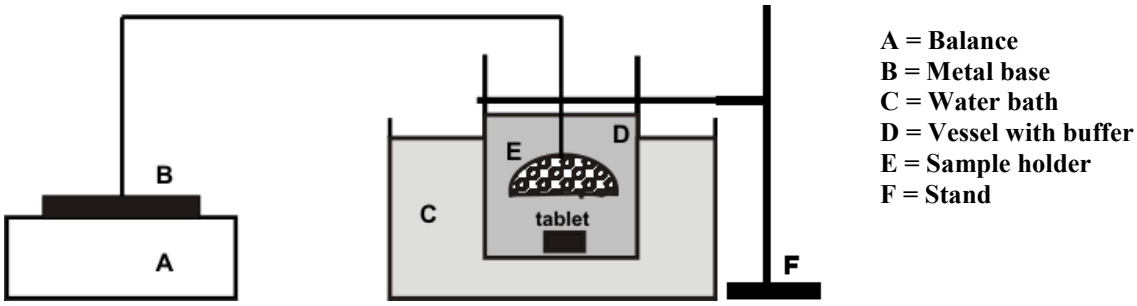


Figure 4 Experimental setup for the determination of the floating strength.

A sample holder (E) was connected to a metal base (B) placed on a balance (A) via a metal pole. A vessel (D), held by a stand, was hanging in a water bath (C) which was heated up at 37°C to simulate body temperature. For floating strength measurements, a tablet was placed in the vessel filled with buffer, covering the whole sample holding device (E). First, the tablet sank to the bottom of the vessel and the balance could be adjusted to zero. After a floating lag time, the tablet ascended towards the sample holder. The sample holder caught the ascending tablet and prevented its emersion on the buffer surface. The resulting floating strength of the tablet was determined as the weight decrease on the balance over time. Floating strength was measured frequently as long as a floating strength could be determined with a maximum time of 24 hours. The experiment was stopped when the tablet sank to the bottom of the vessel. Floating strength

was determined in general in triplicate. Results are specified as characteristic floating strength values over time of buffer contact.

2.7 Monitoring of floating lag time and floating duration

For the determination of floating lag time, tablet samples were placed in the vessel of an automatic dissolution tester (PTWS 310, Pharmatest Apparatebau, Hainburg, Germany) filled with 900 ml of SGF at 37°C and 50 rpm. The floating lag time was defined as period of time which was needed by the tablet to emerge on the surface of the medium. The floating lag time of the coated floating tablets should be below 10 minutes. The floating duration was defined as period of time where the tablet was floating on the surface of the medium and should be more than 24 hours.

2.8 Stress test of hydrated 2-layer tablets using texture analyzer

A texture analyser (EZ Test, Shimadzu, Japan) was used to analyse the robustness of the Metformin-HCl containing floating tablets upon hydration. Therefore, 2-layer tablets E (coating 3 and 6) were placed in a beaker with 500 ml of buffer (SGF and phosphate buffer pH 4.5) of 37°C, which was agitated using a magnetic stirrer. The hydrated tablets were removed from buffer at predetermined time intervals and adhering water on the surface was removed using paper tissues. The tablets were subjected to the sample holder of the texture analyser. Robustness analysis was performed by penetration of a 10 mm in diameter stainless steel probe into the balloon-like tablets with a speed of 0.5 mm/ minute and a maximum force of 2.4 N (0.03 N/mm^2 = 300 mbar). When the maximum force of 2.4 N was detected (upon contact of the probe and tablet), the steel probe was stopped for 6 seconds and removed afterwards from the tablet surface for 1 minute. Same procedure was repeated for another 2 times for each time point per tablet (3 phases of mechanic stress in total). The tablets were placed back to the buffer afterwards. The floating lag time and intactness of the tablets was determined for each time point of stress analysis over 8 hours of buffer contact. Photographs of the stress test procedure were taken using a digital camera (µ850 SW, Olympus, Japan). The measurements were carried out in triplicate.

2.9 Determination of water uptake behavior of Metformin-HCl containing 2-layer tablets

2.9.1 Determination of water uptake behavior by means of weighing

To analyse the impact of buffer pH on water penetration, the water uptake of 2-layer tablets was analysed. Therefore, 2-layer tablets E were placed into 700 ml of buffer (SGF or phosphate buffer pH 4.5 Ph. Eur.) at 37°C and 50 rpm using a dissolution tester. Samples were taken at

predetermined time intervals and adhering water on the surface of tablets was removed using paper tissues. Tablets were weighed and dried in a drying oven at 50°C until constant mass was achieved. Water uptake was calculated as amount of penetrated water related to dry tablet mass. Measurements were carried out six fold.

2.9.2 Determination of water uptake behavior by means of ^{1}H NMR

^{1}H NMR experiments were performed on a low-field benchtop NMR spectrometer (Maran DRX2, Oxford Instruments Molecular Biotools, Oxfordshire, UK) equipped with an air flow temperature regulation and a 3D imaging unit. Transverse magnetization decays were obtained by application of CPMG pulse sequences at 37°C. Each pulse sequence was detecting 30 720 echoes and a relaxation delay time of 30 s. The transverse magnetization decays were fitted with WinDXP analysis software (Oxford Instruments, Abingdon, UK) and T_2 distribution with 256 points were calculated in the relaxation time range from 10 µs to 20 s. Each tablet was subjected to a test tube with 1 ml of buffer (SGF or phosphate buffer pH 4.5 Ph. Eur.). The decrease of free water due to water penetration inside the tablet was analysed by measuring the area under the curve (AUC) of the free water signals (relaxation time around 3 s) over time of buffer contact using NMR data PXP tool box. Due to a changed mobility of water which was incorporated inside the tablet (interaction with polymers), signals with shorter relaxation times could be found and the signal of the free water decreased. The AUC of the free water signal, which was detected during the first measurement (t = 0), was used as 100 % value. Amount of water uptake inside the tablets was calculated by subtraction of the actual AUC of the free water signal from the 100 % value. The unit-free values were converted into mg water by equalizing the 100 % value with the used amount of free water in mg. All experiments were performed in triplicate.

2.10 Determination of carbon dioxide generation of Metformin-HCl containing 2-layer tablet cores

To analyse the influence of buffer pH on amount of carbon dioxide generation of 2-layer tablets E, precipitation reactions were carried out as follows. Four 2-layer tablet cores E (without coating) were subjected to a vessel with 15 ml of buffer (SGF or phosphate buffer pH 4.5). The vessel was closed with a lid with an incorporated tube immediately after the tablet transfer. The angulated tube ended in a vessel with 30 ml of barium hydroxide solution R (Ph. Eur.) in which pH indicator dye phenolphthalein was incorporated to control the pH and the completeness of barium carbonate generation. Carbon dioxide, which was generated after hydration of tablet core by reaction of $NaHCO_3$, water and citric acid, was transferred through the tube to the barium hydroxide solution were barium carbonate was formed as precipitate. The precipitate

was filtered (Munktell-Filter Grade 1289) after a reaction time of 15 minutes. The filtrate was dried in a drying oven at 60°C until constant mass was achieved. The amount of barium carbonate which was found on the filter was analysed. All experiments were carried out in triplicate.

2.11 Microacidity measurements using a pH indicator dye

Tablets, containing bromocresol purple (1 mg/layer) as pH indicator dye, were prepared as described before. 2- and 3-layer Placebo tablets were subjected to 100 ml of buffer pH 3 (see 2.5.2). Cefdinir containing tablets were subjected to 100 ml of simulated gastric fluid with a resulting pH of 1.2 as a medium which is typically used as dissolution media for gastroretentive systems (Talukder and Fassihi, 2004). Photographs of the tablets as whole and cross-sectioned were taken after predefined time intervals of contact with buffer with a digital camera (µ850 SW, Olympus, Japan). Every tablet could be analysed only once, therefore, a new tablet incubated in the buffer for the dedicated time interval was used for every photograph. The pH of the buffer was analysed regularly and showed a stable pH of 3.0 or 1.2 depending on the used buffer.

2.12 Microacidity measurements using multispectral fluorescence imaging

2-layer Placebo matrix tablets, containing the fluorescence dye Carboxy SNARF®-1 (0.2 µmol/g powder), were used. The tablets were placed into tubes with the diameter of the tablets and two open ends to allow a constant measuring area and a one-dimensional hydration only from top and bottom of the tablet. The tubes with incorporated tablets were transferred to 100 ml of buffer pH 3 (see 2.5.2). They were removed from the buffer after different time intervals and analysed by fluorescence imaging. The measurements were done with a Maestro™ *in vivo* imaging system (Cambridge Research & Instrumentation, Woburn, USA). A green and a yellow filter set were used. Multispectral imaging cube sets were acquired in 2 nm steps using automatic exposure times. Averaged spectra were extracted from different image regions to allow a pH_M calculation of both tablet layers. The ratios of the maxima were determined. Corresponding pH_M values were calculated using a calibration curve of the fluorescence dye. Furthermore, pseudo-coloured fluorescence images were generated by separating the microacidities of the measured images using an acidic spectrum (assigned colour red) and a neutral spectrum (assigned colour green) of the spectra library. The measured spectrum of each data point was assigned to the closest matching spectrum. Therefore, acidic domains of the measured tablets appear red; areas with a pH > 6 appear green within the pseudo-coloured images.

2.13 Microacidity measurements using spatial spectral EPR imaging

Tablets containing EPR spin probe AT (1 µmol/g powder) were used. Measurements were performed with a L-band EPR spectrometer (Magnettech GmbH, Berlin, Germany) using following parameters: B_0-field 48.9 mT, scan range 8 mT, scan time per projection 30 s, modulation amplitude 0.1 mT, attenuation 6 dB, maximum gradient of 2.5 mT/cm, 1024 points per projections, 31 projections/ 6 missing projections, image reconstruction giving an image matrix of 512 * 512 points and a spatial resolution of about 200 µm. For 2-/3-layer Placebo matrix tablets, the KSR/ KSR-P layer of the tablet used for analysis was glued to a plastic bar which was placed into 100 ml of buffer pH 3 (see 2.5.2)The plastic bar with the affixed tablet was removed from the buffer at different time points. Adhering water on the surface of the tablet was removed carefully using absorbent paper before measuring. Two dimensional EPR images were collected for all tablet compositions after 10 minutes, 30 minutes, 1, 2, 3, 4 and 6 hours of buffer contact. The pH of the buffer was analysed regularly and showed a stable pH of 3. For Cefdinir containing tablets, the 2-layer tablet used for analysis was placed into 100 ml of simulated gastric fluid. The tablet was removed from the buffer and placed on a marked point of a plastic bar with floating layer up at different time points. Adhering water on the surface of the tablet was removed carefully using absorbent paper before measuring. Two dimensional EPR images were collected for all tablet compositions after 30 minutes, 1, 2, 3, 4, 6 and 8 hours of buffer contact. The pH of the buffer was analysed regularly and showed a stable pH of 1.2.
The EPR spectra of the different image layers were extracted from the EPR images. Only image domains with signal intensities over 30 % were used for further analysis. The values of $2a_N$ (distance 1st to 3rd peak) were determined from the extracted spectra. Resulting pH_M values were obtained using a pH calibration curve of AT and plotted against the spatial position within the tablet. Experiments were performed in triplicate.

2.14 Monitoring of hydration behaviour by means of NMR benchtop imaging

NMR imaging experiments were performed on a BT-MRI spectrometer working at a frequency of 20 MHz and using a static magnetic field (B_o) of 0.5 T (Maran DRX2, Oxford Instruments Molecular Biotools, Oxfordshire, UK). A standard spin-echo sequence was used with an echo time of 9.8 ms and a repetition time of 300 ms leading to an acquisition time of about 5 min for each image. Sixteen scans were accumulated to obtain 64 x 64 pixel images with a field of view of 4 cm^2, which led to an in-plane resolution of 312.5 µm. 2- and 3-layer Placebo matrix tablets were placed in a USP paddle dissolution apparatus with 900 ml of buffer pH 3 of 37 °C, stirred at 50 rpm, or in a beaker with 100 ml of same buffer at room temperature without stirring. The tablets were removed for MRI measurements after predefined time intervals and transferred to a

sample holder. T_1-weighted MRI images were measured after 10 min, 30 min, 1 h, 2 h, 3 h, 4 h and 6 h of contact with buffer. Experiments were performed in triplicate. MRI intensity profiles of resulting images were investigated using Oxford Instruments RIImageJ VO.NIX as plug-in for Image J.

2.15 Determination of compatibility of Cefdinir with excipients

Different excipients were analysed for their compatibility with Cefdinir. For this purpose, 1:1:1 mixtures of excipient, Cefdinir and purified water were prepared by mixing 100 mg of each component. The samples were stored at 37°C in a drying oven (Memmert GmbH & Co KG, Schwabach, Germany) for 8 h or 24 h. After 8 h or 24 h hours, the appearance of the samples was analysed and documented by photographs using a digital camera (µ850 SW, Olympus, Japan). The samples were dissolved in 100 ml of phosphate buffer solution pH 6.0 R2. Ph. Eur. (buffer pH 6.0) afterwards. For determination of Cefdinir content, 0.1 ml of resulting solutions were diluted with 2 ml of buffer pH 6.0 and analysed measuring the UV absorption at 318 nm. Cefdinir content was calculated using calibration curves of the drug. Samples were measured again after 24 hours of buffer addition.

2.16 Determination of material properties of Cefdinir by DSC, melting point and X-ray diffraction

To determine possible interactions between Cefdinir and excipients, differential scanning calorimetry (DSC) studies were carried out. Pure substances, mixtures and pestled tablets were analysed using a DSC 200 (Netzsch-Gerätebau GmbH, Selb, Germany) operating with a heating rate of 10 K/min within a range of 30°C to 250°C. Nitrogen was used as a flushing gas with a flow rate of 10 ml/min. The samples were placed into aluminium pans with a pierced lid.

The melting behaviour of Cefdinir was analysed by observing a small amount of the drug heated up with a rate of 4°C per minute from room temperature until 250°C using a Magema K8 (VEB Wägetechnik Rapido, Radebeul, Germany).

Powder x-ray diffraction was carried out to analyse the crystalline structure of Cefdinir using a powder diffractometer (Type STADI P MP) and corresponding powder diffraction system software from Stoe (Stoe& Cie GmbH, Darmstadt, Germany). The powder was analysed as transmission sample. The obtained intensity spectrum was compared with a spectrum of crystalline anhydrous Cefdinir using the powder diffraction files (PDF) data base.

2.17 Monitoring of storage induced changes in film coat composition by means of ^{1}H NMR

The film coat of Cefdinir containing tablets B1 and B6 was analysed by ^{1}H NMR to determine storage induced changes in film coat composition. The aim was to analyse, if a high amount of pH modifying substance (calcium hydroxide) in the tablet core could change the polymer ratio of the coating polymers, especially the content of poly(vinyl acetate)/ Kollidon® SR. Therefore, tablets B1 (without calcium hydroxide) and B6 (with 40% calcium hydroxide) were analysed after storage of 3 months at 20°C and 40 % relative humidity. The film coat of the tablets was peeled of using a razor blade. These coating samples were freeze dried for 24 hours using a Christ Alpha 1-2 freeze drier (Christ Gefriertrocknungsanlagen, Osterode, Germany). 25 mg of each film coat sample were dissolved in 1 ml of DMSO-D6. 900 µl of the supernatant were analysed using a 400 MHz ^{1}H NMR spectrometer (Varian Gemini 2000, Varian GmbH, Darmstadt, Germany). ^{1}H NMR experiments were performed in triplicate for each tablet type.
The amplitude of characteristic peaks for both polymers (Kollidon® SR at 4.74 ppm and Kollidon® IR at 4.41 ppm; Strübing, 2008c) was compared for the different film coat samples.

2.18 Observation and variation of wetting behavior of Cefdinir

Cefdinir was wet granulated with different solubilizers (Sepitrap™ 80, Sepitrap™ 4000, Ryoto® sugar ester S1670 and Brij® O10) to analyse the impact on the wetting behaviour. Therefore, 1 g of pure Cefdinir was wetted with 0.5 ml of a saturated solution of solubilizer in a 10 % ethanol-water mixture. Resulting paste-like material was mixed and dried in a drying oven (Memmert GmbH & Co KG, Schwabach, Germany) at 50 °C for 2 hours. One drop of simulated gastric fluid was added to 50 mg of resulting dry granules and pure Cefdinir. The wetting behaviour of the different granules was optically analysed using a microscope (Olympus SZX 9, Olympus Deutschland GmbH, Hamburg, Germany) and documented by photographs using a digital camera (µ850 SW, Olympus, Japan).

2.19 Optimization of Cefdinir tablet disintegration

Different Cefdinir formulations were analysed for their disintegration behaviour using a disintegration tester (PTZ-E, PharmatestApparatebau GmbH, Hainburg, Germany) filled with 400 ml of simulated gastric fluid of 37°C. Tablet cores of formulation B5 and C3 were analysed as well as drug layer formulations using different filling materials (Table 18).

Table 18 Drug layer formulations I-III.

Components [%]	I	II	III
Cefdinir	41.7	41.7	41.7
MCC 200	31.8	-	-
PEG 8000	-	31.8	-
Mannitol	-	-	31.8
$NaHPO_4$	10.0	10.0	10.0
Eudragit E	10.0	10.0	10.0
Kollidon Cl	5.0	5.0	5.0
Magnesium stearate	1.0	1.0	1.0
Aerosil	0.5	0.5	0.5

Tablets of 300 mg of drug layer formulations I-III were produced as described in chapter 2.2.3. In addition, 300 mg of drug layer formulation III were mixed with 30 mg of Sepitrap 80 or Sepitrap 4000 and biconvex tablets with a weight of 330 mg were produced. All tablets were analysed for their disintegration time as mentioned above.

2.20 Determination of Cefdinir solubility

The solubility of Cefdinir in buffers of different pH was determined (simulated gastric fluid pH 1.2; 0.05 M Phosphate buffer solution pH 4.5. Ph. Eur; Phosphate buffer solution pH 6.0 R2. Ph. Eur.; 0.2 M Phosphate buffer solution pH 7.5. Ph. Eur.. Therefore, saturated solutions of Cefdinir in different buffer solutions were prepared and stored at 37°C. Samples of 0.5 ml were withdrawn at predefined time intervals and analysed for the dissolved amount of Cefdinir. Cefdinir content was determined after sufficient dilution in same buffer by measuring the UV absorption at 318 nm and calculated using calibration curves of the drug. Solubility experiments were carried out over 4 days and performed in duplicate.

3 Results and Discussion

3.1 Balloon-like floating devices for freely soluble model drug Metformin-HCl

Metformin-HCl was found to be a suitable candidate for GRDDS as described before (see 1.5) and was used as easily soluble model drug.

Coated, balloon-like FDDS should be developed as once-a-day formulation showing high floating strength, short, pH independent FLT and a stable drug release independently from surrounding pH, ionic strength and buffer agitation.

3.1.1 Influence of coating composition on drug release and floating characteristics

The initial coating composition was prepared according to Strübing, 2008c to achieve a polymer ratio of Kollicoat SR to Kollicoat IR from 8.5:1.5. This ratio was found to be optimal concerning stability and floating characteristics before. The preparation method was slightly modified to prevent a possible damage of Kollicoat SR suspension. Therefore, only the pigment suspension was homogenized using an Ultra Turrax (see 2.3). Furthermore, talcum was substituted by Syloid as anti-tacking agent (Coating 1, see Table 15) because of the tendency of talcum to sediment during the coating process despite continuous stirring of coating dispersions. No effect on drug release and floating characteristics could be observed for this substitution. Nevertheless, the handling of coating dispersion was simplified (no sedimentation). The coating of balloon-like floating tablets should be optimized regarding floating characteristics. Plasticisers are often added to a coating suspension to improve the mechanical properties of the polymeric films, such as flexibility or distensibility of the polymeric material.

Figure 5 shows the influence of plasticiser content (hydrophilic plasticiser Triacetin) on drug release and floating lag time of coated 1-layer tablets A (see Table 3). When the plasticiser content was increased from 4.5 % (w/w) polymer content (Coating 1) to 12.8 % (w/w) polymer content (Coating 2), the water permeability of coating membrane increased. The tablet surrounding water could penetrate faster which led to an accelerated carbon dioxide generation. A shortened FLT was the result which decreased from around 22 minutes (Coating 1) to 9 minutes (Coating 2). Furthermore, Metformin-HCl was dissolved faster and could diffuse through the coating more easily which led to a faster drug release.

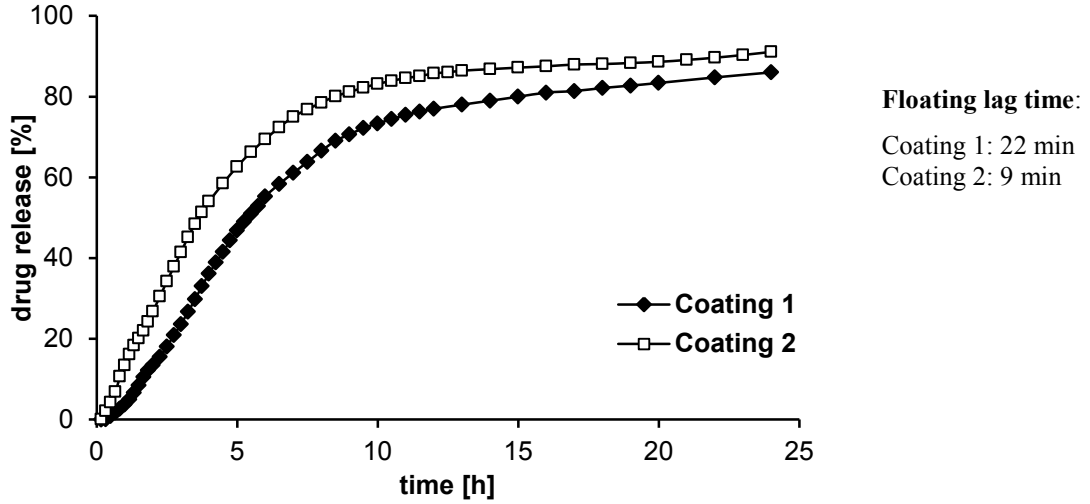


Figure 5 Influence of plasticizer content on Metformin-HCl release and floating lag time of 1-layer tablets A (Coating 1: Triacetin content 4.5 % (w/w) from polymer content; Coating 2: Triacetin content 12.8 % (w/w) from polymer content).

Figure 6 illustrates the influence of plasticiser material on drug release and FLT of 2-layer tablets C. The more lipophilic plasticiser ATEC was used instead of Triacetin within Coating 3. Goole et al. (2008b) described an increase in drug release and floating strength as well as a decrease in FLT when ATEC was used instead of the more hydrophilic plasticiser triethyl citrate (TEC) within ammonio methacrylate copolymer containing coating formulation. This finding was attributed to the slower leaching of the lipophilic plasticiser out of the coating membrane which was told to enhance the flexibility of the film for a prolonged period of time.

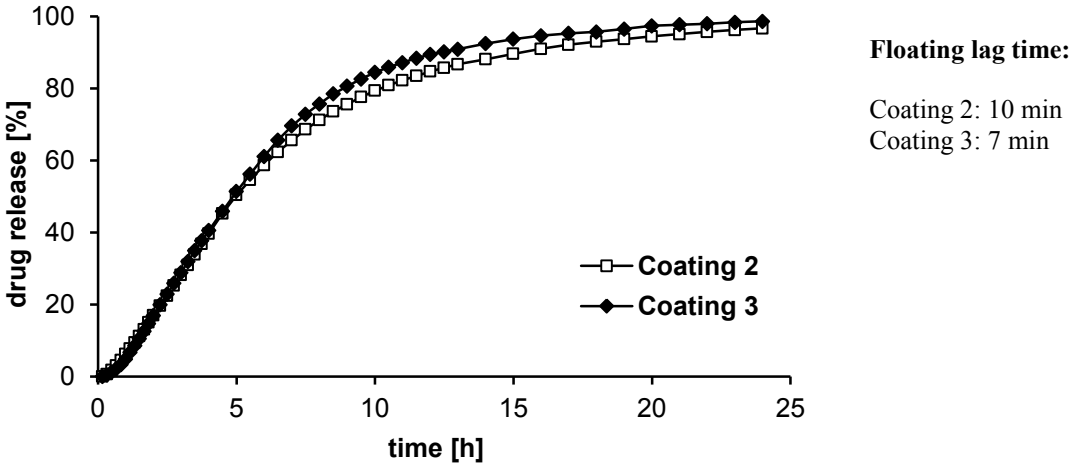


Figure 6 Influence of different plasticizers on Metformin-HCl release and floating lag time of 2-layer tablets C (Coating 2: Triacetin; Coating 3: Acetyl triethyl citrate (ATEC)).

No obvious difference of the drug release of tablets with Coating 2 and 3 could be detected. The floating lag time was slightly shortened for Coating 3 (around 7 minutes instead of around 10 minutes for Coating 2). Stability of Coating 3 was reduced (floating duration of some tablets below 24 hours). The more lipophilic plasticiser ATEC within Coating 3 showed no advantage

concerning floating characteristics and drug release. Therefore, Coating 2 was used as optimized coating composition unless stated otherwise, showing best properties concerning stability, floating characteristics and drug release.

3.1.2 Influence of tablet core formulation on drug release and floating characteristics

A coated 1-layer tablet formulation with Metformin-HCl as highly water soluble model drug was prepared according to Strübing 2008c. The tablet core was further optimised by incorporation of sodium hydrogen carbonate combined with citric acid to achieve a pH-independent carbon dioxide generation behaviour. This addition led to an independence of FLT of resulting tablets from pH of surrounding buffer. The advantage of a pH independence of the floating process is the constant floating behaviour under different *in vivo* conditions as can be seen in fasted and fed state of the human stomach. After ingestion, the pH of the human stomach can increase to values above pH 6 while it is normally below pH 2 in the fasting state (Arora et al., 2005). Floating tablets should be in general taken after meals to enable enough time to overcome the FLT of the devices by a reduced motility of the stomach during time of ingestion (see 1.3.2, p. 4/5). Therefore, a pH independent floating behaviour is crucial for a prolonged gastric retention time of floating devices. Furthermore, biconvex tablet cores were compressed instead of flat-faced tablets with bevelled edges which facilitated the coating process and reduced the sensitivity of the devices for surface defects within the coating on the tablet edges due to the more obtuse angle. A tight coating is essential for this type of floating tablets because the coating needs to withstand the pressure which is formed by carbon dioxide generation.

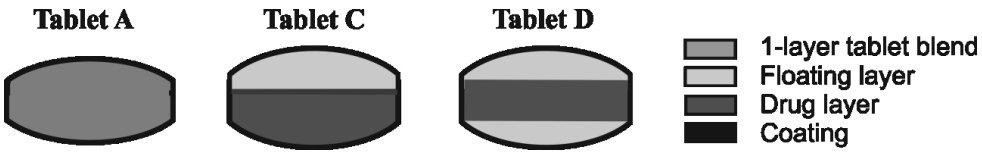


Figure 7 Schematic composition of 1- / 2- and 3-layer tablets.

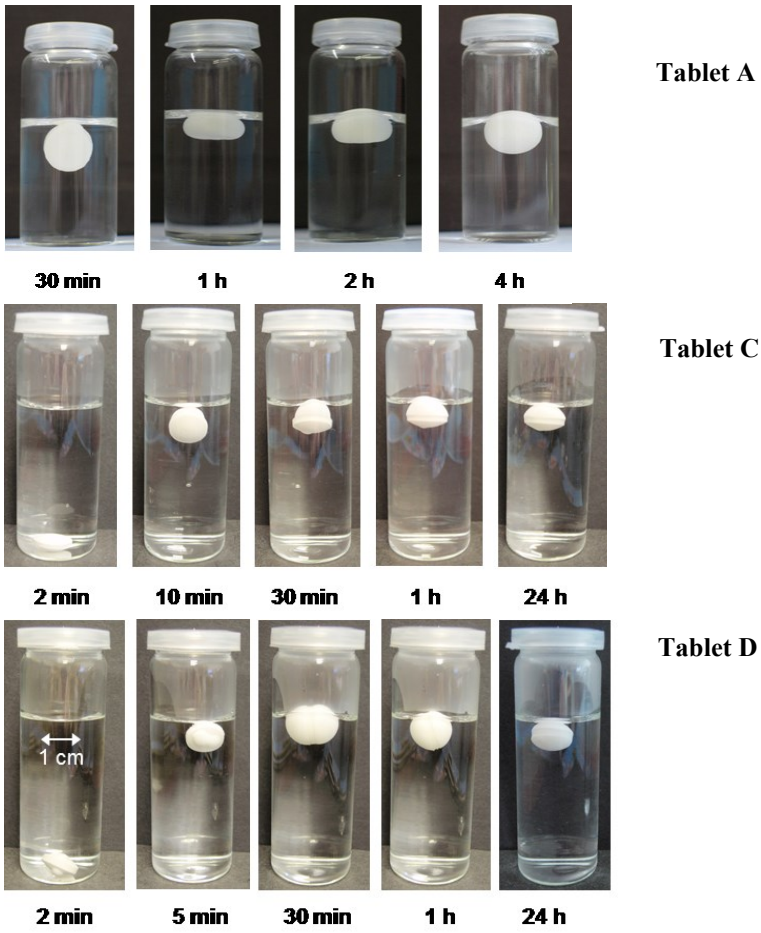


Figure 8 Floating behaviour of coated 1-/ 2- and 3-layer tablets in SGF at room temperature after different time intervals of buffer contact.
Tablet A: 1-layer tablet core, Coating 1;
Tablet C: 2-layer tablet core (FL2), Coating 2;
Tablet D: 3-layer tablet core (FL2), Coating 2

Figure 8 shows photographs of the floating process of Tablets A (Coating 1) at different time intervals of contact with SGF. The tablet was initially sinking. Development of carbon dioxide started after hydration of polymer film because of the reaction of sodium bicarbonate with citric acid in aqueous environment. At the beginning of this process, carbon dioxide accumulated on one side of the tablet bar leading to an expansion of the film coat and to the ascension of the tablet to the surface of the buffer solution. Some small gas bubbles, leaving the edges of the tablet, could be observed during hydration. The coating seemed to achieve its maximum of elasticity and stability not until complete hydration. After around 15 minutes of buffer contact, no further escape of carbon dioxide bubbles could be observed. Self-healing effects of a similar coating composition were described in literature before (Ensslin et al., 2009). Further carbon dioxide accumulation on the top side of the tablet led first to a dome shaped structure which formed a balloon like floating devise after around 2 hours of buffer contact. The floating duration was found to be more than 24 hours. Nevertheless, although this formulation showed a long floating duration and a FLT independent from pH of surrounding buffer, the FLT was

around 10 minutes even for tablets with optimised coating (Coating 2). To further reduce the FLT and the risk of dose dumping (disintegration of tablet core after coating rupture) and to have the possibility to optimise floating behaviour and drug release independently from each other, 2- and 3-layer tablets with a separation of gas generating excipients and drug were developed (see 2.2). These tablets consisted of a drug layer and one or two floating layers (Figure 7). Kollidon SR was included within the drug layer of these formulations which had the additional advantage of an improved safety. The risk of dose-dumping was strongly reduced even with a ruptured coating because of the matrix-forming characteristics of Kollidon SR leading to a controlled release of the drug out of the tablet core.

Figure 8 shows furthermore the floating behaviour of 2- and 3-layer tablets C and D over time of buffer contact. 2-layer tablets C were forming a dome-shaped structure upon hydration which was caused by a carbon dioxide generation only on one side of the tablet. In case of 3-layer tablets D, a water-wing-shaped structure could be observed. The carbon dioxide generation on the top and the bottom of the tablet led to a rotation of the tablet. The tablet core was floating in a 90°angle compared to the 2-layer tablet. The floating duration was more than 24 hours for both tablet formulations.

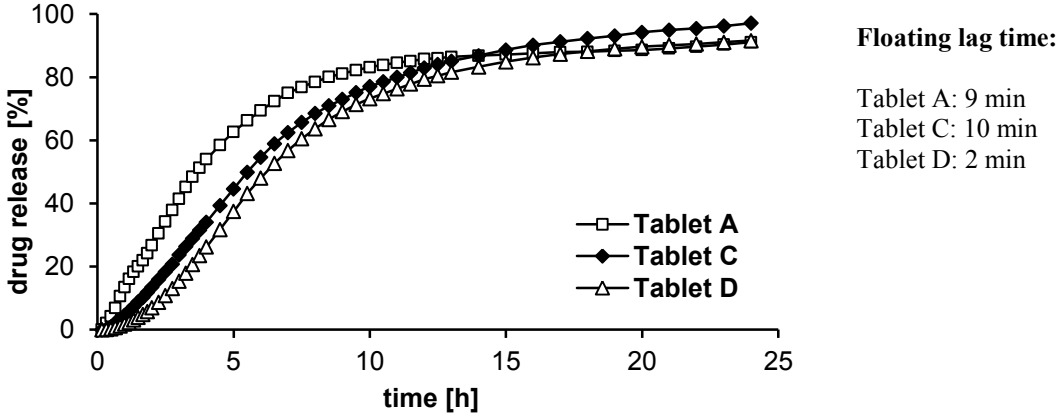


Figure 9 Influence of tablet core composition on drug release and floating lag time. (Tablet A: 1-layer tablet core; Tablet C: 2-layer tablet core (FL2); Tablet D: 3-layer tablet core (FL2)).

Figure 9 shows the influence of the tablet core composition on drug release and FLT. The release of Metformin-HCl was slower for 2-layer tablets C and 3-layer tablets D compared to 1-layer tablets A. This finding could be explained by the facilitated water penetration inside the 1-layer tablets A due to carbon dioxide generation which worked as disintegrant. Therefore, more pores were formed within the tablet core matrix through which Metformin-HCL could be released more easily. 2-layer tablets C and 3-layer tablets D showed a similar drug release because both formulations had the same drug layer composition. The different orientation of the inflated tablets (see Figure 8) seems to have no influence on the drug release of 2-and 3-layer tablets. The floating lag time was around 10 minutes for 2-layer tablet C and 2 minutes for 3-

layer tablet D. MCC was used as filling material for the floating layer. Therefore, the water penetration inside the floating layer was facilitated because of the wicking effect of MCC which led to a faster carbon dioxide generation and shorter FLTs. In comparison, the floating layer of 2-layer tablets B consisted of Kollidon SR (FL1) instead of MCC (FL2-4). A FLT of more than 30 minutes was observed for tablets B due to the hindered water penetration inside the floating layer which led to a delay in carbon dioxide generation. 3-layer tablets D showed the shortest lag time. Two floating layers on top and bottom of the tablet led to a huge contact area between penetrating water and sodium hydrogencarbonate, resulting in a fast carbon dioxide generation and very short FLTs. Disadvantages of this formulation were the high labour input and the higher deviations within the release values compared to 2-layer formulations. This finding may be caused by the very fast carbon dioxide generation which possibly led to small cracks within the coating of tablets and might be the reason for the higher variability of the dissolution curves. To further speed up the FLT of 2-layer tablets, the amount of gas generating excipients was enhanced (2-layer tablets E). These tablets showed a FLT of around 4 minutes and comparable drug release.

Table 19 shows the optimisation process of floating behaviour of tablet formulations A – E in summary. The optimised formulations D and E showed FLTs below 5 minutes, a floating duration of more than 24 hours and a controlled drug release of the core tablet which minimised the risk of dose-dumping by coating defects. Beside these advantages, the drug release of the 2- and 3-layer formulations was somewhat decreased compared to 1-layer tablets A due to the enhanced integrity of the drug containing matrix layer. Another aspect which has to be taken into account was the increase in manufacturing efforts. For commercialisation, a multi-layer tablet press need to be used for tablet core preparation. This reduces the manufacturing speed which could impact the costs of production as well. Especially 3-layer tablets D were not further analysed due to their time-consuming production as well as the higher deviations of drug release compared to 2-layer tablets. For this reason, tablets E were used for further analysis.

Table 19 Floating behaviour of tablets A –E (Coating 2) in simulated gastric fluid (SGF).

Formulation	**Floating lag time**	**Floating duration (SGF)**	**Observations**
1-layer tablet A	9 min	> 24 h	Deviation of drug dissolution profiles, possible dose dumping, balloon-like structure upon hydration
2-layer tablet B	> 30 min	> 24 h	Very slow gas formation/ drug release
2-layer tablet C	10 min	> 24 h	Dome-shaped structure upon hydration, high stability
3-layer tablet D	2 min	> 24 h	Water-wing-shaped structure upon hydration
2-layer tablet E	4 min	> 24 h	Optimized formulation concerning safety, stability and reasonable short FLT

Multi-unit minitablet system (MUMS) cores were prepared by mixing minitablets consisting of the drug layer with a defined amount of floating layer (see Figure 10 and 2.2.1) to analyze the influence on drug release and floating characteristics. Figure 11 shows the floating behaviour of MUMS tablets L. Hydrated MUMS tablets L showed no consistent shape due to the absence of a continuous insoluble drug layer which stabilized hydrated 2- and 3-layer tablets. Therefore, these tablets were difficult to handle when transferred out of the buffer. The drug release was much faster (see Figure 12) compared to the 2- and 3-layer tablets which might be caused by shorter diffusion distances of Metformin-HCl out of the matrix of the minitablets compared to the drug layer of 2- and 3-layer tablets. The floating lag time was around 2 minutes and floating duration more than 24 hours in SGF at 37°C. These tablets were not further investigated due to the time consuming production, the risk of dose-dumping and the fast drug release.

Figure 10 Schematic composition of multi-unit minitablet system (MUMS) Tablets L.

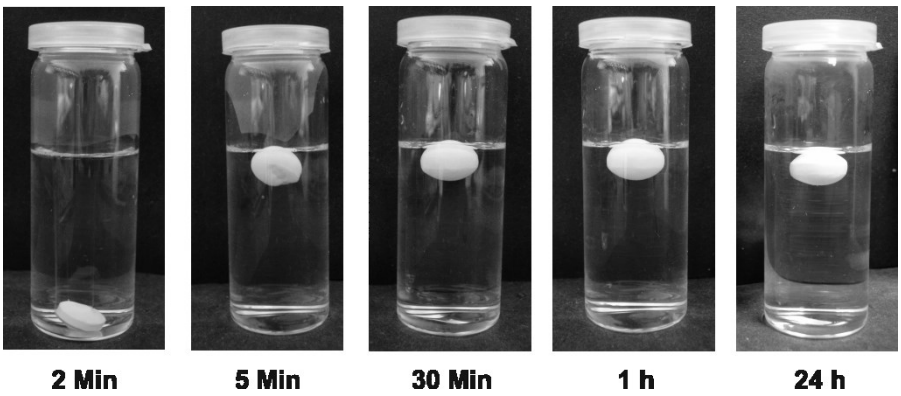


Figure 11 Floating behaviour of Tablet L in SGF at room temperature over 24 h.

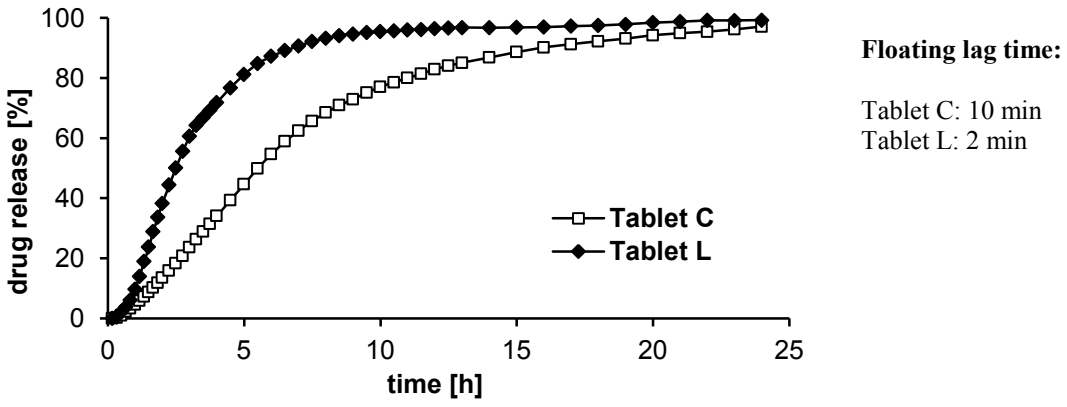


Figure 12 Influence of tablet core composition on Metformin-HCl release and floating lag time. (Tablet C: 2-layer tablet core (FL2); Tablet L: Multi-unit minitablet system (MUMS)).

3.1.3 Floating strengths measurements

Floating strength measurements (see 2.6) were carried out on 2-layer tablets E to gain a deeper insight into the floating behaviour of balloon-like floating tablets and its possible applicability *in vivo*. Floating strength was depending on coating level showing higher maximum values and lower floating lag times at decreasing coating levels which was in accordance with Strübing, 2008c. The disadvantage of low coating levels was the reduced coating stability during time of hydration. Drug release of tablets with a coating level below 6 mg/cm^2 showed high deviations and small cracks within the coating. A coating level of 8 to 9 mg/cm^2 was found to be optimal concerning coating stability and reasonable drug release/ FLTs. Tablet samples were subjected to curing conditions of 50°C in a drying oven for 24 hours after coating. Resulting tablets showed similar floating properties like uncured tablets. Floating strength increased somewhat slower and maximum values were lower than without curing. Floating strength of coated tablets was determined at buffers of different pH to analyse the pH dependence of the floating properties. The different pH values should simulate different conditions within the human stomach from fasted to fed state. Floating lag time and occurrence of maximum floating strength was found to be similar for different buffer preparations as can be seen in Figure 13. The floating strength of the tablets in SGF showed high values over more than 4 hours. An interesting finding was the short floating duration of the tablets (2-4 hours) when phosphate buffers pH 4.5 and 6.0 was used. This observation could not be attributed to osmotic effects. A reduced reaction rate of the carbon dioxide formation at increased pH might be a reason. The observed maximum floating strength values were considerably high compared to values found in literature, especially when floating matrix tablets were analysed. An example is the floating strengths of marked floating products as Valrelease and Madopar HBS as so called hydrodynamically balanced systems (see 1.3.2) which show maximal floating strength values in the range of 100 – 200 mg (Timmermans and Moës; 1990).

Coated 2-layer tablets E were able to ascend through highly viscous media (400 mPas) which can be found within the human stomach during ingestion as well (Abrahamsson et al., 2005). Therefore, a reasonable floating strength is crucial for the success of the floating principle to prolong gastric retention times. The floating lag time was increased 2.5 fold and the maximum floating strength values were decreased (around 50 mg less) and slightly delayed when a viscous medium was used. Nevertheless, tablets were able to reach the surface of the medium/ sample holder without obvious difficulties and stayed there for more than 24 hours. It has to be considered that this kind of coated floating tablets should be administered with a glass of water to facilitate the water penetration through the tablet and therefore to accelerate the carbon dioxide generation.

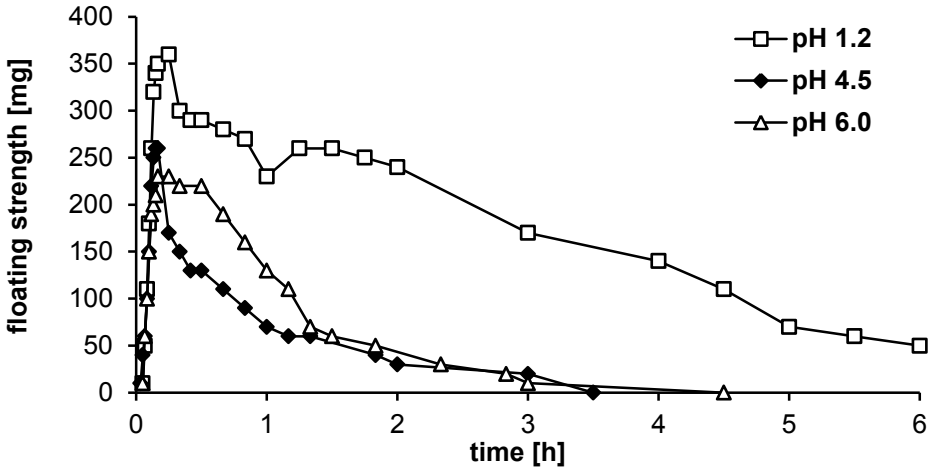
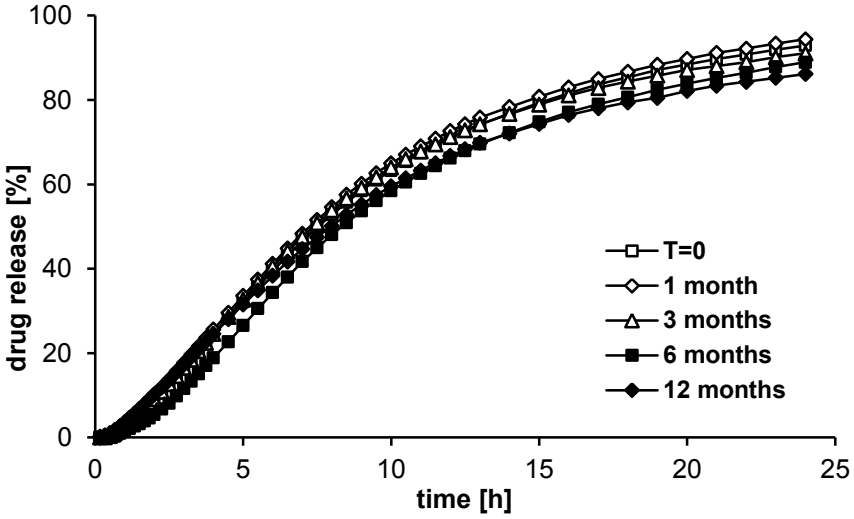


Figure 13 Influence of buffer pH on floating strength of coated 2-layer tablets E (n = 1, replications gave similar results; pH 1.2: simulated gastric fluid without enzymes; pH 4.5: phosphate buffer pH 4.5 Ph. Eur.; pH 6.0: phosphate buffer pH 6.0 Ph. Eur).

3.1.4 Stability studies of balloon-like floating devices

Stability studies were carried out on coated 2-layer tablets C and E and 3-layer tablets D to analyse the effect of storage and storage conditions on drug release and floating behaviour. Therefore, coated tablets (with and without 24 hours of curing at 50°C after coating of tablet cores) were stored at 20°C/ 40 % relative humidity or 20°C/ 75 % relative humidity over 12 months. The tablets which were exposed to curing conditions showed a slightly slower release and a longer FLT in general. Otherwise, deviations of release values were decreased and the drug release over 12 months more stable for these tablets in general. Otherwise, the deviation of release values was smaller and the drug release over 12 months more stable for these tablets in general. Figure 14 shows the influence of storage on drug release of cured 2-tablets C. No definite difference was found between the release curves over 12 months of storage. There was a slight trend of decrease of the drug release over time of storage, especially for coated 3-layer tablets D (without curing). But the release after 24 hours of buffer contact of all tablets after 12 months of storage was not below 95 % from the Metformin-HCl release at T0 which is within the common range of shelf life specifications. Figure 15 shows photographs of 2-layer tablets C, which were stored for 1 month at 20°C and 75 % relative humidity. An enhanced relative humidity of 75 % showed to be responsible for a premature carbon dioxide formation of the stored tablets which was visible by distortions of the tablet coat. The accumulation of carbon dioxide below the coating membrane let to an immediate floating of the tablets. No floating lag times could be observed after 6 and 12 months of storage under these humid conditions. Although no clear influence of this finding on the drug release over more than 6 months could be detected (see Figure 16), floating tablets should be stored under moisture protection to prevent obvious change in tablet appearance.



Floating lag time:

t_0: 10 min
1 month: 12 min
3 months: 11 min
6 months: 17 min
12 months: 13 min

Figure 14 Influence of storage (20°C/ 40 % RH) on Metformin-HCl release of coated 2-layer tablets C (with 24 hours of curing at 50°C after coating of tablet cores) in SGF.

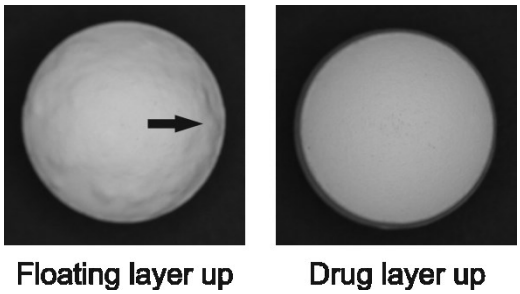
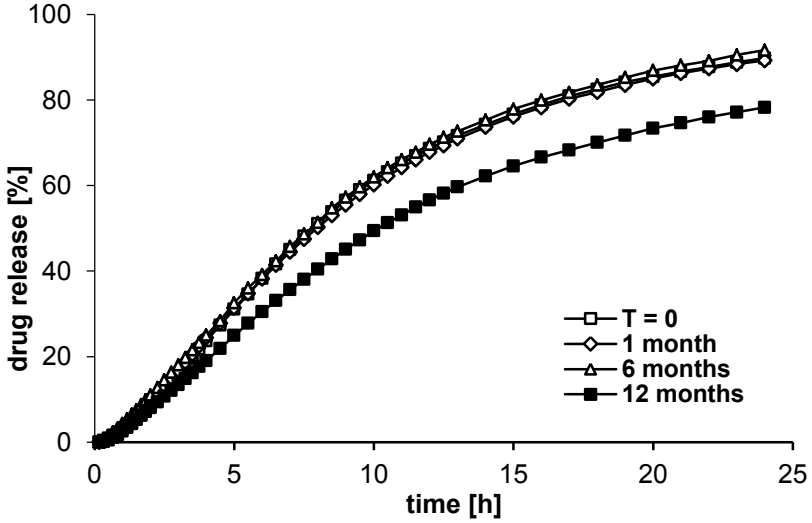


Figure 15 Photographs of 2-layer tablets C which were stored at 20°C/ 75 % relative humidity for 1 month. The arrow marks an area with visible distortions of the coating which is next to the floating layer. The coating next to the drug layer shows no visible changes.



Floating lag time:

t_0: 10 min
1 month: 2 min
6 months: none
12 months: none

Figure 16 Influence of storage conditions (20°C/ 75 % r.H.) on Metformin-HCl release of coated 2-layer Tablets C.

3.1.5 Industrial feasibility study of floating and non-floating coated 2-layer tablets

Floating and non-floating coated 2-layer Placebo tablets were produced as industrial feasibility study by Piramal under GMP conditions (see 2.2.2). Both tablet formulations had the same weight and diameter, only the thickness of the tablets was slightly different (see Table 20) which was due to the different filling materials of the drug layer. Kollidon SR could not be used as filling material for the non-floating tablets. Because of its low relative density, Kollidon SR containing tablets started to float immediately after contact with buffer up to 24 hours of buffer contact when prepared by Piramal. These finding could not be observed with tablets which were produced under conditions described before (see 2.2.1). These tablets sank to the bottom of the vessel and did not rise to the surface of the buffer for more than 24 hours. The different behaviour might be caused by different equipment and tableting settings during manufacturing of tablets.

Table 20 Comparison of technical characteristics of floating and non-floating coated 2-layer placebo tablets produced by Piramal.

Tablet core characteristics	Floating 2-layer placebo tablets	Non-floating 2-layer placebo tablets
Diameter [mm]	11.0	11.0
Band Thickness [mm]	3.2	1.9
Overall Thickness [mm]	5.4	3.9
Hardness before Curing [N]	100	70
Hardness after Curing of 2 h at 50°C [N]	194	140

FLTs below 2 minutes could be observed in case of the floating 2-layer placebo tablets. The floating duration of the Piramal floating tablets was more than 24 hours. In comparison, non-floating 2-layer placebo tablets did not appear on the surface of the buffer solution over more than 24 hours. Floating strength profiles in comparison to placebo floating tablets from the pilot scale and handmade production are shown in Figure 17. The tablets from the pilot scale at Piramal showed a fast generation of high floating strength values which even exceeded the values of the handmade production. Otherwise, the floating duration of these tablets were unsteady and was found to be below 24 hours. The Industrial scale tablets of Piramal started to float immediately after buffer contact which was caused by the low relative density instead of carbon dioxide generation. Therefore, the floating strength was low at the beginning. The increase in floating strength was delayed compared to 2-layer tablets from the handmade production. The coating characteristics and consistence seemed to be changed by the used manufacturing conditions despite same coating composition and materials were used (see 2.2.2). The penetration of tablet surrounding water and therewith associated carbon dioxide generation

was delayed. The maximum floating strength was lower for the Piramal tablets as well. Otherwise, the floating strength showed high, constant values over a prolonged period of time.

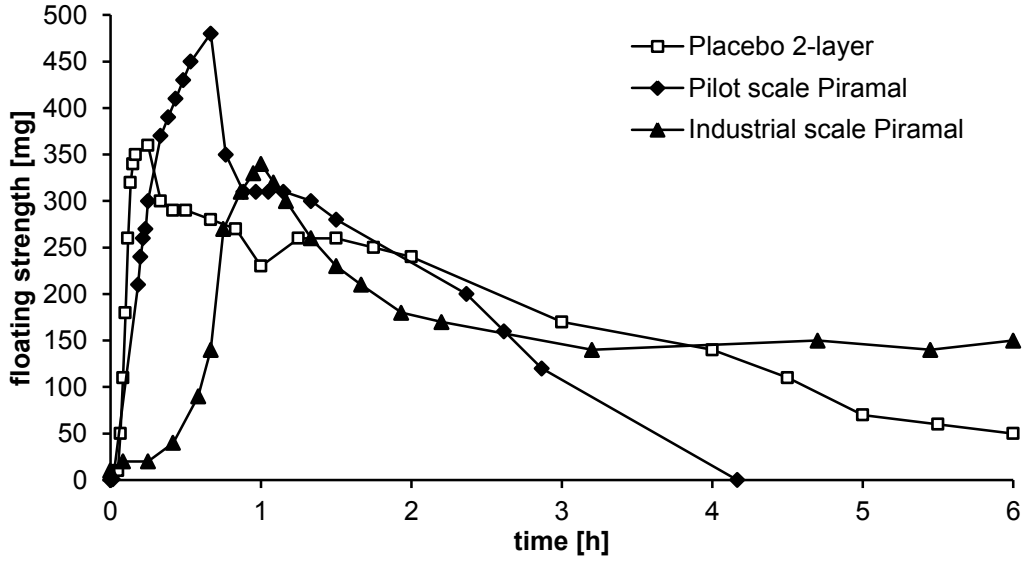


Figure 17 Influence of manufacturing process on floating strength profiles of 2-layer placebo tablets. Placebo 2-layer: Placebo 2-layer tablets MLU Halle; Pilot scale Piramal: placebo 2-layer tablets from the pilot scale at Piramal; Industrial scale Piramal: placebo2-layer tablets of the final industrial scale production at Piramal.

Floating and non-floating Placebo tablet formulations could be used as clinical samples for a human pilot study. The non-floating tablets should act as control and enable information, if the floating of tablets has an influence on gastric retention times. Therefore, gastroretention times of floating and non-floating tablets, each of similar size, weight and both with an insoluble coating, should be detected by MRI measurements over time of tablet intake for comparison purposes. Black iron oxide was incorporated in the drug layer of both tablet formulations as non-toxic MRI contrast enhancing agent. The iron oxide enables a certain differentiation between clinical samples and possible food components or gas bubbles within the human stomach as described in literature before (Knörgen et al., 2010). To gain deeper insight into the mechanism of gastric retention, floating matrix tablets (see 3.1.6.1) and swelling systems (see 3.1.6.2) should be analysed for their retention times within the human stomach as well. All studies have to be carried out under same conditions to enable a conclusion about the efficiency and safety of different methods to prolong gastric retention within the human stomach compared to an insoluble control. No suitable *in vitro* model can be used to compare the different methods and clarify their possible success *in vivo*. The usage of animal models is not constructive as well because of the huge differences within important physiological characteristics (stomach structure, ingestion behaviour, position: upright walk of humans) which makes the transfer of the results from animal models to humans impossible (Waterman, 2007). Food and position (sitting, laying, walking) effects have to be taken into account as well (1.3.2, p 4/5). Necessary

documents (study protocol, application to the Ethics Committee and to the health authority) for the realisation of a clinical study were prepared. Nevertheless, the application of the study was not approved by the health authority within the time period of this work.

3.1.6 Evaluation of further gastroretentive systems for comparison purposes

3.1.6.1 Floating matrix tablets

Floating matrix tablets K were prepared to analyse drug release, robustness and floating behaviour of a different floating system. These tablets consisted mainly of Kollidon SR and drug. Kollidon SR has been used for the preparation of floating matrix systems before (Strübing, 2008c). Because of its low relative density and ability to entrap air during the compression process, these tablets were able to float even without carbon dioxide generation for more than 24 hours under normal dissolution conditions (paddle apparatus, Ph. Eur.). Nevertheless, floating strength of these tablets was very low and tablet flotation was interrupted in some cases. Figure 18 shows the influence of dissolution method on drug release and floating behaviour. The Metformin-HCl release of floating matrix tablets K showed to be similar for both dissolution settings over more than 2 hours of buffer contact. 50 % Metformin-HCl were released after around 2 hours independently from used dissolution method. In comparison, the release was nearly completed after around 6 hours under dissolution stress test (DST, see 2.5.2) conditions and after around 16 hours under Ph. Eur. conditions. Tablets K did not float after the occurrence of pressure wave sequences. The drug release of floating matrix tablets K was controlled and within a reasonable time range and seems to be robust concerning mechanical stress. These tablets showed a high strength of shape. Mechanical stress and buffer pH showed only minimal influence on drug release of Metformin-HCl.

Nevertheless, floating properties were assumed to be insufficient to enable a prolonged retention within the human stomach. This assumption can only be clarified by a human *in vivo* study using an imaging technique to determine the position of tablet after intake over time. Otherwise, Kollidon SR containing tablets were found to be a suitable retarding principle to achieve a stable, controlled release for many drugs (Shao et al., 2001; Siepmann et al., 2010; Strübing et al., 2008b).

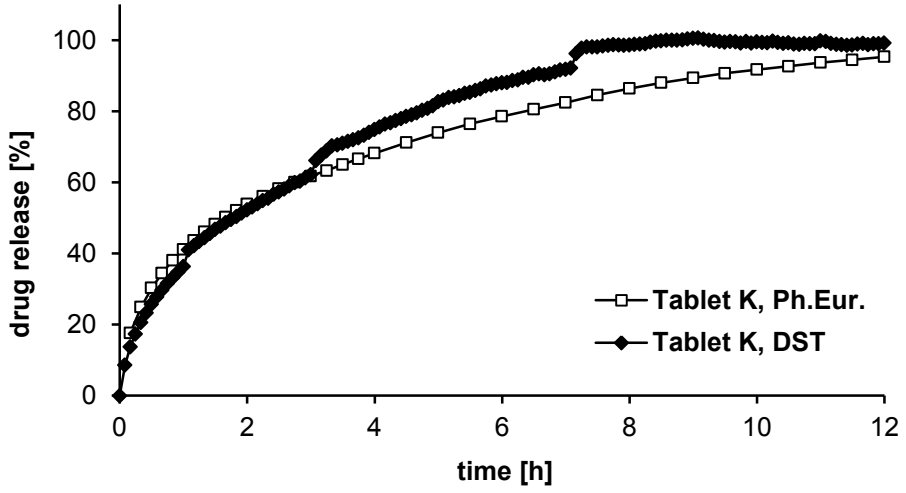


Figure 18 Influence of different dissolution conditions on Metformin-HCl release of floating matrix Tablets K in phosphate buffer pH 4.5. (Tablet K, Ph. Eur.: floating matrix tablets, Ph. Eur. apparatus 2 (paddle apparatus); Tablet K, DST: floating matrix tablets, dissolution stress test apparatus (Garbacz et al., 2008; phases of mechanic stress caused by pressure waves were applied after 1,3,5,7 and 9 h by three symmetric pressure waves of 6 s duration and a magnitude of 300 mbar)).

3.1.6.2 Glumetza™ 500 mg tablets

The release of Glumetza™ 500 mg tablets (metformin HCl extended release tablets) using Acuform™ delivery technology (patented, polymer-based technology from Depomed) was analysed under different release conditions. It is claimed, that the tablets are retained in the stomach for approximately 8 to 9 hours because of a swelling of incorporated polymers (http://www.glumetzaxr.com/hcp/about-glumetza/advanced-delivery-system.asp). The release of Metformin-HCl was determined in SGF and phosphate buffer pH 4.5. No obvious difference of drug release in buffers of different pH could be detected for Glumetza™ 500 mg tablets. Figure 19 shows the influence of different dissolution conditions on the drug release of Glumetza. The release of Metformin-HCl was controlled but accelerated when using the dissolution stress test apparatus (DST; see 2.5.2) compared to paddle method Ph. Eur. (see 2.5.1; 50 rpm). No bursts of Metformin-HCl release could be observed during the occurrence of pressure waves when using DST apparatus. Glumetza 500 mg tablets seemed to be robust concerning drug release under mechanical stress. Nevertheless, the release was dependent from mechanical stress showing higher release values for DST method than for paddle method. The release was nearly completed after around 6 to 7 hours of buffer contact under DST conditions compared to around 19 hours under Ph. Eur. conditions (50 % release: after around 2 hours under DST, 3 hours under Ph. Eur. conditions). This accelerated release under dissolution stress test conditions was less distinct for Tablets K (floating matrix formulation of Kollidon SR, see Figure 18). This formulation seems to have a higher robustness against shear forces compared to Glumetza ™ 500 mg hydrogel formulation.

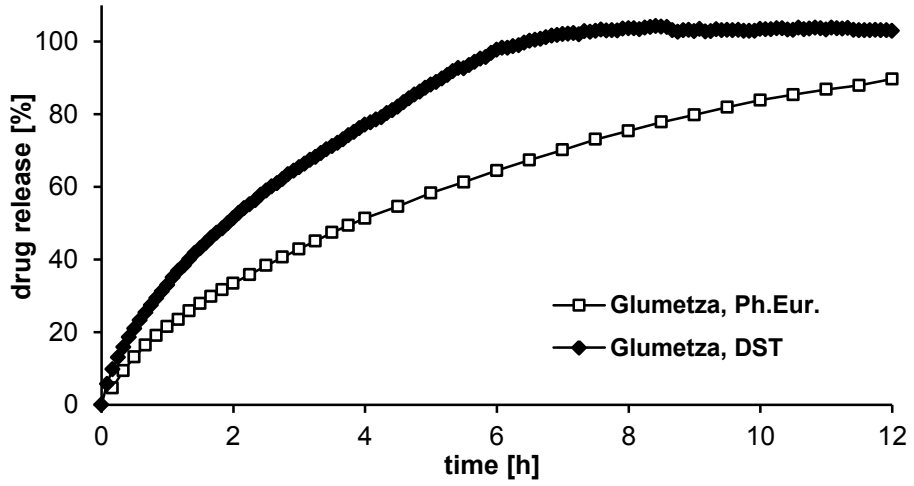


Figure 19 Influence of different dissolution conditions on Metformin-HCl release of Glumetza™ 500 mg tablets in phosphate buffer pH 4.5. (Glumetza Ph.Eur.: Glumetza™ tablets, Ph. Eur. apparatus 2 (paddle apparatus); Glumetza, DST: Glumetza™ tablets, dissolution stress test apparatus (Garbacz et al., 2008; phases of mechanic stress caused by pressure waves were applied after 1,3,5,7 and 9 h by three symmetric pressure waves of 6 s duration and a magnitude of 300 mbar)).

The release of Metformin-HCl from Glumetza™ 500 mg tablets was compared to the release of coated 2-layer tablets J (Figure 20). Both formulations had a content of 500 mg Metformin-HCl as a common dose of marked products. The release of the Glumetza™ 500 mg tablets was considerably faster than the drug release of tablets J. 90 % of Metformin HCl of Glumetza™ 500 mg tablets were release after 12 h of buffer contact. In contrast, only around 86 % of Metformin-HCl was released out of coated 2-layer tablets J after 24 h of buffer contact. The release kinetics of both formulations were different as well. Glumetza™ 500 mg tablets showed approximately first-order kinetics with a fast release at the beginning of tablet dissolution which slowed down over time of buffer contact. Similar release curves were found for most hydrogel-forming matrix systems where the drug release is dependent from diffusion through the gel and abrasion of the outer low viscous gel layers (Siepmann and Peppas, 2001; Sriamornsak et al., 2007). Coated 2-layer tablets J showed a more linear release over time of buffer contact. The release through insoluble membranes is dependent from pore formations of soluble ingredients and diffusion of drug through the membrane. This diffusion process is ideally independent from time of buffer contact. Therefore, a linear release is often possible for the main part of drug amount. The assumption, that the swelling of Glumetza™ 500 mg tablets or floating of coated 2-layer tablets can enable a secure gastroretention, can only be verified with a human *in vivo* study using an imaging technique to determine the position of tablets over time after intake.

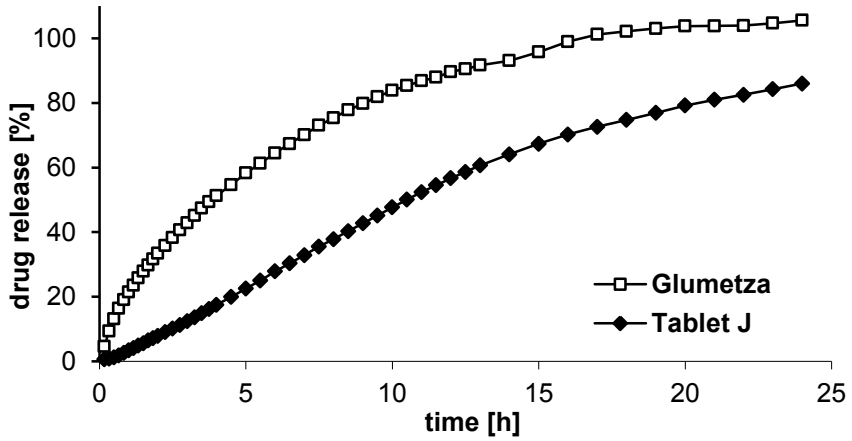


Figure 20 Influence of drug delivery device on Metformin-HCl release in SGF (Glumetza: Glumetza™ 500 mg tablets; Tablets J: coated 2-layer Tablets J with 500 mg of Metformin-HCl).

3.1.7 Evaluation of polymer materials for balloon-like floating devices

Different polymer materials for the manufacturing of coated floating tablets should be evaluated concerning robustness, release control, pH dependence of drug release and floating characteristics of 2-layer tablets E. Ammonio methacrylate copolymer, type A (Ph. Eur.; Eudragit® RL) and poly(vinyl acetate) (Ph. Eur., Kollicoat® SR) were found to be the most frequently used polymers for gas-entrapping membranes due to their high flexibility and elasticity.

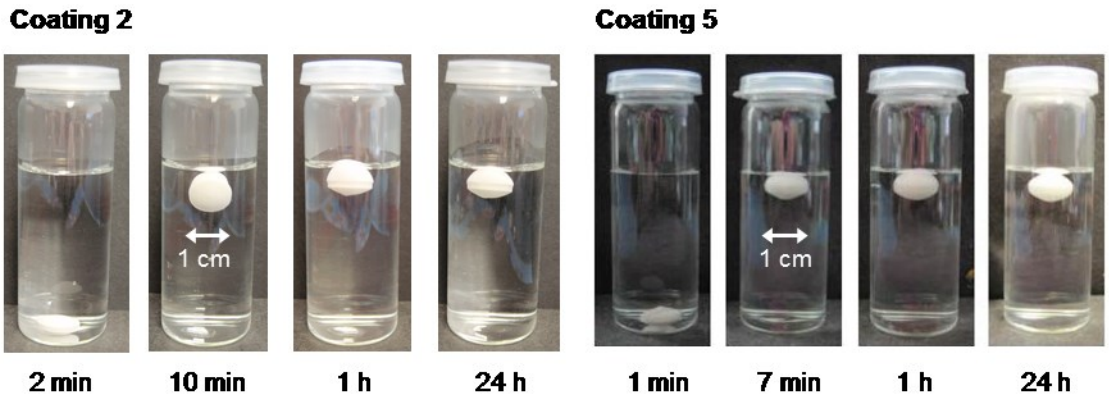


Figure 21 Floating behaviour of coated 2-layer tablets E (10 mg polymer/cm²) in SGF at room temperature after different time intervals of buffer exposure (Coating 2: Coating polymer poly(vinyl acetate) (Ph. Eur.; Kollicoat® SR); Coating 5: Coating polymer ammonio methacrylate copolymer, type A (Ph. Eur.; Eudragit® RL)).

The floating process of 2-layer tablets E coated with both polymers is shown in Figure 21. The floating lag time was comparable (< 10 minutes) with a slightly shorter lag time when the methacrylate was used as coating polymer (Coating 5, see 2.3). Floating duration of both formulations was more than 24 hours. Coating consisting basically from poly(vinyl acetate) (Coating 2) seemed more dimensionally stable. No cracks of the coating were visible over time

of analysis. The methacrylate coating (Coating 5) was nearly transparent and very soft. Cracks or holes within the coating have been observed in some cases.

The floating lag time of both formulations was dependent from the coating level (see Figure 22). The water first needed to penetrate the coating before it was able to react with the sodium hydrogen carbonate and the citric acid of the floating layer to generate carbon dioxide. The carbon dioxide which was entrapped within the coating membrane was responsible for the floating of the tablets. The thicker the coating, the more time was needed for the penetration of water and the therewith associated carbon dioxide generation. Therefore, the floating lag time increased with increasing coating level.

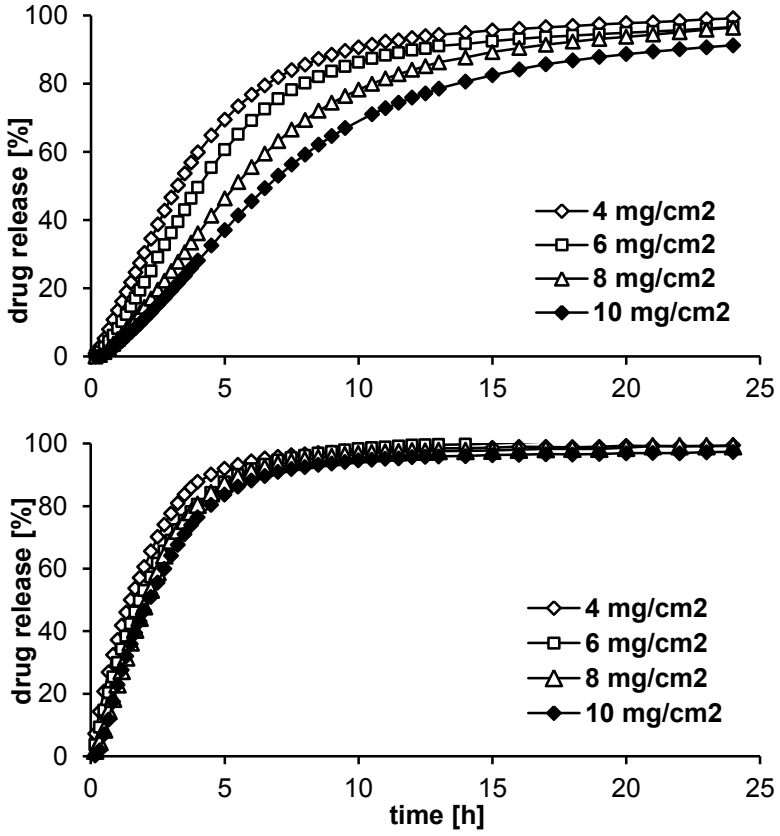


Figure 22 Influence of coating level on Metformin-HCl release and floating lag time of 2-layer tablets E; (Coating 2: Coating polymer poly(vinyl acetate) (Ph. Eur.; Kollicoat® SR); Coating 5: Coating polymer ammonio methacrylate copolymer, type A (Ph. Eur.; Eudragit® RL)).

The drug release of tablets E/ Coating 2 was dependent from the coating level as well. The thicker the coating, the slower was the release of Metformin-HCl over time of buffer contact (see Figure 22; Coating 2). Poly(vinyl acetate) was able to control the drug release within this formulation. However, it is a challenging task to optimise the drug release as well as the floating lag time by the coating level. Resulting tablets showed a slow, controlled drug release of Metformin-HCl over more than 24 hours. Therefore, this coating seems to be disadvantageous

for drugs showing poor solubility. Although the drug release was depending from the coating level, a certain coating level was needed for a secure floating behaviour.

In comparison, the drug release of tablets E/ Coating 5 was hardly influenced by the coating level (see Figure 22; Coating 5) and almost as fast as without coating (see Figure 23). Therefore, it can be expected that the ammonio methacrylate copolymer was too permeable to control the drug release of Metformin-HCl within this formulation. The high permeability of this polymer can be advantageous when a formulation for drugs showing poor solubility needs to be developed. However, the coating formulation has to be modified by incorporation of polymers showing low permeability (f. e. Ammonium methacrylate copolymer Typ B) if the membrane has to be responsible for a controlled drug release. Otherwise, it would be possible to control the drug release by an improved matrix system of the core tablet.

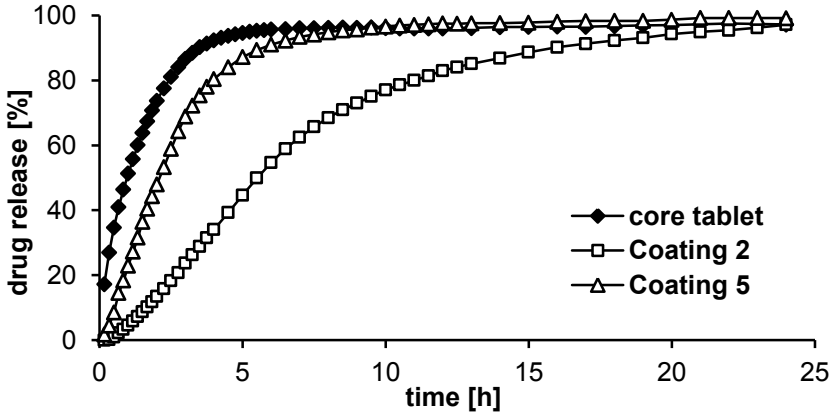


Figure 23 Influence of coating membrane on Metformin-HCl release; (core tablet: uncoated 2-layer tablet E; Coating 2: Coating polymer poly(vinyl acetate) (10 mg/cm²); Coating 5: Coating polymer ammonio methacrylate copolymer, type A (Ph. Eur.) (10 mg/cm²)).

To further optimise the drug release, both coating compositions were modified. Insoluble Poly(vinyl acetate) (PVAc) was associated with soluble Macrogol Poly(vinyl alcohol) grafted copolymer Ph. Eur. (MPVA; Kollicoat IR) within Coating 2 in a ratio of 8.5:1.5. MPVA acted as pore former within this formulation. It accelerated the water penetration and the drug release through the coating. A different ratio of both polymers was used to further speed up the drug release. PVAc and MPVA were used in a ratio of 8:2, related to each other as dry mass (Coating 4). Figure 24 shows the influence of coating polymer ratio on drug release and floating behaviour. The drug release could be accelerated by an increase of the MPVA content. Tablets E with Coating 4 showed a reasonable release of Metformin-HCl over 10 to 12 hours. Disadvantage of this formulation was the instability of the coating. All tablets showed small cracks within the coating and loss of tablet core material over time of buffer contact. The floating duration was found to be below 24 hours in some cases. Therefore, Coating 4 was not further investigated for the manufacturing of coated floating tablets.

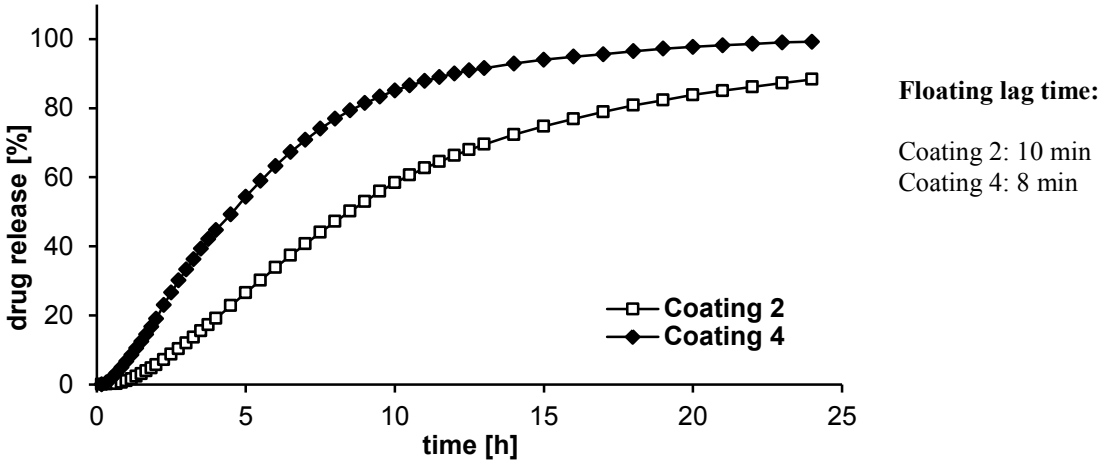


Figure 24 Influence of coating polymer ratio on Metformin-HCl release and floating characteristics of 2-layer tablets E (Coating 2: Kollicoat SR/IR 8.5:1.5; Coating 4: Kollicoat SR/IR 8:2).

A mixture of Ammonio Methacrylate Copolymer, Type A (Eudragit RL) and B (Eudragit RS) was used to slow down the drug release compared to pure Eudragit RL coating. Eudragit RS shows a low permeability in contrast to Eudragit RL (Evonic Industries AG, 2012). Both polymers were mixed in a Eudragit RL:RS ratio of 8:2, related to each other as dry mass (Coating 6) to allow reasonable short FLTs (El Samaligy, 2010). El Samaligy analysed the influence of polymer ratio and FLT. The more Eudragit RS was incorporated within the coating formulation, the higher was the FLT because of the delayed water penetration. The incorporation of 20 % Eudragit RS was found to have no influence on drug release and floating characteristics. 20 % of low permeable methacrylate copolymer seems to be not sufficient to slow down the drug release of Metformin-HCl within this formulation. Optimized ratios of both polymers have to be evaluated to achieve requested release profiles depending on solubility of the used drug. This was beyond the scope of this work.

The drug release of tablets E/ Coating 5 showed a slight dependence on the pH value of the surrounding buffer showing the fastest release at pH 4.5 (see Figure 25). Similar behaviour was observed before by Bodmeier et al. (1995). The “pH dependence” was explained by ion exchange processes where the anionic buffer species and not the pH showed to have a significant effect on the hydration and release from coated beads. Nevertheless, as the anionic buffer species can vary within the human stomach depending from composition of meals, it might impact the *in vivo* drug release as well. There was no influence of buffer pH/ anionic buffer species detectable on the release of tablets E/ Coating 2. The floating lag times were not influenced by the pH of the different buffers showing a pH independent floating behaviour for both formulations. An interesting finding was the short floating duration of the tablets (2-4 hours), independently from used coating formulation, when phosphate buffer pH 4.5 and 6 were used for dissolution studies. This observation could not be attributed to osmotic effects. A reduced reaction rate of the carbon dioxide formation at increased pH could be a reason.

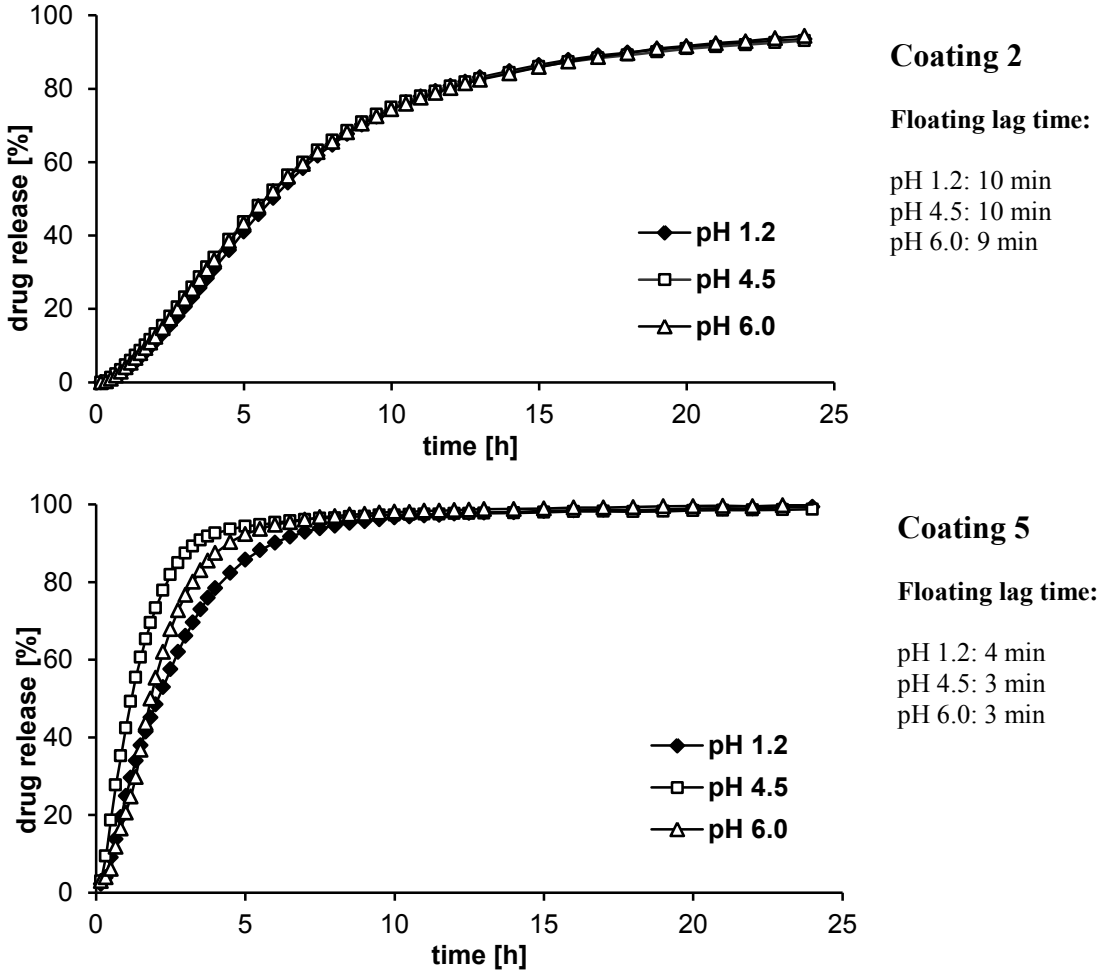


Figure 25 Influence of buffer pH on Metformin-HCl release and floating lag time of 2-layer tablets E using simulated gastric fluid (pH 1.2), phosphate buffer Ph. Eur. pH 4.5 and 6.0; floating duration of tablets at pH 4.5 and 6.0 was below 24 hours. (Coating 2: Coating polymer poly(vinyl acetate) (Ph. Eur.; Kollicoat® SR); Coating 5: Coating polymer ammonio methacrylate copolymer, type A (Ph. Eur.; Eudragit® RL)).

Floating strength measurements of both coating formulations showed similar results (see Figure 26). The floating strength of tablets E with both coating formulations strongly decreased after around one hour of buffer contact when phosphate buffer pH 4.5 and 6 were used. These tablets sank to the vessel bottom after around 3 to 4 hours which was similar to the dissolution studies.

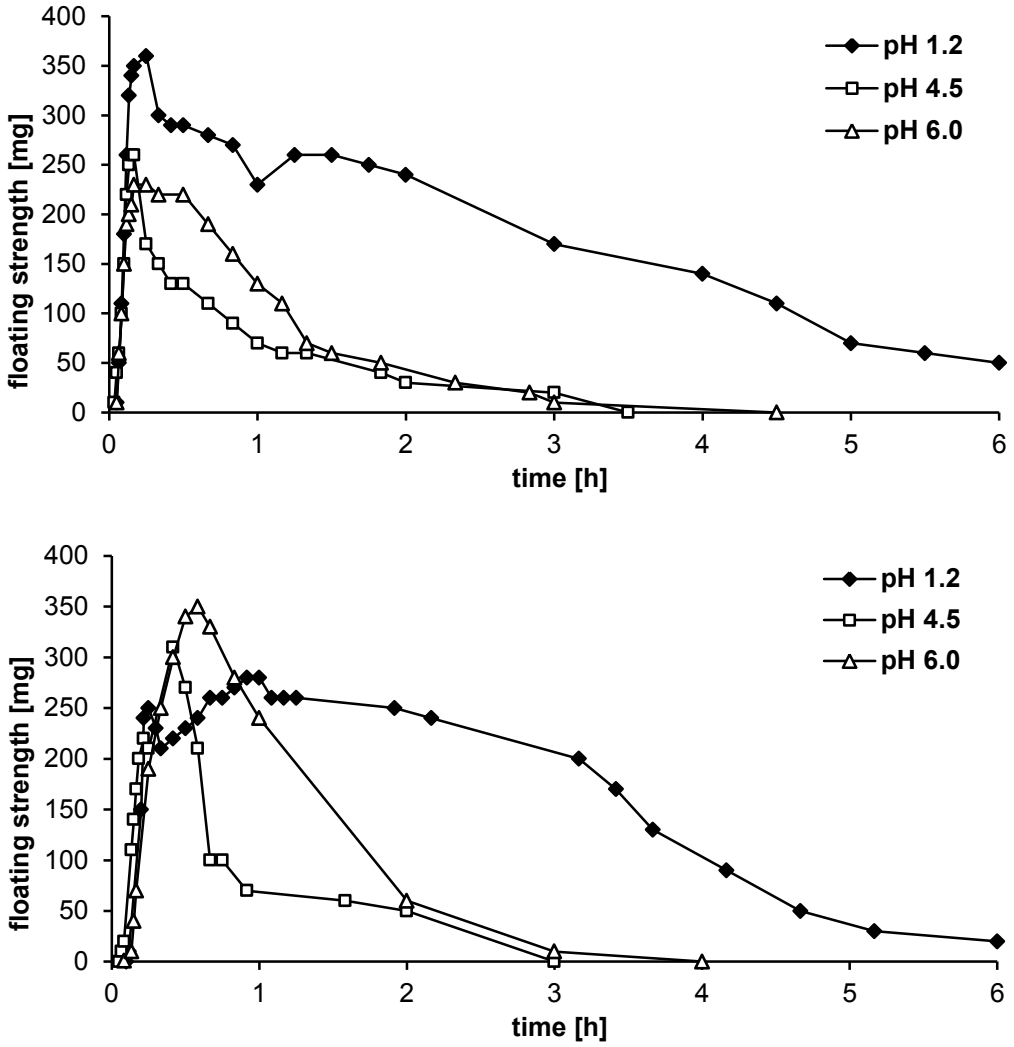


Figure 26 Influence of buffer pH on floating strength of coated 2-layer tablets E (pH 1.2: simulated gastric fluid, pH 4.5 and 6.0: phosphate buffer Ph. Eur. pH 4.5 and 6.0) (Coating 2: Coating polymer poly(vinyl acetate) (Ph. Eur.; Kollicoat® SR); Coating 5: Coating polymer ammonio methacrylate copolymer, type A (Ph. Eur.; Eudragit® RL)).

Poly(vinyl acetate) and ammonio methacrylate copolymer, type A should be analyzed for their ability to manufacture balloon-like coated floating devices. Therefore, robustness of both coatings to mechanical stress should be investigated. Different rotation speeds of the paddles during dissolution testing showed almost no effect on the drug release independent from used coating formulation (see Figure 27). Both polymers showed apparent robustness under these conditions. All tablets independent from used stirring speed floated for more than 24 hours on the surface of dissolution medium (SGF). No loss of tablet core material could be monitored.

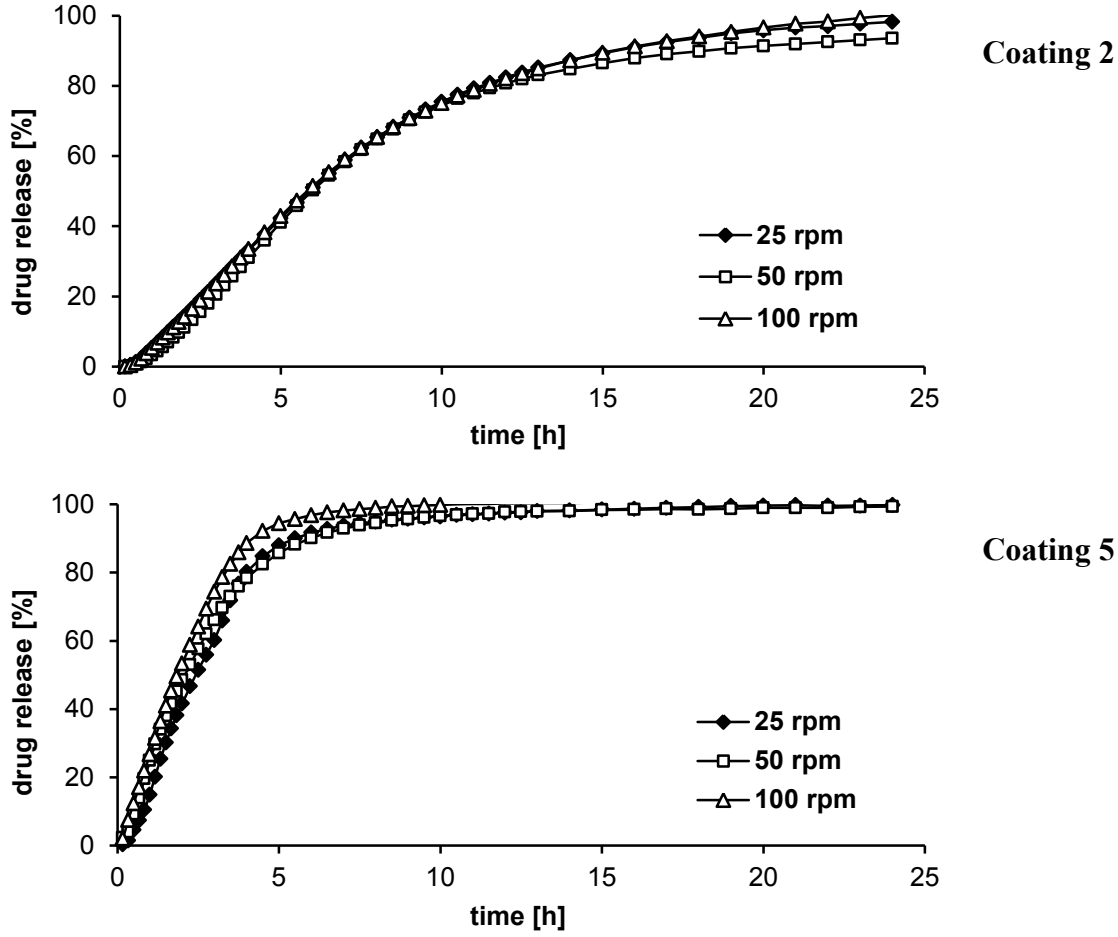


Figure 27 Influence of agitation on Metformin-HCl release in SGF using different stirring speeds of the paddles (25, 50 and 100 rpm); (Coating 2: Coating polymer poly(vinyl acetate) (Ph. Eur.; Kollicoat® SR); Coating 5: Coating polymer ammonio methacrylate copolymer, type A (Ph. Eur.; Eudragit® RL)).

Samples of tablets coated with Coating 2 and 5 were analysed using a texture analyser to monitor the behaviour of the balloon tablets under direct mechanical stress (see 2.8). A punch of 10 mm in diameter was used with a force of 2.4 N (around 300 mbar) because of its physiological relevance within the human stomach (Garbacz et al., 2010). Figure 28 shows the process of stability testing of tablet E/ Coating 2 using the texture analyser. During the force action, the entrapped gas left the balloon tablet which became flat after compression. The tablet sank to the vessel bottom after transfer to the buffer medium. After a short FLT, the tablet showed a surprising fast recovery and started to float again. The time which was needed from the tablet to float again after compression after different time intervals of buffer contact, can be seen in Table 21 for both formulations in SGF and phosphate buffer pH 4.5. Tablets with Coating 2 and 5 showed a recovery after 2 and 4 h of buffer contact in both buffers whereas only tablets E/ Coating 2 in SGF were still floating after compression after 8 hours of buffer contact. Again, an influence of the buffer pH could be monitored. Tablets E/ Coating 2 in phosphate buffer pH 4.5 showed only a slow recovery after stability testing at 4 hours and did not float any more after stability testing at 6 hours. Tablets E/ Coating 2 seemed more stable and

robust at all. There were no visible cracks within the coating or loss of tablet core material which could be observed in the case of Tablets E/ Coating 5 after 4 – 6 hours of buffer contact (see Figure 29).

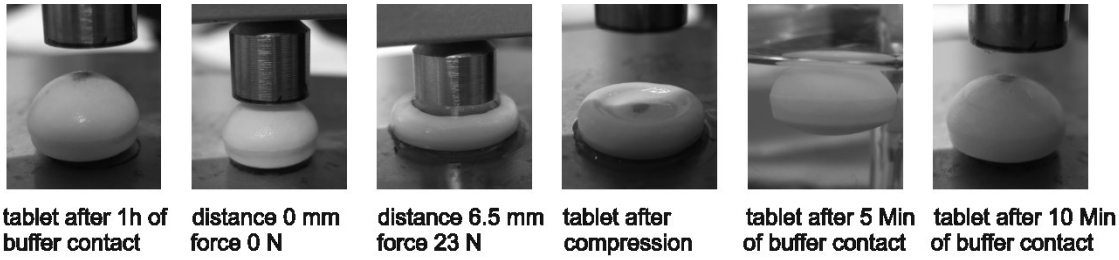


Figure 28 Procedure of stability testing of a tablet coated with poly(vinyl acetate) using texture analyser.

Table 21 Floating lag time of 2-layer tablets E after texture analyser procedure after different time intervals of buffer contact in simulated gastric fluid (SGF) or phosphate buffer pH 4.5.; Coating 2: Coating polymer poly(vinyl acetate) (Ph. Eur.; Kollicoat® SR); Coating 5: Coating polymer ammonio methacrylate copolymer, type A (Ph. Eur.; Eudragit® RL); n.f.: not floating; broken: crack within coating/ loss of tablet core material.

	Time of buffer contact previous to stability testing			
Coating/ buffer	**2 h**	**4 h**	**6 h**	**8 h**
Coating 2/ SGF	0 min	0.2 min	0.1 min	0 min
Coating 2/ pH 4.5	2 min	30 min	n.f.	n.f.
Coating 5/ SGF	0.6 min	8 min	n.f.; broken	n.f.
Coating 5/ pH 4.5	0 min	2 min	0; broken	n.f.

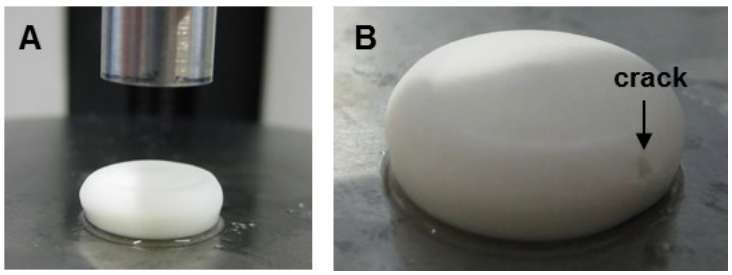


Figure 29 2-layer tablet E coated with methacrylate polymer and incubated for 6 hours in phosphate buffer pH 4.5 after texture analyser procedure.
A: tablet after compression;
B: enlargement of compressed tablet, the arrow marks a visible crack, tablet was still floating afterwards but tablet core material was lost.

To analyse the influence of similar harsh conditions on the drug release, tablets E/ Coating 2 were tested using a stress test apparatus (see 2.5.2, Garbacz et. al., 2008). The results can be seen in Figure 30. It was shown that the floating behaviour and the drug release of the tablets during the test were depending on used pressure strength and buffer pH. A pressure of 300 mbar during testing is similar to the pressure conditions used during the texture analysis. A burst release could be observed during the pressure wave procedures independent from applied

pressure strengths and pH of surrounding buffer while the drug release was controlled between the pressure waves. The tablets did not float after the first pressure cycle when buffer pH 4.5 was used as dissolution medium. Under a reduced pressure of 100 mbar, the influence on the drug release was less pronounced and tablets continued floating for around 3 hours. In SGF, tablets did recover after the pressure waves and started floating again until the pressure sequence after 6 hours of buffer contact. No loss of tablet core material could be observed. The coated tablets were optically intact but nearly deflated after 12 hours of analysis. Although the drug release was increased when the DST method was used compared to USP dissolution method, there was no observation of complete drug dissolution within the pressure wave procedures. These stress tests applied a very high pressure on the tablets which could occur within the fasted human stomach during the so-called "housekeeping waves". Therefore, it could be shown that even under this high pressure, the tablets showed a reasonable stability concerning drug release and floating behaviour. This finding can be attributed to the embedding of the drug into a polymer matrix where the drug release is controlled even when the tablet coating shows defects in tightness. The fast recovery of the tablets after the pressure procedure might be caused by the self-healing properties of the coating formulation which was described in literature before (Ensslin et al., 2009). Nevertheless, it might be that the stability and elasticity of the coating are pH dependent. Further elasticity analyses of coating membranes, which were hydrated in buffers of different pH, have to be carried out using texture analyser to investigate this finding for both coating formulations.

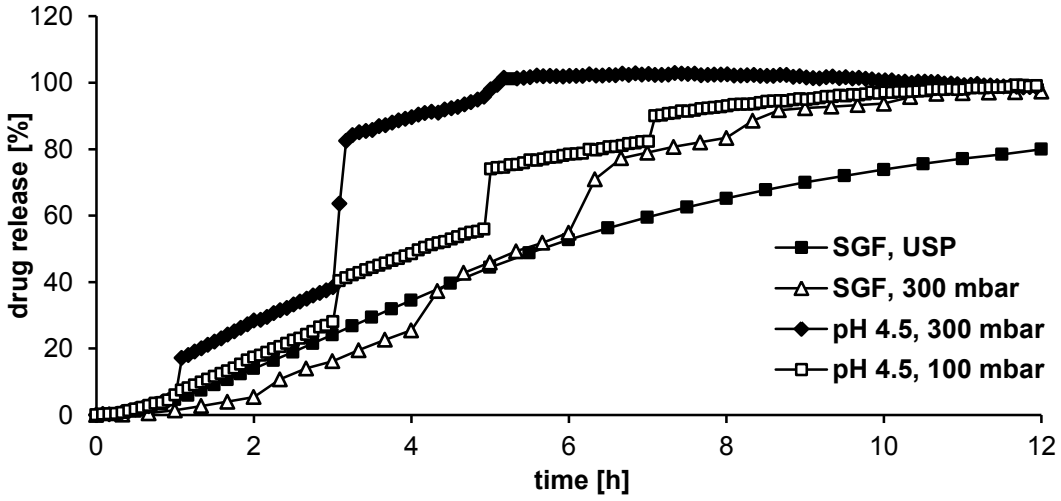


Figure 30 Influence of dissolution method, buffer pH and pressure on Metformin-HCl release of 2-layer tablets E/ Coating 2 using USP dissolution apparatus and stress test apparatus [Garbacz et al., 2008; phases of mechanic stress caused by pressure waves were applied after 1h, 3h, 5h, 7h and 9 h (pH 4.5) or after 2h, 4h, 6h and 8 h (SGF) by three symmetric pressure waves of 6 s duration and a magnitude of 100/ 300 mbar]. USP: dissolution studies were carried out using USP dissolution apparatus; other graphs: stress test apparatus was used; SGF: simulated gastric fluid; pH 4.5: phosphate buffer pH 4.5 Ph. Eur.

3.1.8 Influence of buffer pH on water uptake behaviour and carbon dioxide generation of coated 2-layer tablets

The floating strength and duration of tablets E over time of buffer contact was found to be strongly dependent from pH of surrounding buffer as can be seen in Figure 13, while the FLT showed to be independent from pH of surrounding buffer. One possible explanation for this behaviour could be osmotic effects of the different buffers leading to different water uptake inside the tablet core. To analyze the influence of osmotic effects on the floating behavior of 2-layer tablets E, buffers with same pH but different osmotic strength were used. A 0.1 M HCl solution was used as release medium in comparison to SGF buffer. Furthermore, drug release in phosphate buffer pH 4.5 with and without sodium chloride addition was analyzed. No noteworthy influence of the osmotic pressure on the floating characteristics could be detected.

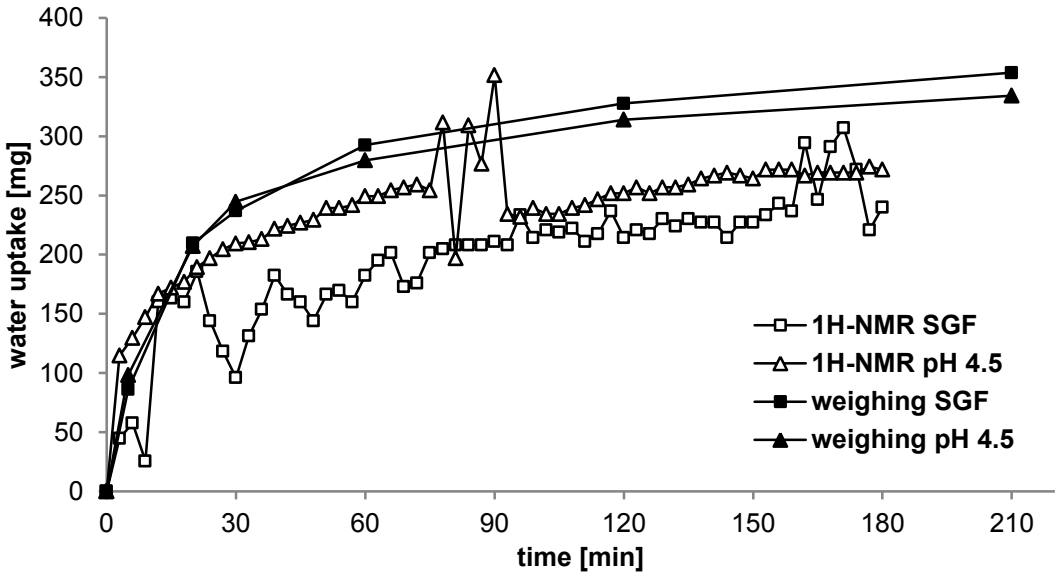


Figure 31 Determination of water uptake behaviour of coated 2-layer tablets E in buffers of different pH over time of buffer contact by means of weighing and ^{1}H NMR; SGF: water uptake [mg] in simulated gastric fluid pH 1.2; pH 4.5: water uptake [mg] in phosphate buffer pH 4.5 Ph. Eur.

Therefore, different experiments were carried out to clarify the source of pH dependence on the floating behaviour. As one aspect, the water uptake behaviour of coated 2-layer tablets E was determined in buffers of different pH over time of buffer contact by means of weighing and ^{1}H NMR (see 2.9). If more water would penetrate into the tablet core dependent from pH of surrounding buffer, the density of the tablet would increase which might lead to a sinking of the tablets. Figure 31 illustrates, that the water uptake of 2-layer tablets E in buffers of different pH was comparable independent from the method which has been used (weighing or ^{1}H NMR). The water permeability of the coating seems to be independent from pH of surrounding buffer. Furthermore, the results of both methods were comparable as well. The determination of water uptake by weighing generated slightly higher values which could be caused by the additional detection of free water on the tablet surface. Another disadvantage of this method was the

transfer of the tablets from the buffer to the balance which might have caused damage to the balloon-like tablet and therewith associated loss of penetrated water. In contrast, it was possible to generate numerous data of the free water amount over time of buffer contact without direct contact to the analyzed tablets by using ^{1}H NMR. The values which were generated by ^{1}H NMR showed some fluctuations at different time points of buffer contact which might be caused by a tablet movement (rising or sinking of the tablets inside the test tube) during the measurements.

$$NaHCO_3(aq) + H_3O^+(aq) \leftrightarrow H_2CO_3 + H_2O + Na^+ \leftrightarrow CO_2\uparrow + 2H_2O + Na^+(aq) \quad \textit{Equation 1}$$

The effervescent reaction of sodium hydrogen carbonate in water to carbon dioxide and water is only possible under acidic conditions (see Equation 1). Therefore, the extent of carbon dioxide generation is dependent from surrounding pH. As more acidic the buffer is, as more is the equilibration state shifted to the formation of carbon dioxide. Therefore, the influence of buffer pH on amount of generated carbon dioxide within coated 2-layer tablets E was evaluated using a precipitation reaction (see 2.10). The amount barium carbonate which could be recovered after reaction of 2-layer tablets E in phosphate buffer pH 4.5 Ph. Eur. (mean 53,7 mg, SD 5,3 mg) was only around 66 % of the recovered amount after reaction of 2-layer tablets E in SGF (mean: 81,8 mg; SD 18,3 mg). These finding might be a hint that an uncompleted and/or retarded carbon dioxide generation could be responsible for the sinking of coated 2-layer tablets E after some hours of buffer contact in phosphate buffer pH 4.5 and 6.0. Nevertheless, the construction of the reaction setting allowed no complete recovery of formed carbon dioxide because of leakage and carbon dioxide loss in the beginning of the experiments. Furthermore, the carbon dioxide did not pass completely to the Barium hydroxide solution. The detection of the endpoint of the carbon dioxide formation was challenging as well. Therefore, all experiments were abandoned after 15 minutes of reaction time. This method was not suitable to allow a safe complete determination of generated carbon dioxide amount. Different analytical settings would be necessary to confirm the assumption of an incomplete carbon dioxide formation in buffers of pH $\geq$ 4.5. Furthermore, analysis of internal pH within tablet core should be accomplished to gain information about pH conditions inside the tablet during time of hydration.

3.1.9 Optimisation of tablet core of coated 2-layer tablets regarding pH independent floating duration

Different formulation experiments were carried out to achieve a pH independent floating duration for coated 2-layer tablets.

To analyze, if the composition of the floating layer is able to change the floating behavior of 2-layer tablets in phosphate buffer of pH 4.5 and 6.0, an optimized stoichiometric ratio of sodium

hydrogen carbonate and citric acid was evaluated according to Krögel and Bodmeier, 1999/ Anderson et al., 1982. The floating behavior of resulting 2-layer tablets F changed for the worse. The floating duration of tablets F was below 3 hours even in SGF (see Table 22). Thereupon, new drug layer formulations with an additional small amount of sodium hydrogen carbonate and citric acid and 10 %/ 20 % of HPMC 15.000 were developed (2-layer tablets G/H). These formulations were analyzed for their ability to trap some of the carbon dioxide which is formed during hydration within the tablet core.

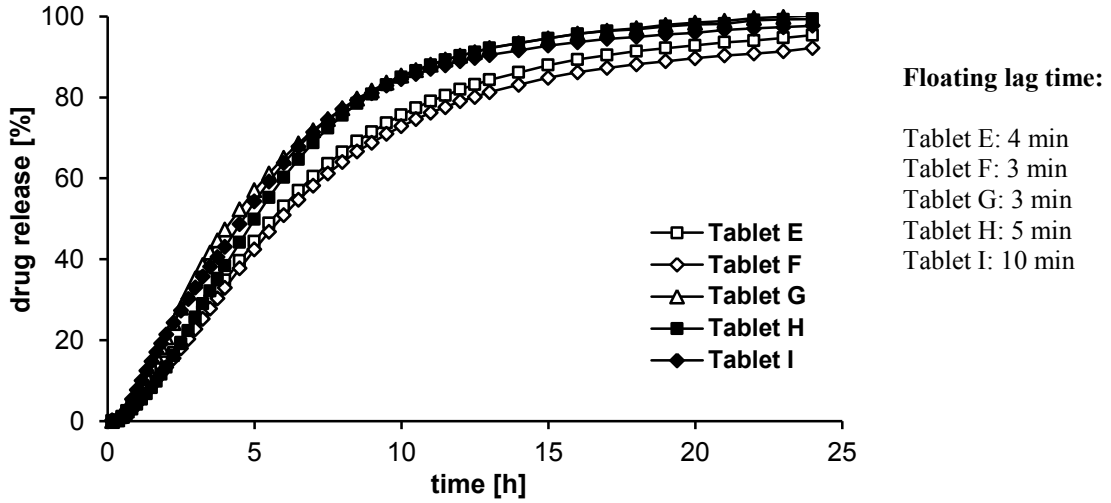
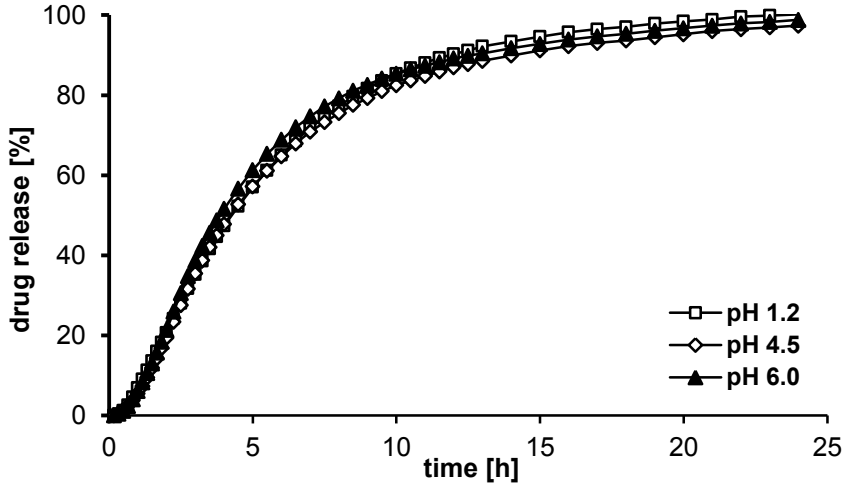


Figure 32 Influence of tablet core composition on Metformin-HCl release and floating characteristics. Tablet E: 2-layer tablet core (DL1/FL3); Tablet F: 2-layer tablet core (DL1/FL4); Tablet G: 2-layer tablet core (DL2/FL3); Tablet H: 2-layer tablet core (DL3/FL3); Tablet I: 2-layer tablet core (DL4/FL3).

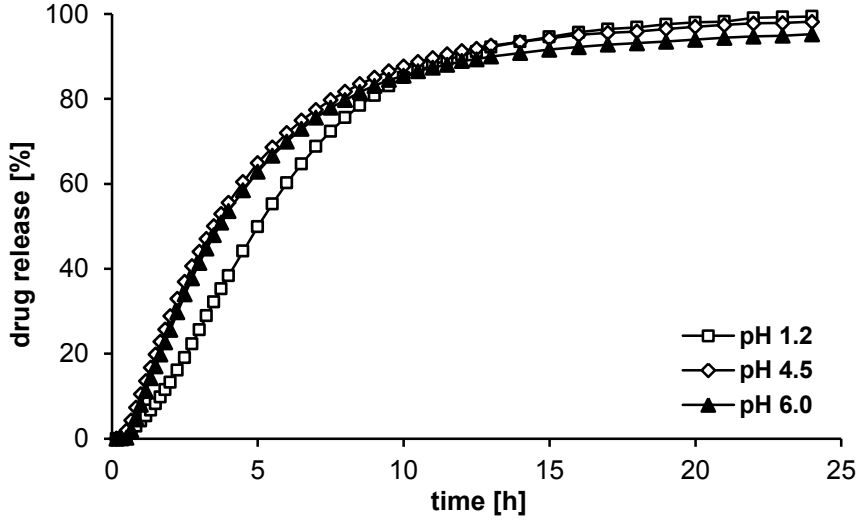
The Metformin-HCl release of both formulations was slightly increased compared to the release of tablets E (see Figure 32). The formation of holes within the coating was observed for both formulations. The holes were plugged with gel, formed by the incorporated HPMC 15.000. Although these observations of coating instabilities, most tablets G and H floated for more than 24 hours in SGF, phosphate buffer pH 4.5 and 6.0 (see Table 22). The drug release of formulation G was not influenced by pH of surrounding buffer (Figure 33a) while the release of Metformin HCl was slower at pH 1.2 than at pH 4.5 and 6.0 for formulation H (Figure 33b). This finding might be caused by osmotic effects of the different buffer preparations which influenced the gel formation. The floating behavior of tablets H seemed to be more stable compared to the floating behavior of tablets G (some tablets sank to the vessel bottom after around 3 hours of buffer contact for a short while). Because of the higher amount of gel forming HPMC, the formulation H might be able to compensate holes within the coating more effectively with a more viscous gel.



a)

Floating lag time:

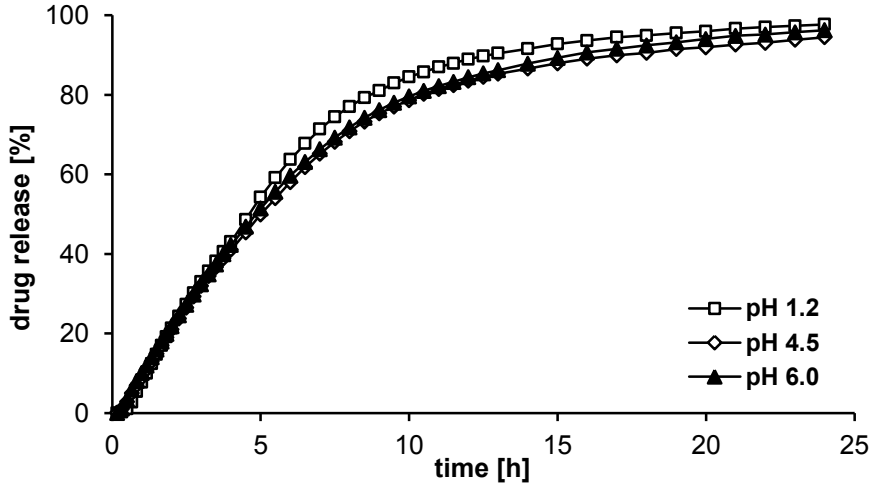
pH 1.2: 3 min
pH 4.5: 2 min
pH 6.0: 3 min



b)

Floating lag time:

pH 1.2: 5 min
pH 4.5: 4 min
pH 6.0: 7 min



c)

Floating lag time:

pH 1.2: 10 min
pH 4.5: 8 min
pH 6.0: 8 min

Figure 33 Influence of buffer pH on Metformin-HCl release and floating behaviour of different 2-layer tablet formulations .
a) 2-layer tablets G; b) 2-layer tablets H; c) 2-layer tablets I

10 % of citric acid were incorporated within drug layer of tablets I to acidify the internal pH of the tablets upon hydration. These tablets showed again a slightly enhanced drug release (less matrix-forming Kollidon SR; see Figure 32) compared to tablets E. The floating lag time of tablets I was enhanced compared to tablets E. Nevertheless, these tablets showed a floating duration of more than 24 hours in all 3 buffers (see Table 22) without the formation of visible holes within the coating or loss of tablet core material. The release of Metformin HCl out of formulation I was very slightly enhanced at pH 1.2 compared to the release at pH 4.5 and 6.0 (see Figure 33c). Although this formulation seems promising, further analysis will be necessary to gain more information on the effect of the different internal pH on the elasticity of coating membrane and floating duration of Tablets I as well as on the robustness of the inflated tablets using dissolution stress apparatus and texture analyser. Other topics of interest would be the comparison of floating strength in buffers of different pH over timer of buffer contact and a carbon dioxide quantification related to the pH of surrounding buffers.

Table 22 Floating duration of tablets E-I in buffers of different pH.

Tablet formulation	FD in SGF	FD in phosphate buffer pH 4.5	FD in phosphate buffer pH 6.0
2-layer tablet E	> 24 h	< 4 h	< 2 h
2-layer tablet F	< 3 h	-	-
2-layer tablet G	> 24 h	> 24 h	> 24 h (2/3)
2-layer tablet H	> 24 h	> 24 h	> 24 h
2-layer tablet I	> 24 h	> 24 h (2/3)	> 24 h

3.2 Monitoring of microenvironmental pH within non-floating matrix tablets for analytical method establishment

The microenvironmental pH within multi-layer tablets should be monitored to enable the development of a formulation with suitable microacidity for an optimised, pH independent release of Cefdinir. Therefore, analytical methods for the determination of microacidity had to be established (Eisenächer et al., 2011). Non-floating 2- and 3-layer tablets were used for method establishment. Multi-layer tablets can be used for different purposes. It is possible to separate incompatible substances as well as to combine immediate- and prolonged- release profiles of an active compound. Furthermore, floating multi-layer tablets for gastric retention can be found in literature, consisting of a floating and a drug-containing tablet layer (Ingani et al., 1986; Wei et al., 2001; Rahman et al., 2006 and introduced multi-layer formulations within this work). The aim of this study was to investigate the influence of (1) the presence or absence of pH modifying substances within tablet layers, (2) the variation of matrix forming excipients, (3) the variation of the pH of surrounding buffer and (4) the incorporation of an additional

lipophilic inter layer on the pH_M within multi-layer tablets. The influence of the pH_M on the drug release of two model drugs, Metformin-HCl and Ketoprofen, was also analysed. An internal buffer system (IBS) composed of citric acid and disodium hydrogenphosphate was used as pH modifier. The IBS was incorporated in one or two tablet layers to generate a pH_M gradient within the tablets. Furthermore, different matrix forming excipients were analysed for their ability to maintain a specified pH_M over time of buffer contact. Hydroxypropylmethyl cellulose (HPMC) was analysed as most frequently used hydrophilic polymer which is able to form hydrogel matrices upon contact with water. HPMC is a non-ionic cellulose ether forming a stable hydrogel over the pH range of 3-11. Kollidon SR, which was describes before (see 1.5), was used as well. Three different techniques were used to determine the pH_M within multi-layer tablets for comparison of results regarding application spectrum and expenses, in particular, a pH indicator dye, fluorescence imaging and EPR imaging. In addition to the analysis of the pH_M, the hydration behaviour of 2- and 3-layer tablets was monitored using nuclear magnetic resonance imaging (NMR-imaging/ MRI) in order to gain a deeper insight on hydration and erosion processes during contact with buffer. MRI has proven to be a non-invasive, well established method to investigate drug delivery systems in vitro and in vivo (Richardson et al., 2005; Metz and Mäder, 2008; Nott, 2010). A commercial, low-cost benchtop MRI (BT-MRI) system was used as alternative to common superconducting MRI machines. Recently, BT-MRI has been successfully used to characterise different solid drug delivery devices (Metz et al., 2007; Strübing et al., 2008a,b; Malaterre et al., 2009). Therefore, BT-MRI was intended to provide detailed information about the differences in the hydration behaviour of 2- and 3-layer tablets.

3.2.1 Microacidity measurements using a pH indicator dye

The microenvironmental pH of hydrated multi-layer matrix tablets was visualised using the pH indicator bromcresol purple with a transition pH range of 5.2 to 6.8 (see Figure 34) and a colour change from yellow to purple. This dye was used to differentiate between tablet layers which assumed the pH of the surrounding buffer and areas with incorporated IBS (Na_2HPO_4/citric acid). The tablet layers with incorporated IBS were supposed to generate a pH_M of around 6 upon hydration while the pH of the surrounding buffer was 3 which enabled the monitoring of different colours depending on presence or absence of IBS. In addition, the colour change from yellow to purple could be easily monitored. Figure 35 shows the difference in colour generation over the pH range of 4 to 8 depending on used polymer. For this purpose, tablets consisting of pure Kollidon SR and pure HPMC with incorporated pH indicator dye were prepared and allowed to equilibrate in buffers of different pH for around 3 hours. Pictures of the hydrated tablets were taken to allow a more precise pH_M estimation of the different tablet layers.

Figure 34 Colour gradients of pH indicator dye bromcresol purple in buffers of different pH.

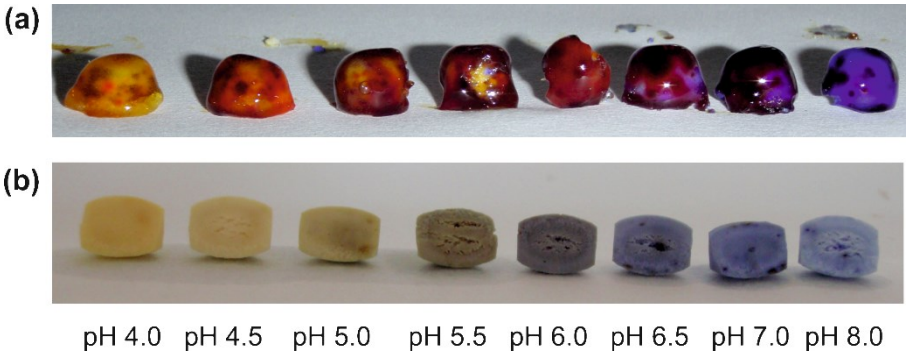


*Figure 35 Colour gradients of tablets with incorporated pH indicator dye bromcresol purple in buffers of different pH **(a)** HPMC tablets. **(b)** Kollidon SR tablets.*

Photographs of tablets **A-F** as whole and cross-sectioned after defined time intervals of contact with buffer are shown in Figure 36. After 10 minutes of buffer contact, a differentiation between formulation **A, B** and **C** and **D, E** and **F** is easily possible. The HPMC-P and KSR-P layer of tablets **A** and **D** turned purple/ blue immediately after contact with buffer, indicating a pH above 5. This finding corresponded to the expectation because the IBS was incorporated into both layers. The pH_M of the exterior region of the KSR-P layer changed to yellow after 2 hours whereas the HPMC-P layer appeared mainly purple over more than 4 hours. The HPMC layer of tablets **B** and **E** (without IBS) turned yellow after contact with buffer. In the case of tablet **B**, the HPMC layer changed into purple, indicating a pH_M above 5, after 30-60 minutes of buffer contact. In contrast, the HPMC layer of tablet **E** maintained a yellow/ orange colour over the analysed time interval of 6 hours. The KSR layer of tablets **C** and **F** (without IBS) turned yellow after contact with buffer. No obvious change in colour could be observed over the analysed time. The pH indicator method allowed the differentiation between the tablet formulations because of their differences in local pH and therewith associated colour changes. Furthermore, it was possible to monitor the shifting of pH_M within the tablet layers over time of buffer contact and to observe differences in the pH_M shifts of 2- and 3-layer tablets. Nevertheless, this technique allowed only a very rough determination of the pH_M. It was rather difficult to relate a specified pH value to the colour grading of the indicator. Colours indicating same pH appeared different in both matrix forming excipients (HPMC and KSR). In addition, to investigate the pH_M in the interior of the tablet, the tablet had to be cut. It was therefore not possible to analyse the pH_M of one tablet continuously.

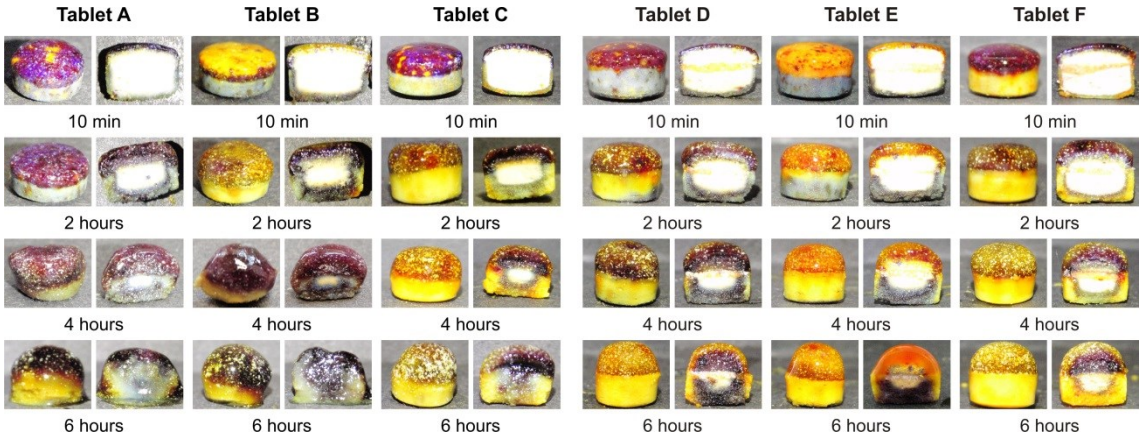


*Figure 36 Images and cross-sectional images of hydrated matrices of tablets **A-F** with incorporated pH indicator dye bromcresol purple after different time intervals of contact with buffer pH 3. Tablets were always placed with the HPMC layer on top and the KSR layer as bottom side. Purple domains indicate a pH >5, yellow domains indicate a pH < 4.5. The dry core appeared white.*

3.2.2 Microacidity measurements using multispectral fluorescence imaging

Multispectral fluorescence imaging of 2-layer tablets was accomplished (see 2.12) to analyse the pH_M of the tablet surface by means of a hydrophilic fluorescence dye. The emission spectrum of this dye undergoes a pH-dependent wave length shift (see Figure 37 (a)). pH_M values could be calculated independently from the intensities for a pH range from pH 5 to 8 by using a calibration curve (see Figure 37 (b); Schädlich et al., 2009). Pseudo-coloured fluorescence images and corresponding pH_M values of both tablet layers of tablets **A, B** and **C** are illustrated in Figure 38. The pH_M of both layers of tablet **A** showed values between pH 6.5 and 7.5 over more than 6 hours. Higher pH_M values were detected within the HPMC-P layer compared to the KSR-P layer. The pH_M of the HPMC layer of tablet **B** increased from a predominantly acidic environment below the dye detection limit of pH 5 to values above pH 6 after about 3 hours of contact with buffer (see Figure 38 (B)). The pH_M shifting was delayed in comparison with the pH indicator results. This observation can be explained by the hindered hydration of the tablets from only two dimensions (see 2.13). The pH_M of the KSR layer of tablet **C** remained below pH 5 over more than 6 hours (see Figure 38 (C)). Fluorescence imaging gave the opportunity to calculate an average pH_M of an estimated domain of each tablet layer using a fluorescence dye with pH dependent changes in the emission spectra. Similar pH gradients were detected compared to the results of the aforementioned method. However, a different hydration setting had to be used to allow a constant measuring area which changed and delayed the hydration process and made comparison with other results rather difficult. Higher pH_M values were detected within the HPMC-P layer compared to the KSR-P layer of tablet **A** (same amount of IBS in both layers). The usage of different excipients could have an impact on the emission spectrum. The influence of the nature of excipient on the pH_M calculation was therefore analysed by fluorescence imaging. Kollidon SR and HPMC showed no clear trend to

enhance or decrease calculated pH_M values (data not shown). A 10 % Kollidon SR suspension in water generates a pH around 4.6 which also influences the resulting pH_M. Furthermore, the photographs of pH-indicator containing tablets showed a yellow discolouration of the surface of the previously blue KSR-P layer after one to two hours (see Figure 36). In contrast, the colour of the HPMC-P layer changed only marginally. With fluorescence imaging, it was only possible to analyse the pH_M of the surface of the tablets because of the limited penetration depth of the excitation and emission light. The pH_M of the surface of the tablet could differ from those of the inner regions which can also contribute to the monitored differences.

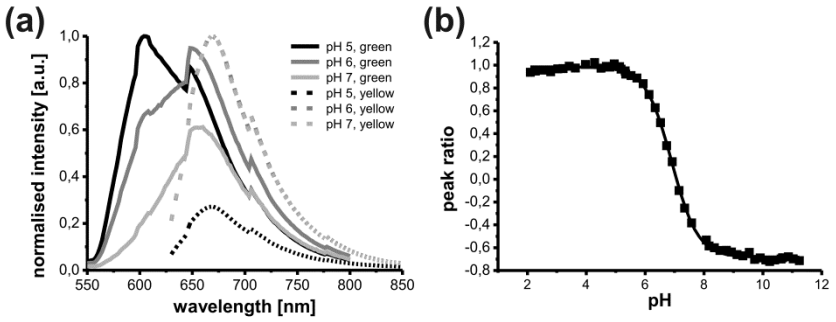


Figure 37 (a) pH-dependent wave length shift of the emission spectrum of the fluorescence dye Carboxy SNARF®-1. A green and a yellow filter set were used. (b) pH sensitivity of the peak ratio of Carboxy SNARF®-1.

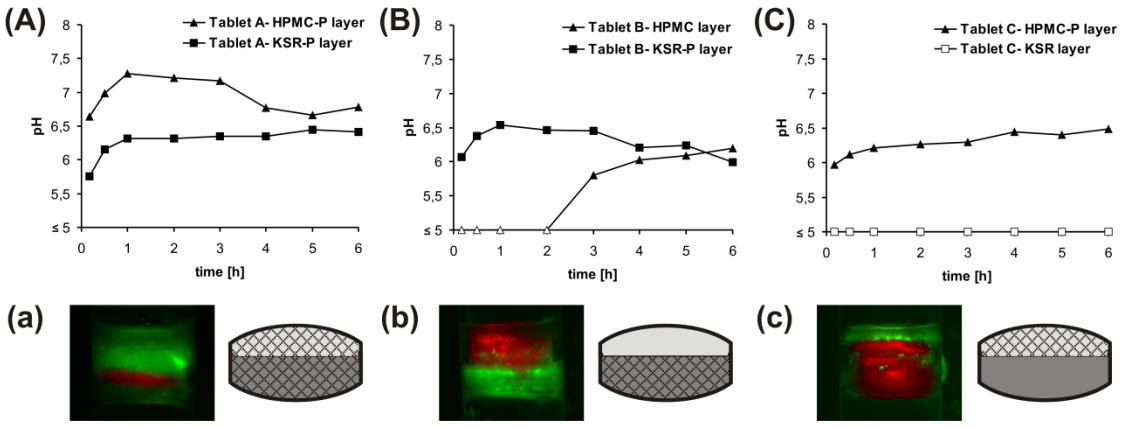


Figure 38 ***(A-C)*** *Mean pH_M values of the surface of both layers of tablets* ***A, B*** *and* ***C*** *from one dimension at different time intervals of contact with buffer pH 3. No values could be determined for areas with a pH < 5 (empty symbols).* ***(a-c)*** *Pseudo-coloured fluorescence images and corresponding schemata of tablets* ***A, B*** *and* ***C*** *after 30 min of buffer contact, red domains symbolise dry and acidic regions (pH < 5), green domains symbolise a nearly neutral pH_M (pH > 6).*

3.2.3 Microacidity measurements using spatial spectral EPR imaging

EPR imaging provides the possibility to obtain spatial information about the pH_M within whole tablets non-invasively (see 2.14). The average pH_M of hydrated inner and outer regions of different cylindrical layers of the tablet can be calculated giving a spatial pH_M resolution from top to the bottom of the tablet. For the investigation of the pH_M by EPR imaging, the stable nitroxide radical 4-Amino-2.2.5.5-tetra-methyl-3-imidazoline-1-oxyl (AT) was used as pH-sensitive spin probe. Protonation of pH-sensitive spin probes leads to changes in the spin density of the nitroxide group (see Figure 39 (b)) and therewith associated changes in the EPR spectra depending on pH (see Figure 39 (a); Khramtsov et al., 1982). In particular, the distance of the first to the third peak ($2a_N$, where a_N is the isotropic hyperfine splitting constant) changes with changing pH of the surrounding buffer. Thus, a quantification of pH is possible by means of a calibration curve of $2a_N$ against buffer pH (Kempe et al., 2010). The pH dependency of the EPR signal of the spin probe AT follows a sigmoid dependence (see Figure 39 (b)). Therefore, the pH_M calculation is only possible in a limited pH range of about ± 1.5 pH units depending of the pK_a of the spin probe (pK_a of AT is 6.1). Other spin probes having different pK_a values can be used to analyse different pH ranges.

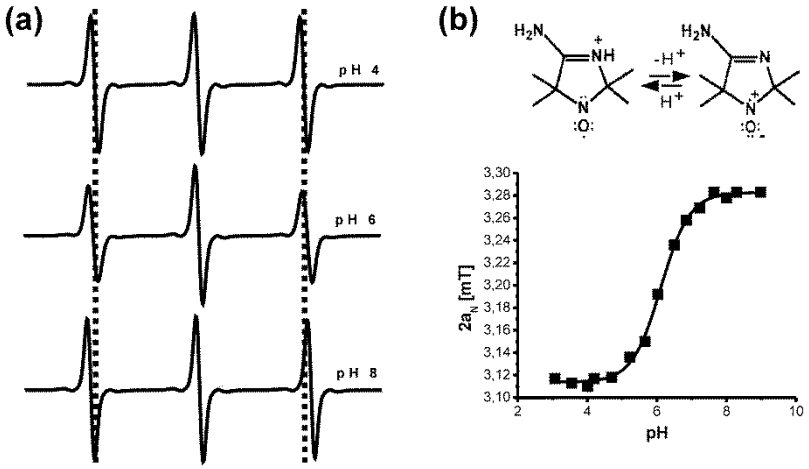


Figure 39 ***(a)*** *EPR spectra (first derivates) of the spin probe 4-Amino-2.2.5.5-tetra-methyl-3-imidazoline-1-oxyl (AT) at different pH values. The dashed line symbolises $2a_N$ (a_N = the hyperfine splitting constant) for the spectrum at pH 4. Note that the distance between the first and the third amplitude is larger for the nonprotonated form (pH 8).* ***(b)*** *Principle of pH sensitivity and calibration curve of AT.*

Tablets of pure HPMC and Kollidon SR with incorporated spin probe AT were exposed to buffers of different pH (same pH range as can be seen in Figure 39b) until complete hydration. The isotropic hyperfine splitting constants of the tablets were determined. Calibration curves for pH_M determination of both tablet formulations were compared to analyse the influence of matrix polymer on pH_M determination by EPRI. Both calibration curves were similar with a slight shift

of the inflexion point. Therefore, pH_M values could be determined independently from the tablet composition.

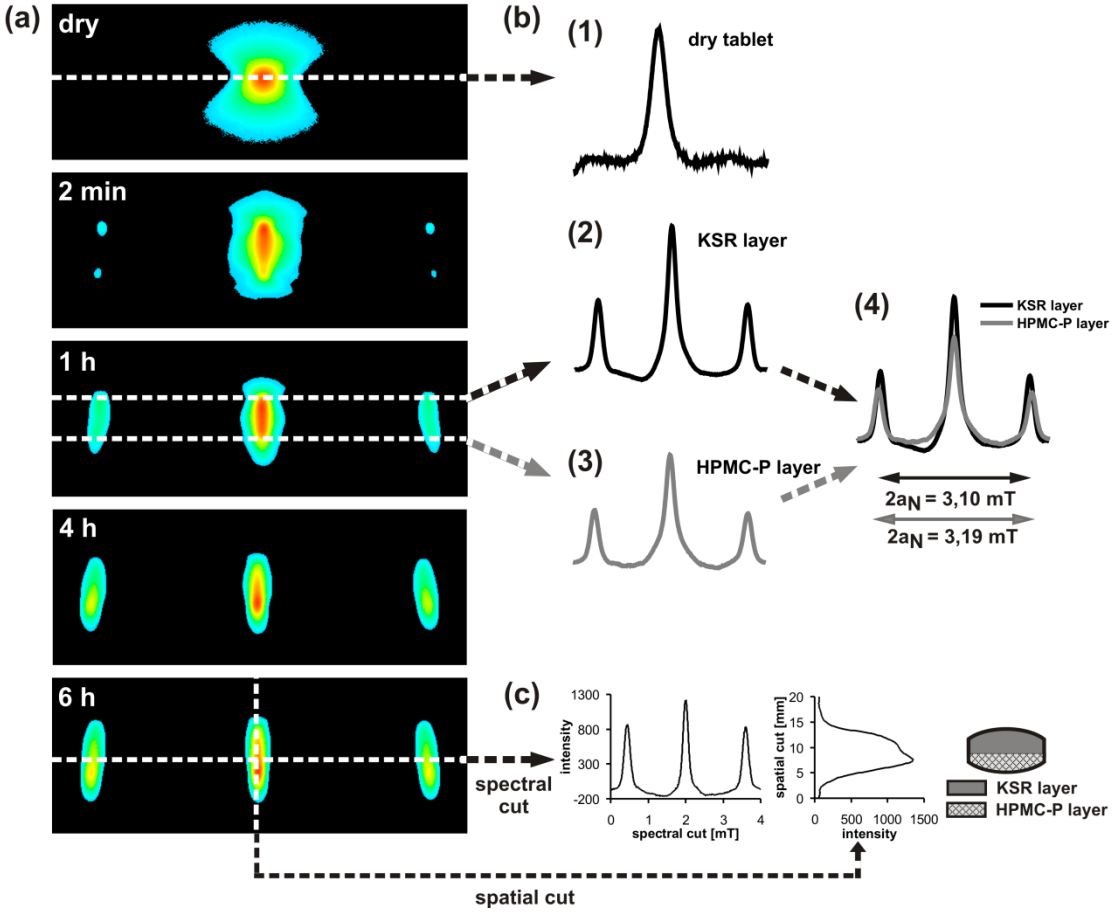


Figure 40 ***(a)*** *EPR images of AT-containing tablet* ***C*** *at different time intervals of contact with buffer pH 3.* ***(b)*** *EPR spectra which were extracted from the images of:* ***(1)****the dry tablet,* ***(2)****a region within KSR-layer after 1 h of buffer contact,* ***(3)****a region within HPMC-P-layer of the same image,* ***(4)*** *relation of spectra (2) and (3) with specified* $2a_N$. ***(c)*** *Spatial and spectral cut of tablet* ***C*** *after 6 h of buffer contact.*

Figure 40 (a) shows characteristic EPR images of tablet **C** at different time points of contact with buffer. The horizontal scale symbolises the spectral resolution (3 peaks of mobile AT) while the upright scale characterises the spatial resolution from the top to the bottom of the tablet (see Figure 40 (c)). The dry tablet shows only one central peak of the immobile spin probe. Contact with buffer led to an increase in mobility of AT in the hydrated regions, visible through the appearance of the outer isotropic hyperfine splitting (Lurie and Mäder, 2005). The proportion of mobile to immobile spin probe increased steadily with time, detecting the liquid penetration to inner tablet regions which can be observed by the increase of intensity of the isotropic hyperfine splitting. It was also possible to follow the swelling process of the tablets because of the increase in spatial signal size of the images over time. The signals indicate a pH gradient within the wet tablet which is visible by the changing distance from first to third peak (both sloped outwards). EPR spectra were extracted out of the horizontal layers of the presented

images. Figure 40 (b) shows typical EPR spectra of: (1) a dry tablet; (2) the KSR layer after 1 hour of buffer contact and (3) the HPMC-P layer of the same EPR image. By comparison of spectrum (2) and (3), a changing distance of $2a_N$ can be found (4). The hyperfine splitting value of spectrum 2 (KSR layer) was below the calculable limit, indicating a pH_M below 4.5. The calculated pH value of spectrum 3 (HPMC layer) was 6.0 which can be explained by the presence of IBS within this layer.

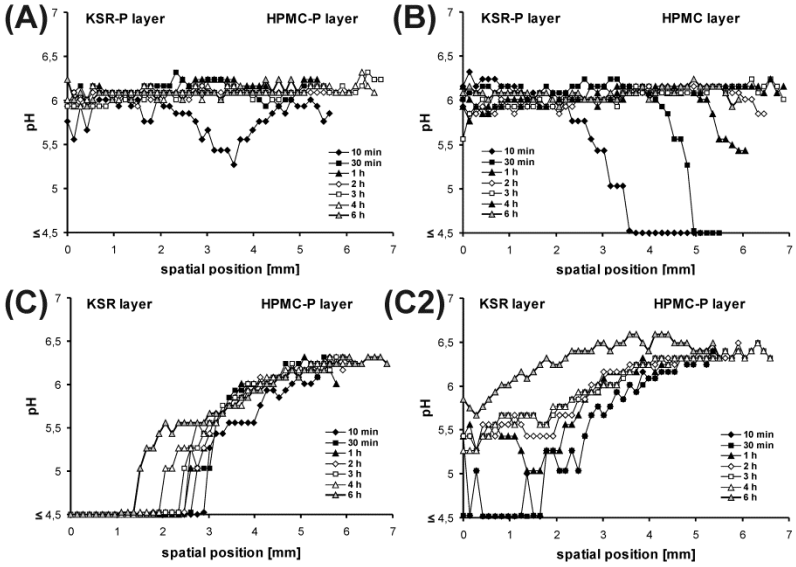


Figure 41 ***(A-C2)*** *pH_M averages within tablets **A, B** and **C** calculated from EPR images which were generated at different time intervals of contact with buffer pH 3. A buffer of pH 5.5 was used in the case of (C2). No values could be determined for areas with a $pH_M \leq 4.5$.*

Spatial resolved pH_M values extracted from the EPR images of tablets **A, B** and **C** at different time intervals of buffer contact are presented in Figure 41. The pH_M of whole tablet **A** was found to be around pH 6 for over 6 hours (see Figure 41 (A)). The HPMC layer of tablet **B** (without IBS) showed an acidic pH_M after contact with buffer but started to change to nearly neutral values after 30 minutes. After 2 hours, the complete HPMC layer showed a pH around 6 (see Figure 41 (B)). A possible reason could be the migration of IBS out of the KSR-P layer into the HPMC layer. In the case of 2- tablet **C** (without IBS), an obvious pH_M gradient over more than 6 hours of buffer contact was determined. The predominantly acidic pH_M of the KSR layer changed only marginally in the centre region of the tablet (see Figure 41 (C)). EPR imaging experiments of tablets **A**-**F** were repeated using a citric acid/ phosphate buffer of pH 5.5 to gain information of the influence of the pH of the surrounding buffer on the pH_M. Similar results concerning the formation of pH_M gradients within tablets over time of buffer contact were obtained. The pH of the buffer strongly influenced the internal pH of tablet layers without IBS. Almost no influence could be monitored in the case of tablet layers with IBS (see Figure 41 (C2)). Figure 41 (C2) shows the pH_M gradients within tablet **C** during contact with buffer pH 5.5. Interestingly, the pH_M of the KSR layer underlay the pH of the surrounding buffer up to 1

hour of buffer contact. A 10 % Kollidon SR suspension in water generates a pH of about 4.6. Thus, Kollidon SR could cause the more acidic pH_M. After 1 hour, the KSR layer assumed the pH of the external buffer. The pH_M increased to values above pH 6 after 6 hours of buffer contact, possibly caused by the penetration of HPMC-P gel of low viscosity.

3-layer tablets with an additional inter layer were analysed subsequently. The inter layer was added to enhance the integrity of both layers as well as to decrease diffusion processes between the layers. Figure 42 demonstrates the differences in the EPR images of a 2- and a 3-layer tablet. The image of the 2-layer tablet **C** shows one homogeneous central signal. The central signal of the image of the 3-layer tablet **F** shows two separate areas of high intensity (red colour/ dark grey). This difference is also obvious in the intensity profiles I in Figure 42 (b). The signal interruption of I_2 was caused by the lipophilic inter layer without spin probe. The transition of HPMC-P to KSR layer could be considerably monitored within the outer signals of image F because of a visible change of the distance of the first to the third peak ($2a_N$). Intensity profiles II and III illustrate a gradient within the right signal which is sloped outwards, thus indicating a pH_M gradient within the tablets.

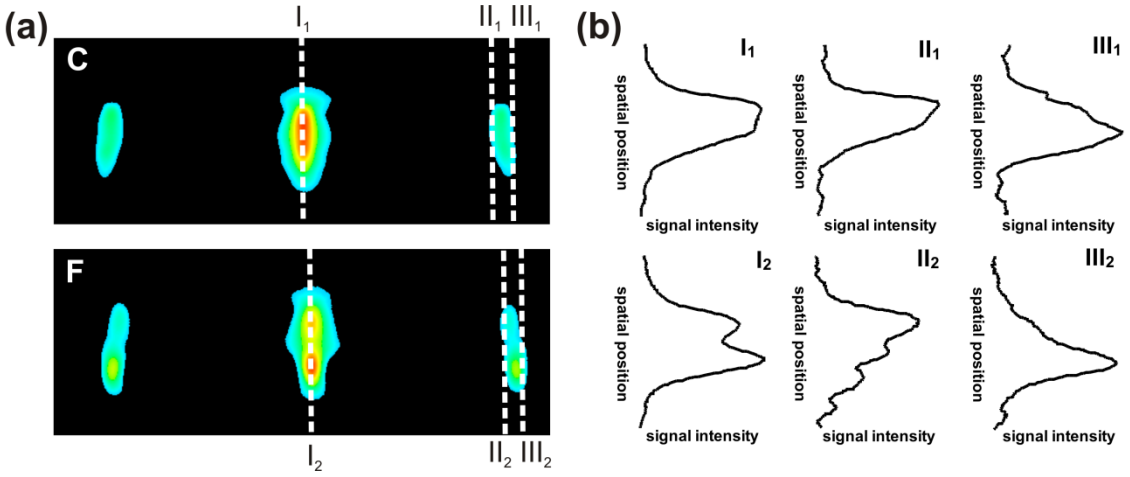


Figure 42 ***(a)*** *EPR images of tablets after 1 h of contact with buffer pH 3, the dotted lines show the position of the intensity profiles displayed in (b).Image* ***C****: 2-layer tablet* ***C****. Image* ***F****: 3-layer tablet* ***F****.****(b)*** *intensity profiles of the EPR signal of:* ***(I)*** *the central peak;* ***(II)*** *the left region of the right peak;* ***(III)*** *the right region of the right peak.*

pH_M profiles of tablets **D-F** over 6 hours of buffer contact are presented in Figure 43 (D-F). Tablet **D** showed similar results like tablet **A**. The pH_M of the HPMC-P and the KSR-P layer laid around pH 6 over the analysed time interval. The HPMC layer of tablet **E** maintained an acidic pH_M over 6 hours, which was different compared to tablet **B**. The inter layer of GMS seemed to hinder the approximation of pH_M of both layers. The protective character of the inter layer became also apparent in the case of tablet **F**. A sharp increase of the pH_M separates the acidic values of the KSR layer (under detection limit) from the nearly neutral values of the HPMC-P layer over more than 6 hours of buffer contact, confirming the protective character of

the inter layer (see Figure 43 (F)). The slight displacement over time may be caused by the swelling of the KSR layer. This finding could also be valuable to separate drugs with different pH stability optima by the usage of multi-layer tablets with an additional lipophilic inter layer. However, the pH_M of the KSR layer of tablet **C** increased only marginally in the centre region of the tablet as well, which was different from the behaviour of the HPMC layer of tablet **B**. The different behaviour of both matrix-forming excipients might possibly be caused by a faster water exchange within the KSR layer in comparison to the HPMC layer. Furthermore, the acidic behaviour of Kollidon SR seems to have an influence on the pH_M generation as well.

Although the analysis with this technique was time consuming, it gave unique information about the internal pH within analysed tablets and made a continuous measurement of one tablet over time of hydration possible. Furthermore, no influence of the nature of surrounding matrix material on the resulting $2a_N$ values could be detected (comparison of calibration curves of pure HPMC/ Kollidon SR tablets). However, the pH_M calculation is only possible in a limited pH interval of about ± 1.5 pH units depending of the pK_a of the spin probe ($pK_a$of AT is 6.1). Therefore, no pH_M values could be calculated in tablet regions showing a pH_M below 4.5. It is possible to investigate the pH_M within more acidic regions of the tablets by using spin probes having lower pK_a-values.

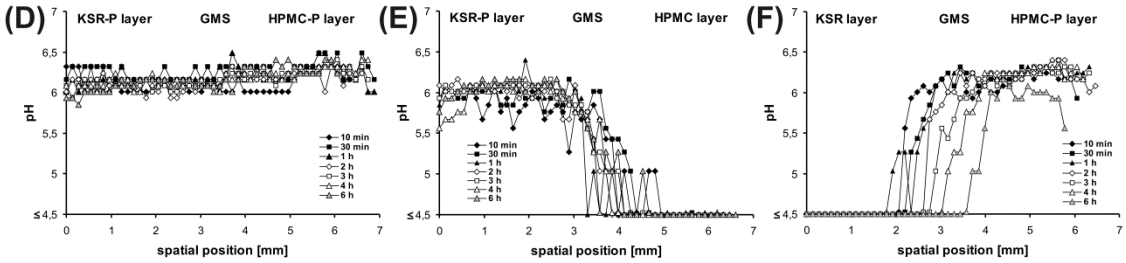


Figure 43 ***(D-F)*** *pH_M averages within tablet* ***D, E*** *and* ***F*** *calculated from EPR images which were generated at different time intervals of contact with buffer pH 3. No values could be determined for areas with a $pH_M \leq 4.5$.*

3.2.4 Influence of the microenvironmental pH on the drug release

Dissolution studies of two model drugs were carried out to investigate the influence of the pH_M on the drug release. These drugs were incorporated into the KSR/ KSR-P layer of tablet **E/F** (with and without IBS). The anti-diabetic drug Metformin-HCl was used as freely soluble model drug showing pH independent release behaviour. Primarily, the drug release from 2-layer tablets was analysed. Unfortunately, these tablets could not withstand the release conditions and both tablet layers separated after about 2 hours of dissolution testing. The layer separation led to an increase in dissolution rate of Metformin-HCl caused by the increased diffusion area (see Figure 44 (a)). An additional inter layer of glycerol monostearate could considerably enhance the integrity of the tablets and prevent the separation of both tablet layers over the analysed time

interval. Figure 44 (b) demonstrates the release behaviour of Metformin-HCl from 3-layer tablet formulations **E** and **F**. The IBS was present in the KSR-P layer of tablet **E**; while none was present in the KSR layer of tablet **F**. As expected, no influence of the pH_M on the drug release of Metformin-HCl could be found.

In contrast, non-steroidal anti-inflammatory drug Ketoprofen was analysed as model drug showing a pH dependent solubility. Ketoprofen is very slightly soluble at acidic pH (0.28 mg/ml at pH 4) and slightly soluble at pH 6.0 (3.68 mg/ml) (Sheng et al., 2006). The solubility increases with increasing pH because of the cumulative deprotonation of the carboxyl group (pK_a of 4.76). Figure 44 (c) demonstrates the dissolution profiles of Ketoprofen from 3-layer tablets **E** and **F**. Tablet formulation **E** increased the drug release considerably in comparison to tablet formulation **F**. The drug containing KSR-P layer of tablet **E** generated a pH_M of around 6, thus, leading to a higher solubility of Ketoprofen and therefore to an increase in drug release. These finding confirms literature data where the drug release of weak acids could be improved by the incorporation of alkaline excipients (Doherty and York, 1989; Riis et al., 2007; Tran et al., 2008). The formulations were not further optimised regarding drug release, although even a drug release of around 30 % over 12 hours is quite low. Further formulation optimisation would be needed for a reasonable drug release over 12 hours. However, this issue was beyond the scope of this work as it was intended to keep the formulation of the layers constant for comparability purposes. Furthermore, the purpose of this investigation was not to develop an optimised formulation but to show the influence and importance of the pH_M within tablets on the drug release, especially for ionisable drugs.

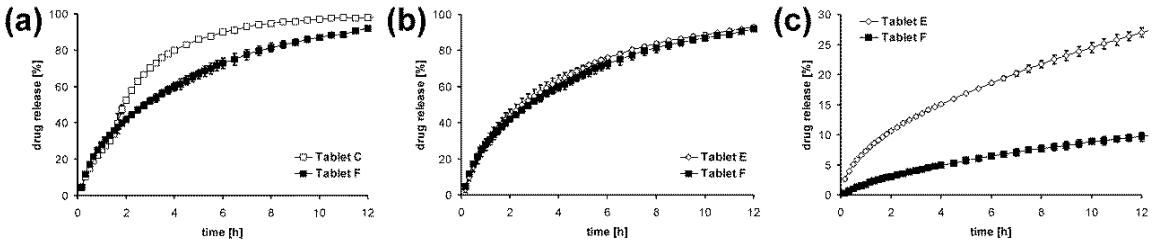


*Figure 44 Drug release in buffer pH 3.**(a)** Metformin-HCl release from 2-layer tablets **C** and 3-layer tablets **F**. **(b)** Metformin-HCl release from 3-layer tablets **E** and **F**. **(c)** Ketoprofen release from 3-layer tablets **E** and **F**.*

3.2.5 Monitoring of hydration behaviour by means of ^{1}H NMR benchtop imaging

Benchtop NMR imaging was accomplished to further analyse the differences in the hydration behaviour of 2- and 3-layer matrix tablets. Figure 45 demonstrates the schematic process of tablet hydration of both tablet constitutions which could be monitored using benchtop MRI equipment over time of buffer contact. No considerable differences could be found between tablet formulations **A, B** and **C**. Therefore, only 2-layer tablets C and 3-layer tablets F were

further investigated. The hydration of 2-layer tablets started at the edges of the tablets but continued between the two layers, leading to a separation of both layers over time of hydration. Diffusion processes between the layers might be facilitated by the hydration of the interface of both layers as well. The swelling of the hydrated regions led to an increase in size. The tablets were completely hydrated after around 4 hours of buffer contact. After 6 hours, both layers were commonly separated. The additional inter layer of the 3-layer tablets prevented the penetration of water between the Kollidon SR and the HPMC layer. Therefore, the hydration process was slower as it continued only from the edges of the tablets to the inner regions. A dry core was existent even after 4 h of buffer contact. The 3-layer tablets did not disintegrate for more than 6 hours of hydration.

Characteristic T_1-weigthed BT-MRI images with corresponding intensity profiles of 2- and 3-layer tablets over time of buffer contact are presented in Figure 46. Dark areas within the tablets refer to low spin densities and /or short relaxation times, which are related to dry parts of the tablets. Hydrated areas appear bright because of the water penetration and therewith associated increase in spin density. Relaxations times in the range of 10 up to hundred milliseconds give the brightest contrast under used measurement conditions (T1 weighted). The HPMC layer appears brighter than the Kollidon SR layer. HPMC forms a gel upon hydration. The water inside the gel layer was not as flexible as in the pores of the Kollidon SR matrix leading to shorter T_1 relaxation times and a brighter signal which could also be confirmed by NMR relaxometry. This issue could also have an influence on the different behaviour regarding the migration of IBS. A swelling of the HPMC and Kollidon SR layer could be monitored by increase in size of the tablets.

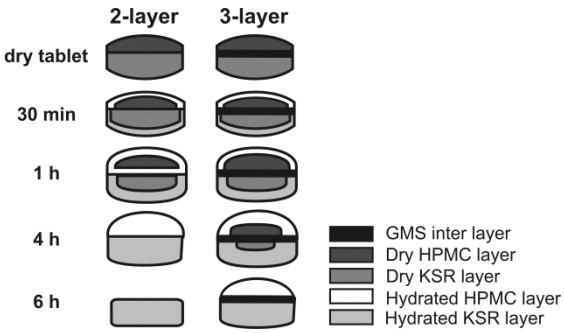


Figure 45 Schematic process of tablet hydration of a 2- and a 3-layer tablet at different time intervals of contact with buffer.

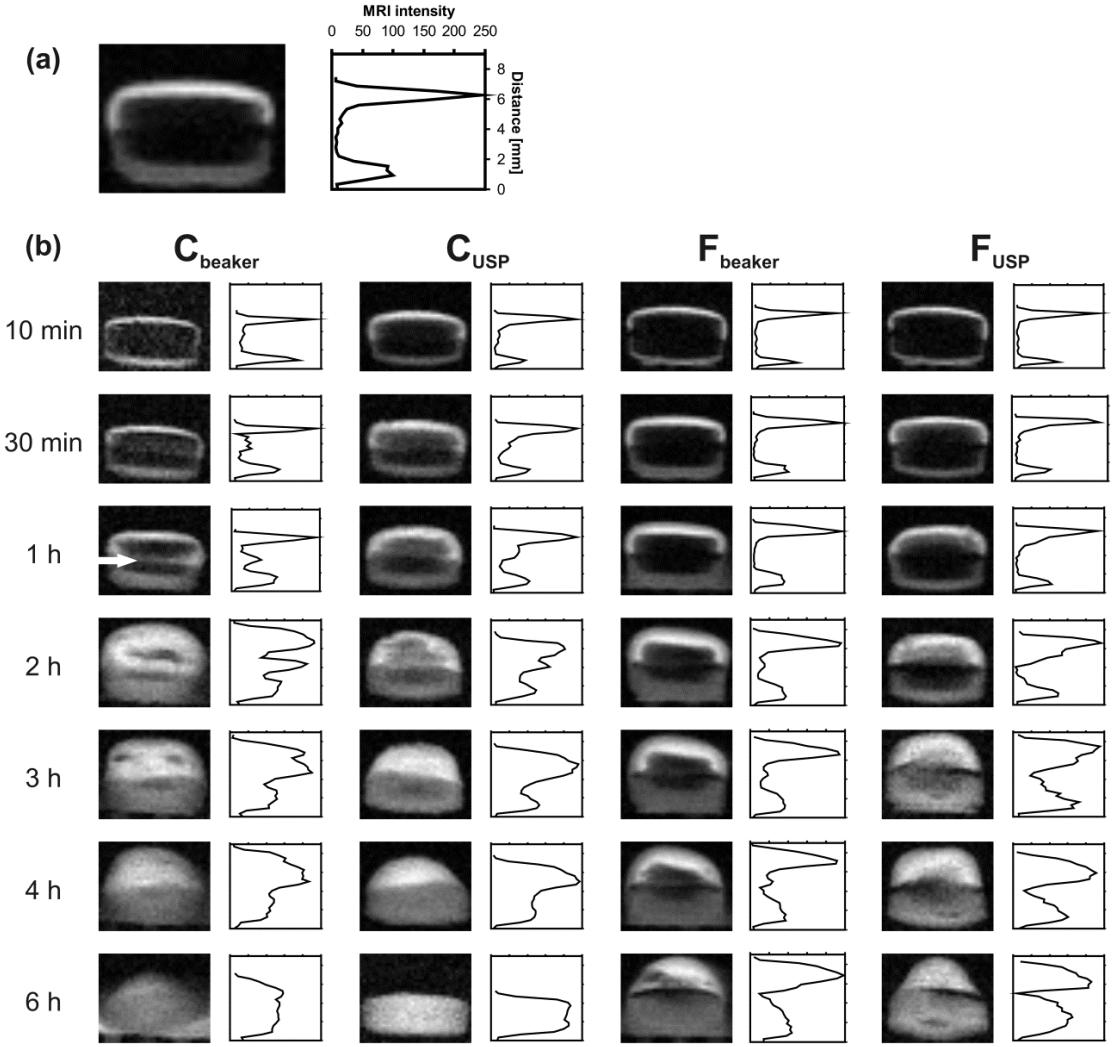


Figure 46 ***(a)*** *^{1}H NMR benchtop magnetic resonance image and corresponding signal intensity profile of tablet preparation* ***F*** *after 30 min of contact with buffer, exemplified for scale labelling of (b).* ***(b)*** *^{1}H NMR benchtop magnetic resonance images and corresponding signal intensity profiles of tablet preparations at different time intervals of contact with buffer.* $\boldsymbol{C_{beaker}}$***:*** *2-layer tablet* ***C****, hydration in unstirred beaker.* $\boldsymbol{C_{USP}}$***:*** *2-layer tablet* ***C****, hydration in USP paddle dissolution apparatus at 50 rpm.* $\boldsymbol{F_{beaker}}$***:*** *3-layer tablet* ***F****, hydration in unstirred beaker.* $\boldsymbol{F_{USP}}$***:*** *3-layer tablet* ***F****, hydration in USP paddle dissolution apparatus at 50 rpm. The arrow indicates the visible water penetration between both layers of tablet* ***C****.*

The different tablet formulations were exposed to two different hydration settings. Tablets exposed to USP dissolution conditions showed a faster water penetration into and erosion of the HPMC layer compared to the unstirred tablets, visible by a faster decrease in size. Water penetration between both layers of the 2-layer tablet **C** could be monitored after 30 min of buffer contact independent from used hydration setting which is also illustrated in the corresponding MRI intensity profiles. After 1 hour, an additional central peak could be monitored within the intensity profiles (see Figure 46 (b); C, 1 h). The water penetration between the tablet layers could enable a fast migration of IBS from the KSR-P to the HPMC layer of tablet **B**. Furthermore, a separation of both layers could be facilitated. In contrast, the hydration of 3-layer tablets **F** proceeded only from the edges of the tablets caused by the

aforementioned interference of the inter layer. The inter layer is clearly visible as black region between the HPMC and the KSR layer over the analysed time interval of 6 hours. Because of its lipophilic character, almost no water penetrated into this region leading to low spin density and a black colour. The MRI intensity profiles illustrated the low signal intensity between the HPMC and the KSR layer even after 6 hours of contact with buffer (see Figure 46 (b); F, 6 h). The lipophilic inter layer improved the integrity of the tablets and possibly hindered the migration process of the IBS (see Figure 46 (F)). In addition, 2- and 3- layer tablets were exposed to two different hydration settings. Tablets exposed to USP dissolution conditions showed a faster water penetration into and erosion of the HPMC layer compared to the unstirred tablets (see Figure 46). These findings are consistent with previous work, showing the dependence of erosion and hydration processes of hydrogel-forming HPMC on mechanical stress (Costa and Labo, 2001; Kavanagh and Corrigan, 2004). Further studies have to be carried out to investigate, if mechanical stress could also change the migration behaviour of the IBS.

3.3 Development of floating devices for weakly acidic drug Cefdinir

The aim of the Cefdinir formulation study was the development of FDDSs with optimised characteristics for a challenging drug showing low and pH dependent solubility. Therefore, the influence of pH-modifiers, solubilizers, filling materials, disintegrants and tablet core preparations on drug release of Cefdinir should be analysed. To be able to gain information on each change of composition independently, numerous formulations were manufactured and analysed (see 2.2.4). Furthermore, the microacidity of Cefdinir-containing formulations upon hydration were determined and compared to corresponding dissolution data. The compatibility of Cefdinir with excipients and the improvement of drug wettability were other topics of interest.

3.3.1 Influence of microenvironmental pH on release of Cefdinir

3.3.1.1 pH dependent solubility

Drugs showing pH dependent solubility/stability are a challenge for formulation development, especially when the physiological pH is inappropriate for a sufficient dissolution of the drug at the site of absorption. A pH dependent release shows also the disadvantage of inter- and intra-individual differences in bioavailability depending on the physiological pH variations. Cefdinir shows lowest solubility at pH 2 to 4, which is a common pH range within the stomach. Therefore, Cefdinir is a challenging drug for a gastroretentive formulation which should prolong the retention time in the human stomach.

To gain information on the influence of drug solubility on the release of balloon-like floating devices, the drug dissolution of 1-layer floating formulation of Metformin-HCl (A1) was compared to release of Cefdinir using same formulation (A2) and replacing only the API. Another formulation of Cefdinir (A3) was produced without $NaHCO_3$ and citric acid to analyse the influence of pH modifying substances on the drug release of Cefdinir. Figure 47 shows the results of the dissolution studies of formulations A1-A3 in SGF. Metformin-HCl is a freely soluble drug showing pH independent solubility. The release of formulation A1 was faster and considerably enhanced compared to the release of Cefdinir formulation A2, indicating a low solubility of Cefdinir. Only 30 % of Cefdinir were released out of formulation A2 after 24 hours of buffer exposure. Furthermore, the floating lag times of the Cefdinir formulation A2 were extremely prolonged in comparison to the Metformin-HCl formulation. This finding supports the low solubility and wettability characteristics of Cefdinir. If the surrounding water upon hydration is hardly able to penetrate though the tablet, only a slow gas formation is taking place resulting in long floating lag times. Formulation A3 showed almost no release of Cefdinir indicating a pH dependent solubility mechanism.

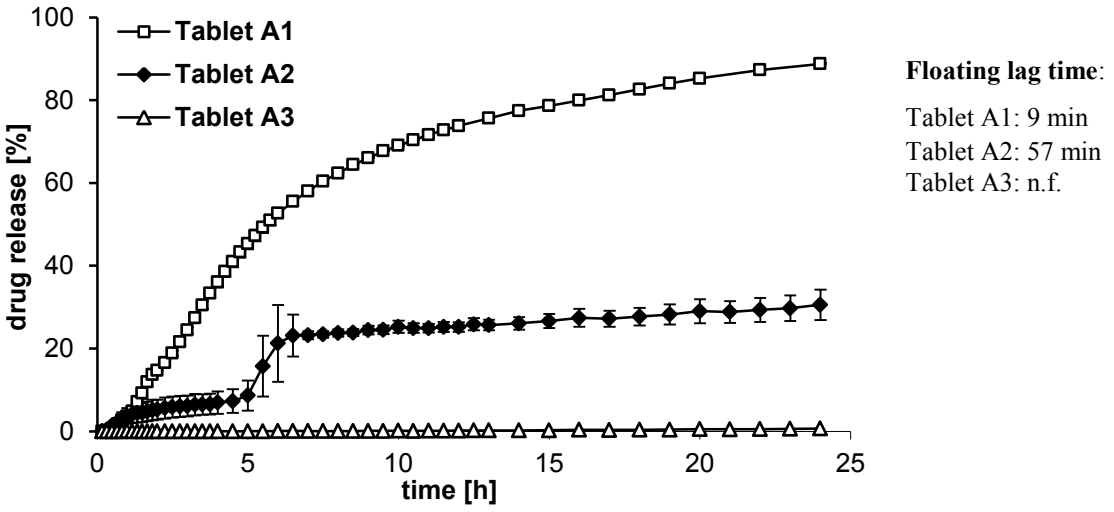


Figure 47 Influence of drug solubility on drug release of coated 1-layer tablets. (Tablet A1: Metformin-HCl (with $NaHCO_3$); Tablet A2: Cefdinir (with $NaHCO_3$), standard deviations specified (temporary above 5 % of the total Cefdinir content); Tablet A3: Cefdinir (without $NaHCO_3$); n.f.: not floating).

Figure 48 shows the ionisation of the functional groups of Cefdinir over the entire pH range. Ionised molecules show a higher solubility in general because of ion-dipole interactions. Therefore, Cefdinir should show an enhanced solubility at low pH (ionised amino group) and at pH over 5 (ionised carboxyl group). Calculated solubility (SciFinder: ACD/Labs) show similar results: Solubility pH 1: 11 mg/ml; solubility pH 4: 1.6 mg/ml; solubility > pH 5: very soluble.

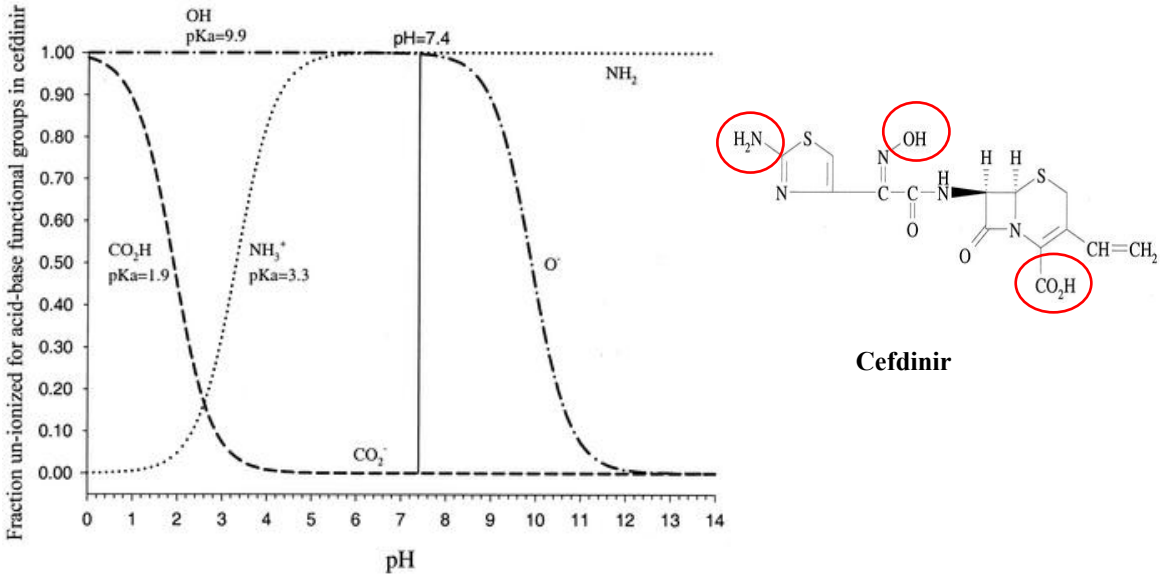


Figure 48 Fraction un-ionized versus pH for each of three acid-base functional groups in Cefdinir. The pK_a values are 1.9 (carboxylic acid group), 3.3 (amino group), and 9.9 (hydroxyl group). (adapted from Lepsy et al., 2003)

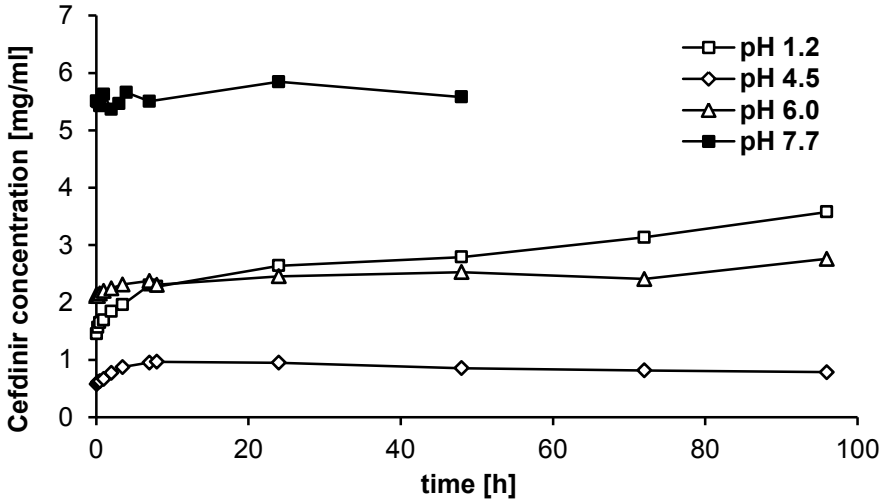


Figure 49 Influence of buffer pH on solubility of Cefdinir (pH 1.2: simulated gastric fluid (SGF); pH 4.5: 0.05 M Phosphate buffer solution pH 4.5. Ph. Eur.; pH 6.0: Phosphate buffer solution pH 6.0 R2. Ph. Eur.; pH 7.7: 0.2 M Phosphate buffer solution pH 7.7. Ph. Eur.).

The solubility of Cefdinir in buffers of different pH was analysed to confirm this supposition (see 2.20). Figure 49 shows the solubility of Cefdinir in buffers of different pH at 37°C over 4 days. Cefdinir shows lowest solubility of around 1 mg/ml at pH 4.5 followed by a solubility between 2-3 mg/ml at pH 6.0 and 2-4 mg/ ml at pH 1.2. The highest solubility of Cefdinir could be achieved in buffer of pH 7.5 (5-6 mg/ml). Otherwise, even the solubility at pH 7.5 is much lower than the calculated solubility (see above). Nevertheless, the solubility of Cefdinir was found to be higher at pH values above 6 compared to acidic pH. Furthermore, sodium hydrogen carbonate (pK_{a1}= 6.46; pK_{a2}= 10.30) is an essential part of gas forming floating formulations.

For these reasons, pH modifying substances, which are able to increase the internal pH above pH 6, should be analysed for their possibility to enhance the solubility and the therewith associated release of Cefdinir. 2-layer formulations B1-B6 consisting of a drug and a floating layer were developed to achieve the possibility to optimise drug release and floating behaviour independently from each other. Tablets with pH modifying substances differing in their solubility were produced and analysed for their release behaviour as well as formulations without pH modifier (see Figure 50). It was found that all formulations showed a low release of Cefdinir over 24 hours. The highest release rates of around 25% release over 24 hours could be achieved by formulations B3(10 % Na_2HPO_4) and B4 (10 % $Ca(OH)_2$). The lowest release was found in case of formulation B6 (40% $Ca(OH)_2$). Formulation B2 (10 % NaCl) failed to improve the drug release of formulation B1 (without pH modifying substance) by enhancing the ionic strength inside the formulation and therefore increase the amount of penetrating water.

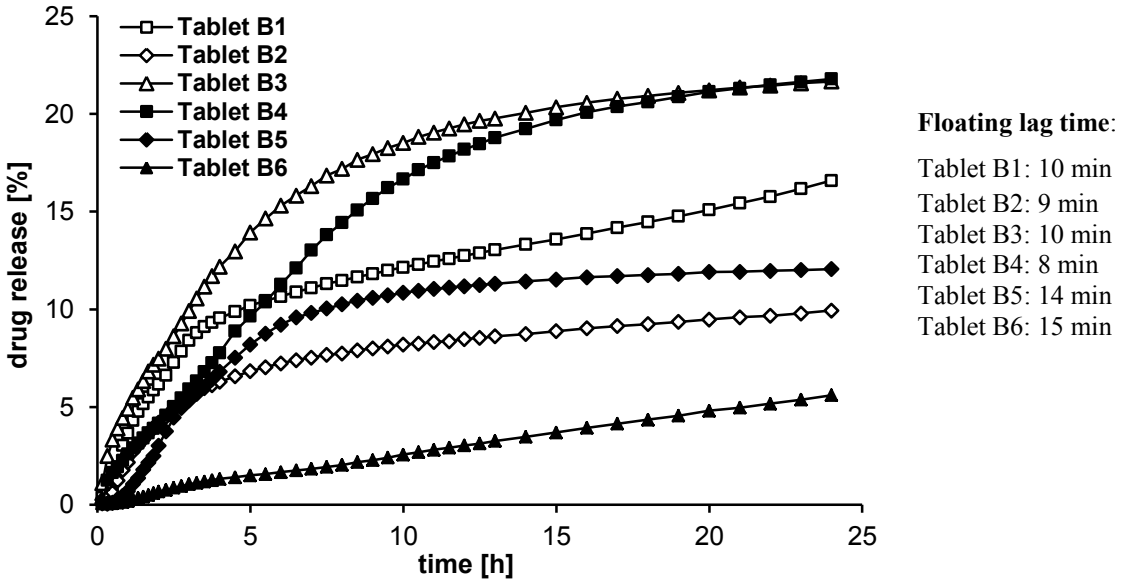


Figure 50 Influence of pH modifiers on Cefdinir release of coated 2-layer tablets B1-B6. (Tablet B1: Drug layer without salt; Tablet B2: Drug layer with 10 % NaCl; Tablet B3: Drug layer with 10 % Na_2HPO_4; Tablet B4: Drug layer with 10 % $Ca(OH)_2$; Tablet B5: Drug layer with 10 % $Ca_3(PO_4)_2$; Tablet B6: Drug layer with 40 % $Ca(OH)_2$ (without Emcompress)).

Figure 51 shows the influence of buffer pH on drug release of 2-layer tablets B1 and B4. Both formulations showed a faster release, when buffer pH 6.0 was used compared to SGF. The release curves at buffer pH 6.0 are similar for both formulations. This finding underlies that the solubility of Cefdinir is dependent on the pH of the surrounding buffer. The incorporated pH modifier (formulation B4) did not enable a pH independent release of Cefdinir. Nevertheless, formulation B4 showed a higher release after 24 hours of buffer contact in SGF compared to formulation B1. The $Ca(OH)_2$, which was incorporated in the drug layer of formulation B4, was able to enhance the pH_M and the therewith associated solubility of Cefdinir. For this reason,

$Ca(OH)_2$ had positive influenced the drug release. However, the pH modifier and/or its used concentration were not sufficient to produce a pH independent release of formulation B4.

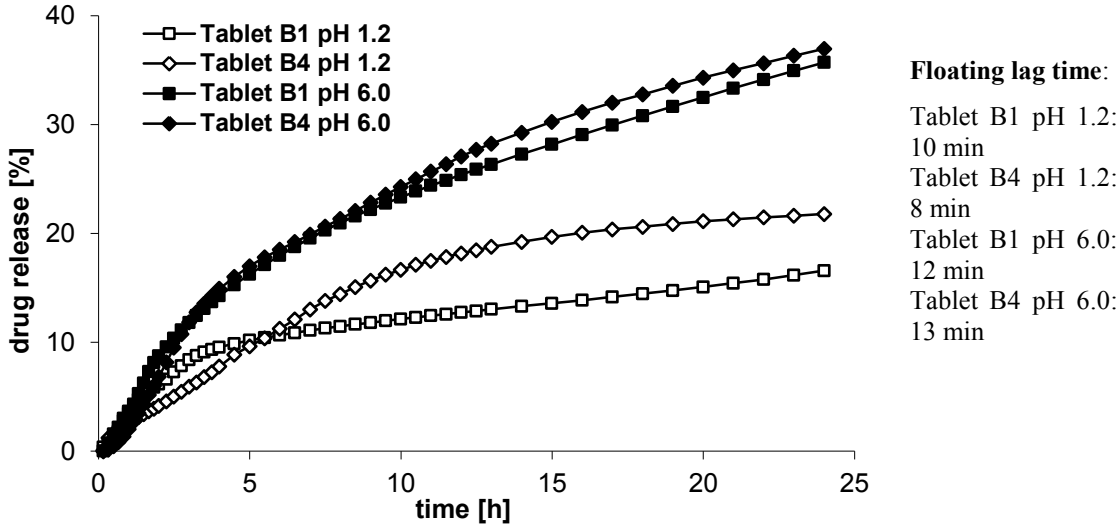


Figure 51 Influence of buffer pH on Cefdinr release of coated 2-layer tablets (pH 1.2: SGF pH 1.2; pH 6: Phosphate buffer solution pH 6.0 R2 Ph. Eur.) (Drug layer B1: without salt; Drug layer B4: with 10 % $Ca(OH)_2$).

3.3.1.2 Microacidity measurements using a pH indicator dye

To be able to analyse the pH_M of Cefdinir containing tablets with an easy evaluable method, tablets B1-B6 with pH indicator dye bromcresol purple were prepared. Images and cross-sectional images of the tablet B6 after different time intervals of contact with SGF can be seen in Figure 52. The floating layer (top layer) of the tablets shows a purple colour for more than 4 hours of contact with acidic buffer indicating a pH_M above 5. This finding was caused by the basic nature of sodium bicarbonate which is incorporated in the floating layer. Another interesting finding was the dry drug layer which could be observed even after 4 hours of buffer contact for all tablet formulations. These findings indicate a slow water penetration inside the drug layer caused by low wettability of excipients (Cefdinir). After 24 hours of buffer contact of formulation B6, the drug layer was completely wetted and showed a purple colour indicating a pH above 5 which was caused by the high concentration of $Ca(OH)_2$. $Ca(OH)_2$ showed a low solubility and was therefore able to modify the pH_M over a long period of time. The floating layer showed yellow colour indicating a pH below 4.5. Sodium bicarbonate is highly soluble in water and reacts under acidic, aqueous conditions (SGF) to form carbon dioxide, water and sodium ions. After 4 to 6 hours, the sodium bicarbonate was exhausted; more acidic SGF penetrated into the tablet core leading to acidic pH_M values of the floating layer.

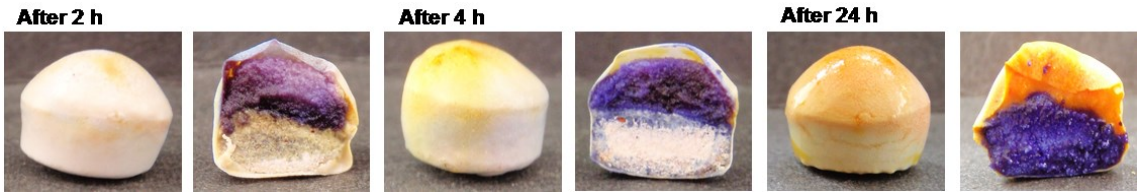


*Figure 52 Images and cross-sectional images of coated 2-layer tablets **B6** with incorporated pH indicator bromcresol purple after different time intervals of contact with SGF. Tablets were always placed with the floating layer on top and the drug layer as bottom side. Purple domains indicate a pH_M >5, yellow domains indicate a pH_M < 4.5. Dry areas and coating membrane appeared white.*

3.3.1.3 Microacidity measurements using spatial spectral EPR imaging

For a better understanding of the findings of the dissolution studies of formulations B1-B6, the microenvironmental pH of the tablets upon hydration in SGF was analysed by EPRI.

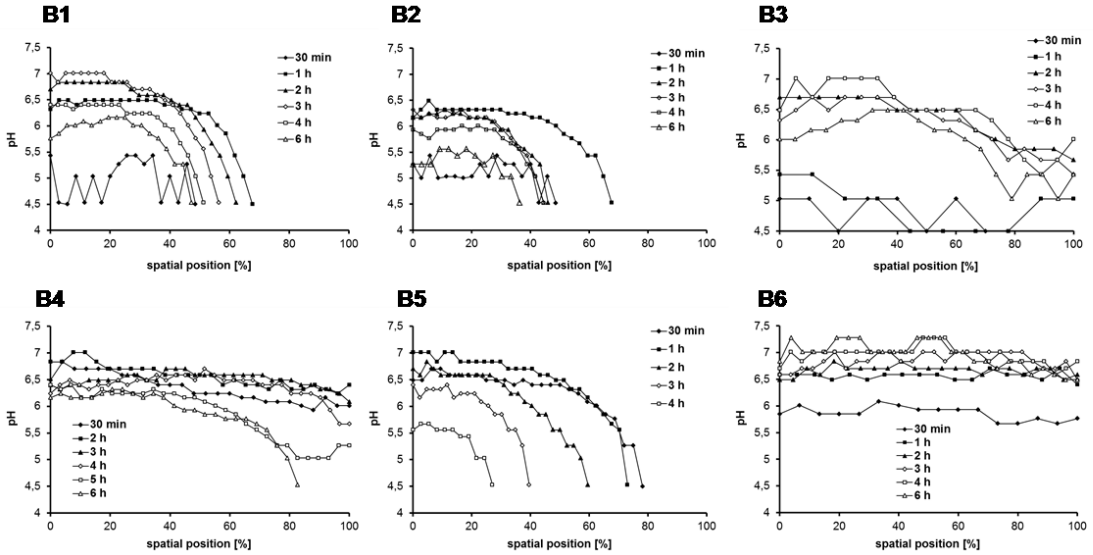


*Figure 53 **(B1-B6)** pH_M averages within coated 2-layer tablets **B1-B6** calculated from EPR images which were generated at different time intervals of contact with SGF. No values could be determined for areas with a $pH_M \leq 4.5$. (B1: Drug layer without salt; B2: Drug layer with 10% NaCl; B3: Drug layer with 10 %Na_2HPO_4; B4: Drug layer with 10 % $Ca(OH)_2$; B5: Drug layer with 10 % $Ca_3(PO_4)_2$; B6: Drug layer with 40 % $Ca(OH)_2$ (without Emcompress)).*

Figure 53 shows pH_M averages within 2-layer tablets B1-B6, calculated from EPR images which were generated at different time intervals of contact with SGF. pH_M averages on the left hand side of each graph characterise pH_M averages of the floating layer, the drug layer is characterised by the pH_M averages on the right hand side. The floating layer of all formulations showed a pH_M of over 6 for more than 4 hours of buffer contact which was consistent with the findings using the pH indicator dye (see 3.3.1.2). If a pH modifying substance was incorporated, the pH_M of the floating layer was above pH 6 over more than 8 hours of buffer contact (except drug layer formulation B5). Furthermore, it was found that the pH_M of the drug layer of formulations B1 and B2 (without pH modifying substances) was below pH 4.5 during entire time range of 8 hours. Na_2HPO_4 and $Ca(OH)_2$ were found to enhance the pH_M of the drug layer

to values between pH 5.5 and 6.5 over 6-8 hours (formulations B3 and B4). Formulation B6 (40% $Ca(OH)_2$) was able to generate pH_M values of more than pH 6.5 within the drug layer over more than 8 hours. $Ca_3(PO_4)_2$ showed no measurable effect on the pH_M of the drug layer which may be caused by its low solubility (formulation B5).

3.3.2 Determination of compatibility of Cefdinir with excipients

3.3.2.1 Cefdinir recovery after drug dissolution

To further explain the low drug release of formulation B6 showing the most convenient pH_M profile of the drug layer, the total Cefdinir recovery of formulation B2, B4 and B6 was determined as described before in chapter 2.5.4. Figure 54 illustrates the loss of Cefdinir in formulations B4 and B6 (10% and 40% of $Ca(OH)_2$) after 24 hours of contact with SGF which may be caused by Cefdinir degradation. Only around 50% of the initial Cefdinir content could be recovered in case of formulation B6. Furthermore, orange discolorations of the drug layer and a modified UV spectrum were noticed in case of these two formulations. A compact drug layer was remaining even after 24 hours of buffer contact. In contrast, over 90 % of Cefdinir could be recovered from formulation B2. To eliminate the possibility that the pH of the used buffer may cause the drug degradation, pure Cefdinir was dissolved in different buffers using same concentration and conditions as were used during dissolution studies. Cefdinir showed to be stable at pH 4.5; pH 6.0 and pH 7.5; at pH 1.2 around 5 % loss could be detected over 24 hours of buffer contact.

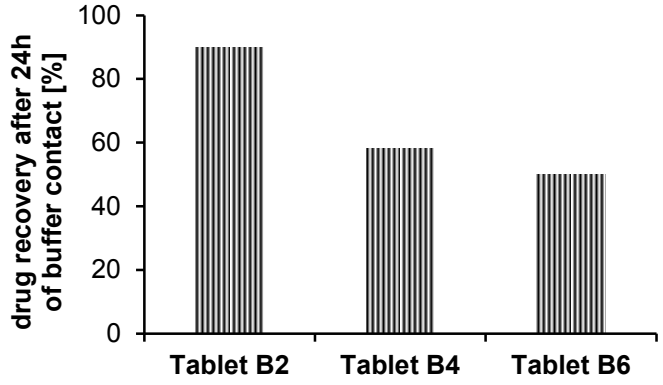


Figure 54 Total Cefdinir recovery of formulations B2, B4 and B6 after 24 hours of contact with SGF. Tablet B2: Drug layer with 10% NaCl; Tablet B4: Drug layer with 10 % $Ca(OH)_2$; Tablet B6: Drug layer with 40 % $Ca(OH)_2$.

3.3.2.2 Compatibility of Cefdinir with excipients

To gain further insight into possible sensitivity of Cefdinir regarding degradation processes, compatibility of Cefdinir with excipients was determined (see 2.15). Figure 55 shows the results of the compatibility study. After the addition of $NaHCO_3$ and water to Cefdinir, a gas generation could be observed which can be attributed to the reaction of the hydronium ion of the carboxylic

group of Cefdinir with $NaHCO_3$ to form carbon dioxide, water and Cefdinir-Sodium. The whole mixture changed colour from white to red. The UV spectrum of retaining Cefdinir was slightly changed as well. Nevertheless, over 70% of initial Cefdinir amount were calculated by the values of UV absorbance even after incubation for 24 hours. Otherwise, UV spectra of possible degradation products of Cefdinir may be similar to the one of Cefdinir leading to imprecise results. Therefore, $NaHCO_3$ should directly contact Cefdinir as little as possible for stability reasons.

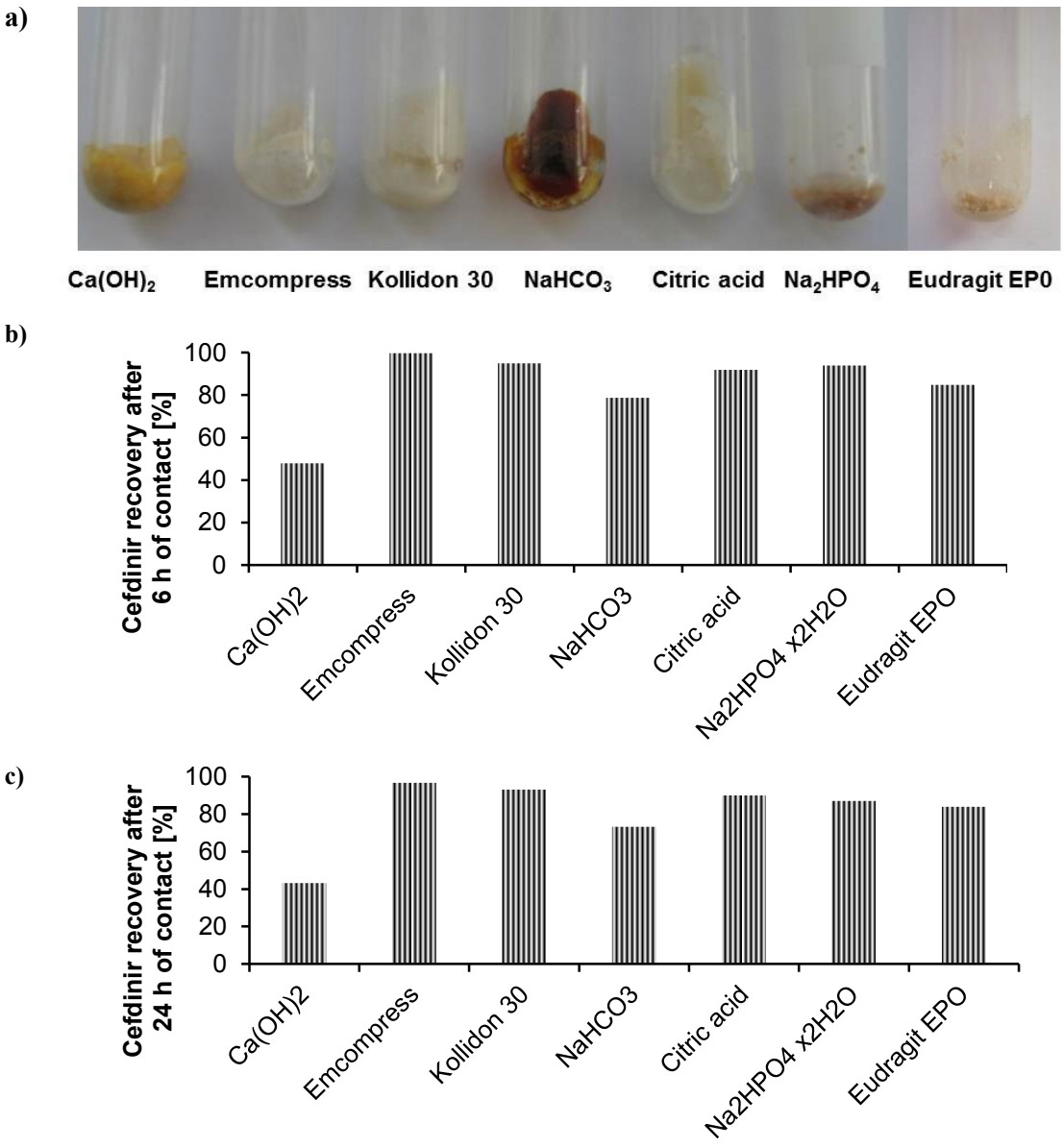


Figure 55 Compatibility of Cefdinir with excipients. Cefdinir was incorporated with each excipient and purified water in the ratio of 1:1:1 for 6 h/ 24 h.
a: photographs of the mixtures after 24 h of contact; b: Cefdinir recovery after 6 h of contact; c: Cefdinir recovery after 24 h of contact.

In the case of $Ca(OH)_2$, only around 40 % of the initial Cefdinir amount could be detected after incubation for 6 hours. The UV spectra were changed and the mixture changed colour to yellow. Because of its strongly alkaline behaviour, the use of $Ca(OH)_2$ as pH modifier seems to be not suitable for Cefdinir formulations regarding drug stability as well as stability of the polymer coat (see 3.3.2.4). In addition, Cefdinir degradation is a possible explanation for the low release rates of Cefdinir from formulation B6 although it generated the best suiting pH_M which was indicated by EPRI measurements (see 3.3.1.3). The incubation of Cefdinir with all other excipients did not lead to visible changes of the UV spectra of Cefdinir. Cefdinir recovery under these harsh conditions was above 80% in general. The mixture of Cefdinir with Na_2HPO_4 showed a slight change in colour from white to pale red. However, because of its promising effect regarding pH_M adjustment and drug release of Cefdinir (formulation B3) (see Figure 50) and the high recovery rate of Cefdinir during compatibility studies, Na_2HPO_4 was chosen as best suiting pH modifier for further formulation development.

Another pH modifying substance, which was analysed more precisely, was Eudragit EPO. This polymer was used for internal pH adjustment of weakly acid drugs before (Rao et al., 2003). In case of Cefdinir containing formulations, Eudragit E was able to control the drug release but seemed to have almost no influence on the internal pH and therewith associated drug solubility.

3.3.2.3 DSC measurements/ melting point/ powder x-ray diffraction

DSC studies were performed (according to 2.16) to further analyse drug degradation during storage or dissolution studies. Unfortunately, no obvious melting point of Cefdinir could be detected which was in conflict with the melting point of 170°C, which was stated in the certificate of analysis of Cefdinir. Therefore, the analysis of possible interactions of Cefdinir with excipients by DSC was not possible.

To further monitor the melting behaviour of Cefdinir, the drug was heated up with 4°C per minute until 250°C. Changes of the crystal structure were visually monitored (see 2.16). At a temperature of around 207°C, a brownish change in colour took place which became darker and finally black over 230°C. Cefdinir carbonised without melting which confirmed the findings of DSC measurements. Powder x-ray diffraction was accomplished to analyse the crystal structure of Cefdinir. The resulting spectrum was compared to the spectrum of crystalline anhydrous Cefdinir of PDF data base and found to be identical. Therefore, the crystallinity of the used Cefdinir could be confirmed by powder x-ray, although DSC data did not show a melting event.

3.3.2.4 Monitoring of storage induced changes in film coat composition by means of ^1H NMR

Table 23 shows a comparison between the ratio of Kollicoat SR peak (4.74 ppm) and Kollicoat IR peak (4.41 ppm) of 2-layer tablets differing in the drug layer of the tablet core after 3 months of storage (20°C/ 40% RH). Within drug layer B1, no additional pH modifier was incorporated

whereas drug layer B6 consisted of 40 % $Ca(OH)_2$. The ratio of the Kollicoat SR peak to the Kollicoat IR peak was different for both formulations. More Kollicoat SR could be found pro rata within the coating of formulation B1 in all 3 samples. The calculated ratio of the amplitude of characteristic peaks of the two coating polymers complied in this case with the mass ratio of the polymers which was used for tablet coating. This finding was confirmed by analysis of coating membranes, containing different ratios of the polymers (Kollicoat SR: Kollicoat IR 8,5:1,5 and 8:2), by further ^{1}H NMR studies. The mass ratio of the polymers was confirmed by the peak ration of ^{1}H NMR studies. In the case of formulation B6, less Kollicoat SR could be recovered in comparison to formulation B1 which indicates a degradation of polyvinyl acetate of Kollicoat SR caused by the high concentration of strong basic $Ca(OH)_2$. This degradation will also have an impact on the release behavior of the formulation which is likely to be increased, caused by the decreased amount of insoluble coating polymer.

Table 23 Influence of tablet core on stability of coating membrane. ^{1}H NMR was accomplished to determine the ratio of coating polymers. The ratio of Kollicoat SR Peak (at 4.74 ppm) and Kollicoat IR peak (at 4.41 ppm) was determined after 3 months of storage (20°C/ 40% RH) of 2-layer tablets differing in the drug layer of the tablet core. Drug layer B1: without salt; Drug layer B6: with 40 % $Ca(OH)_2$.

Sample	Drug layer B1 SR peak: IR peak	Drug layer B6 SR peak: IR peak
1	84.5:15.5	80.8:19.2
2	84.8:15.2	82.2:17.8
3	84.6:15.4	81.3:18.7

3.3.3 Observation and variation of wetting behavior of Cefdinir

Figure 56 shows the difference in wetting behaviour of pure Cefdinir compared to Cefdinir which was granulated with solubilizer solution before addition of simulated gastric fluid to the dry granules (see 2.18). The buffer could hardly wet the pure Cefdinir. A clear interface was formed between powder and liquid. The wetting behaviour of Cefdinir with solubilizer was enhanced obviously. The powder was wetted by the buffer independently from the used solubilizer. Sepitrap 80 and Brij 010 seemed to show best results in the improvement of wetting behaviour of Cefdinir. Brij 010 had the disadvantage of a semisolid consistence which was not suitable for the manufacture of powder mixtures. In contrast, Sepitrap 80 is a free flowing powder of microencapsulated solubilizer which was developed for solid oral drug formulations, in which a solubilizer is needed.

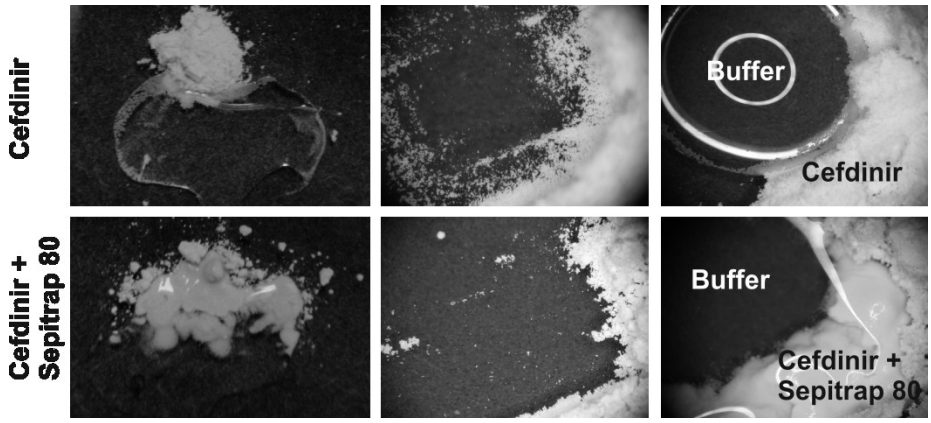


Figure 56 Influence of Sepitrap® 80 on wetting behaviour of Cefdinir.
a: pure Cefdinir with SGF; b: Cefdinir was wetted with a saturated solution of Sepitrap® 80 in an ethanol/water mixture (10 %) and dried afterwards. SGF was added to the dry Cefdinir granules.

3.3.4 Formulation approaches for Cefdinir containing floating devices

3.3.4.1 Coated 2-layer formulations

Formulations C1-3 were developed to improve the release of Cefdinir. For this reason, MCC was used as filling material instead of Emcompress to fasten and enhance the penetration of water through the dry tablet matrix. Di-sodium hydrogen phosphate was used as soluble pH modifier as well as Eudragit EPO as weakly basic polymer which is not able to pass the coating membrane. Furthermore, Sepitrap 4000 was used to improve the solubility and wettability of Cefdinir. The floating lag time of all formulations was again longer than the desired time of 10 min (between 15 and 25 minutes). The lag time of drug release was prolonged as well. The release started not before 2 hours of buffer contact for all formulations (see Figure 57). Formulation C1 without pH modifier showed a very low release of around 6 % after 24 h of contact with SGF. If Na_2HPO_4 in combination with $NaHCO_3$ was incorporated (formulation C2), the release could be increased to around 47 % after 24 h of buffer contact whereas when Eudragit EPO in combination with $NaHCO_3$ was used as pH modifier, a release of around 29 % could be achieved. The standard deviations, especially for formulation C2 were quite high. The coating could not withstand the preasure which was generated by the gas development. The coating of all formulations showed small holes upon hydration which caused a floating duration which was considerably below 24 hours. An interesting finding was the almost linear release of formulation C3. Eudragit EPO seemed to control the drug release of Cefdinir. The drug release of formulation C3 was increased compared to formulation C1 but lower than formulation C2. It can not be clearly stated if Eudragit EPO was able to enhance the release itself or if the combination with $NaHCO_3$ was necessary for the positive results.

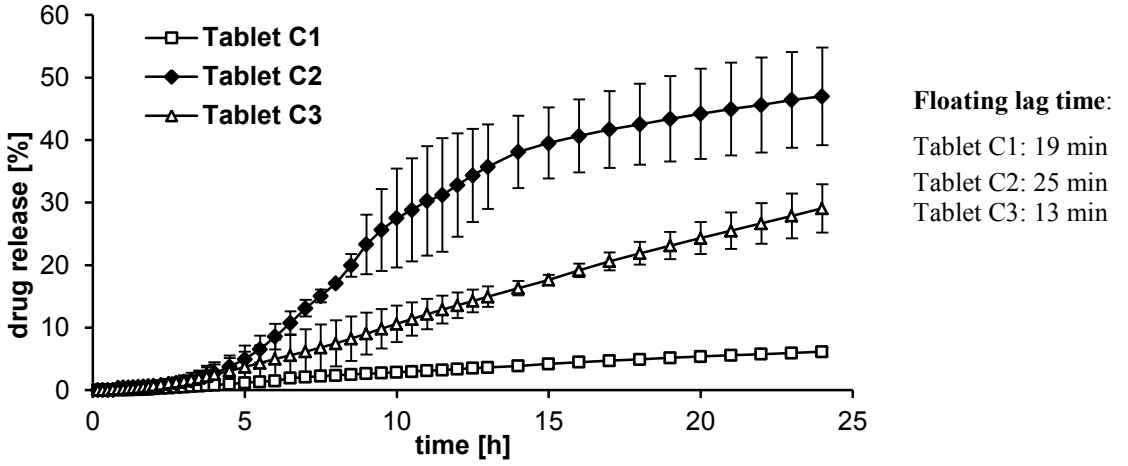


Figure 57 Influence of pH modifiers on Cefdinir release of coated 2-layer tablets over 24 h of contact with SGF. Tablet C1: Sepitrap 4000; Tablet C2: Sepitrap 4000 and Na_2HPO_4; Tablet C3: Sepitrap 4000 and Eudragit EPO. Standard deviations specified (temporary above 5 % of the total Cefdinir content).

It was also analysed, if an addition of 0.01 % Tween 80 to the buffer could further enhance the drug release of formulation C1 and C3 as described in literature for poorly soluble drugs before (Nyström and Westerberg, 1986; Westerberg et. al, 1986). The drug release could be enhanced for about 1/3 for formulation C1 and for around 1/5 in case of formulation C3. Nevertheless, the usage of solubilzer within buffer solutions is controverial discussed (Jantratid et al., 2008) and an influence on the coating stability could not be eliminated. Therefore, no additional solubilizer was used for further dissolution analysis.

The disintegration behaviour of different tablets was determined to analyse the wetting behaviour of tablet cores of formulation B compared with the tablet cores of formulation C (see 2.19). The test was abandoned after 2 hours. Tablet cores of formulation B5 were still intact showing yellow discolourations and a dry core. Tablet cores of formulation C3 showed a disintegration time below 30 minutes which indicated an improvement of wetting behaviour. Nevertheless, further optimisation was needed to shorten the lag time of drug release and enhance the dissolution of Cefdinir. Therefore, tablet cores using different filling materials and Kollidon CL as disintegrant were analysed for their disintegration behaviour (see Table 18). Tablets with PEG 8000 needed around 15 minutes for disintegration wereas tablets with MCC 200 disintigrated after 6 to 7 minutes. The best result achieved tablets consisting of Mannitol as filling material. These tablets showed a disintegration time of around 5 minutes. Therefore, the disintegration behaviour of the drug layer could be optimised by using Mannitol or MCC as filling materials in combination with Kollidon Cl as disintegrant. With a further addition of 9 % solubilizer (Sepitrap 80 or 4000), the disintegration time could be even more shortened to around 2 minutes.

Formulations D1-D4 were developed to analyse if the optimisation of disintegration behaviour had an impact on the lag time of drug release. Furthermore, the influence of the incorporation of

solubilizers (Sepitrap 80 and 4000) and different filling materials (Mannitol and MCC) on the drug release was investigated. Formulation D1 (Sepitrap 80) showed almost no difference in the release behaviour in comparison with formulation D3 (without solubilizer). The drug release of formulation D2 (Sepitrap 4000) was increased from 16 % after 24 hours of buffer contact of formulation D3 to 28 %. The drug release of formulation D4 (MCC instead of Mannitol, no solubilizer) was similar to formulation D3 (18 % after 24 hours of buffer contact). But lag time of drug release was shorter and drug release initially faster for this formulation. This finding might be caused by the wicking which was caused by the incorporation of MCC and which enabled a faster water penetration into the tablet core. Therefore, the drug dissolved faster and the release could start earlier. The release lag time of formulations D1-3 could be reduced by the incorporated disintegrant Kollidon Cl to around one hour of buffer contact in comparison to formulations C1 and C3 (3 to 4 hours of buffer contact). However, it was not possible to enhance the drug release of the coated 2-layer formulations in total. The floating lag time could be decreased to less than 5 minutes. Nevertheless, deviations in drug release were again high and the release in total even lower compared to formulations C2 and C3. Again, the coating showed instabilities, holes appeared and the floating duration of formulation D1 and D2 was below 5 hours.

In summary, 2-layer formulations (formulations B-D) had the possibility of optimisation of floating and release behaviour independently from each other. Furthermore, Cefdinir was separated from $NaHCO_3$ which was positive for stability reasons. Nevertheless, the different tablet core compositions showed to have little influence on drug release in total, the release rates of 2-layer tablets with intact coating were quite low. Furthermore, floating duration and coating stability showed to be quite low which might be caused by high ionic strength inside the tablet core (due to high amount of soluble salts leading to enhanced water influx) or the addition of surface-active solubilizers.

3.3.4.2 Press-coated membrane formulations (Tablets E)

Press-coated formulations E1-E5 were developed to analyse the impact of a different delivery device on the drug release and floating properties of Cefdinir containing tablets. Therefore, different tablet cores consisting of the former drug layer with different solubilizers (see 2.2.4) were press coated with floating layer blend and coated as described before (see 2.3). These tablets were supposed to show a short floating lag time because of the increase of contact area of the floating layer with the penetrating water. Figure 58 shows the influence of the different solubilizers and pH modifiers on drug release of press coated tablets in SGF. The floating lag times of the different formulations differ from 5 to 17 minutes, the lag time of drug release was between 1 and 2 hours. In some cases, the floating duration was again below 24 hours. Especially the coating of formulations with incorporated solubilizers (E2-E4) showed cracks

within the coating and these formulations lost core material upon hydration. Therefore, the release curves of these formulations show high deviations and a fast release after around 1 hour of buffer contact (see Figure 58). The stability of the tablet coating might be influenced by an interaction of the solubilizers with the coating polymers. The high ionic strength inside the tablet cores, caused by the addition of inorganic salts within the formulations, might have a supplementary destabilising effect on the floating properties due to the increased water penetration through the coating layer. Formulation E3 with Sepitrap 80 showed the fastest and highest release of Cefdinir of nearly 100 % (steady state after around 5 hours). Sepitrap 80 seemed to improve the solubility and the release of Cefdinir but seemed to influence the stability of the coating as well. In comparison, the release of formulations E1 and E2 was fast at the beginning but slowed down after around 5 hours (around 60 % in case of formulation E1 without solubilizer, around 80% drug release in case of formulation E2 with Sepitrap 4000). After this time interval, only a marginal release could be observed which may be caused by disintegration problems of the tablet cores and Cefdinir degradation. In case of formulation E3, only around 80 % of Cefdinir could be recovered in total after 24 hours of buffer contact. The contact area of the surrounding floating layer with incorporated $NaHCO_3$ and the drug layer is quite high. Therefore, there is more potential for interactions between Cefdinir and $NaHCO_3$ (see 3.3.2.2), depending on the rate of drug release. Formulation E4 with Lutrol F68 showed an especial slow and incomplete drug release. Lutrol F68 seemed not to be able to increase the solubility and release of Cefdinir and was therefore excluded from further analysis. Formulation E5 with Eudragit EPO showed again a nearly linear release which was slowed down compared to formulation E1-E4. Eudragit EPO seems to work as release controlling matrix within this formulation. The floating behaviour was much more stable for this formulation (floating duration > 24 h).

In summary, press coated formulations E showed higher release rates compared to 2-layer formulations. Formulation E5 (with Eudrait E) floated for more than 24 hours. Disadvantages of these formulations were the time consuming production followed by relativly high Cefdinir degradation for formulations E3-E5 (around 20 %). This finding could be possibly caused by the increased contact area of the surrounding floating layer with incorporated $NaHCO_3$ and the drug layer which increased the potential of interaction between Cefdinir and $NaHCO_3$.

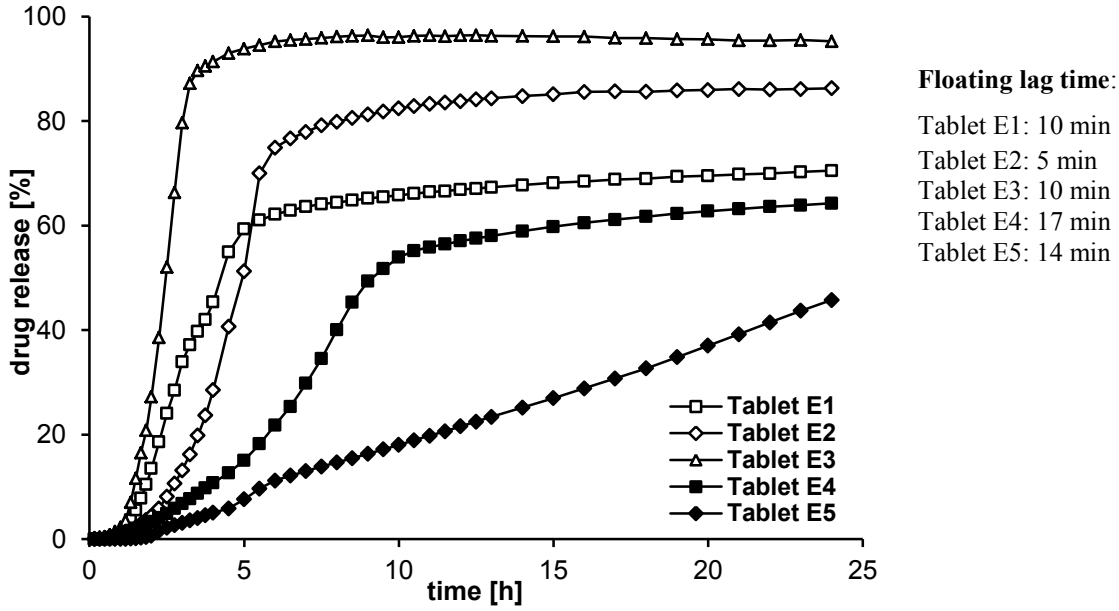


Figure 58 Influence of different solubilizers and pH modifiers on Cefdinir release of press coated tablets in simulated gastric fluid pH 1.2. Formulations E2, E3 and E4 showed high standard deviation of release values caused by untight coating (up to 20 % of the total Cefdinir concentration for the steep). E1: drug layer with 10 % Na_2HPO_4; E2: drug layer with 10 % Na_2HPO_4 and 15% Sepitrap 4000 (Polyoxyl 40 hydrogenated castor oil); E3: drug layer with 10 % Na_2HPO_4 and 15% Sepitrap 80 (Polysorbat 80); E4: drug layer with 10 % Na_2HPO_4 and 15% Lutrol F68 (Poloxamer); E5: drug layer with 15% Eudragit EPO.

3.3.4.3 Coated 1-layer formulations (tablets G and H)

1-layer tablets were developed to analyse the influence of simple formulations on the drug release and the floating behaviour. Similar findings, as mentioned for 2-layer and press-coated formulations before, were valid for the 1-layer formulations as well. When Cefdinir was granulated with Sepitrap 80 solution (see 2.18) before incorporation into the powder mixture (Formulation G3), the release was fast and complete but the coating was not stable. The other formulations could achieve a drug release of around 50 % highest. Especially formulation G2 with Eudragit EPO showed a delayed, decelerated and linear release with only 15 % release after 24 hours of buffer contact. When Fujicalin (Calcium Hydrogen Phosphate, Anhydrous; spray dried granules) in combination with Kollidon CL was used as filling material instead of MCC (formulation G5), the floating lag time was quite short (1.5 minutes) and the release more controlled and higher (around 60 % release after 24 hours of buffer contact) compared to same formulation with MCC (formulation G1, around 50 % release). The floating lag times were dependent from the used formulation and varied from 1.5 minutes in case of formulation G5 to 4 to 5 hours in case of formulation G2 with Eudragit EPO. Again, floating duration was below 24 hours for all formulations. Formulations G1-G6 were coated with an additional coating formulations to analyse the impact of the coating on the drug release. When coating with

Eudragit RL (Coating 5) was used, the release was higher and faster in general. The floating lag time was between 2 and 4.5 minutes and the floating duration below 24 hours.

Formulations H1-H3 were developed to analyse the influence of different solubilizers on the drug release of Cefdinir. Cefdinir was granulated with Sepitrap 80 or Ryoto sugar ester S1670. Eudragit RL was used as coating polymer (Coating 5). Formulation H1 with Ryoto sugar ester showed a very fast release and cracks within the coating. Formulations H1 and H2 had a floating duration of less than 24 hours. Only tablets of formulation H3 with Fujicalin instead of MCC floated for more than 24 hours with only marginal damage of the coating and an almost linear release of around 53 % after 24 hours of buffer contact. The floating lag time of all formulations was between 4 and 6.5 minutes and almost no lag time of drug release could be observed.

In summary, 1-layer tablets were easy to produce but had the disadvantage of a possible interaction of Cefdinir and $NaHCO_3$ (see 3.3.2.2).

3.3.4.4 Matrix formulations (tablets I)

Cefdinir matrix formulations were developed to analyse the influence of a different retarding principle on the drug release of Cefdinir. Matrix tablets are a common principle to prolong the drug release which is also suitable for drugs showing low water solubility. Depending on the used matrix forming excipient, the release is dependent on diffusion through the matrix as well as erosion of the tablet. If a soluble matrix former (HPMC) is used, a complete drug release can be achieved for hardly soluble drugs depending on erosion time of the formulation. Floating properties of Cefdinir containing matrix tablets should be optimised and characterised. Preliminary investigation of different matrix formulations were carried out to optimise floating duration and release of Cefdinir. Formulation I1 showded the longest floating duration (> 8 h) and a release of over 85 % after 24 hours of buffer contact. The remaining percentage of Cefdinir could not be recovered within dissolution medium or tablet residues and seems to be lost by degradation processes which my be mainly caused by the incorporated $NaHCO_3$ (see 3.3.2.2). Nevertheless, this formulation was used for further analysis. The influence of different tablet shapes and compression forces on the drug release and floating properties was analysed. Biconvex tablets showed a marginal slower drug release compared to flat faced tablets. Furthermore, the floating lag time varried from 14.5 minutes for biconvex tablets to 11 seconds for flat faced tablets. Therefore, flat faced tablets were further examined. The influence of the compression force on the drug release and floating behavior was only marginal within the used range (7 to 12 kN). The drug release of tablets which were prepared using a compression force of 7 kN, was slightly faster at the end of the dissolution process (after 7.5 hours of buffer contact). This compression force was used for further matrix tablet production.

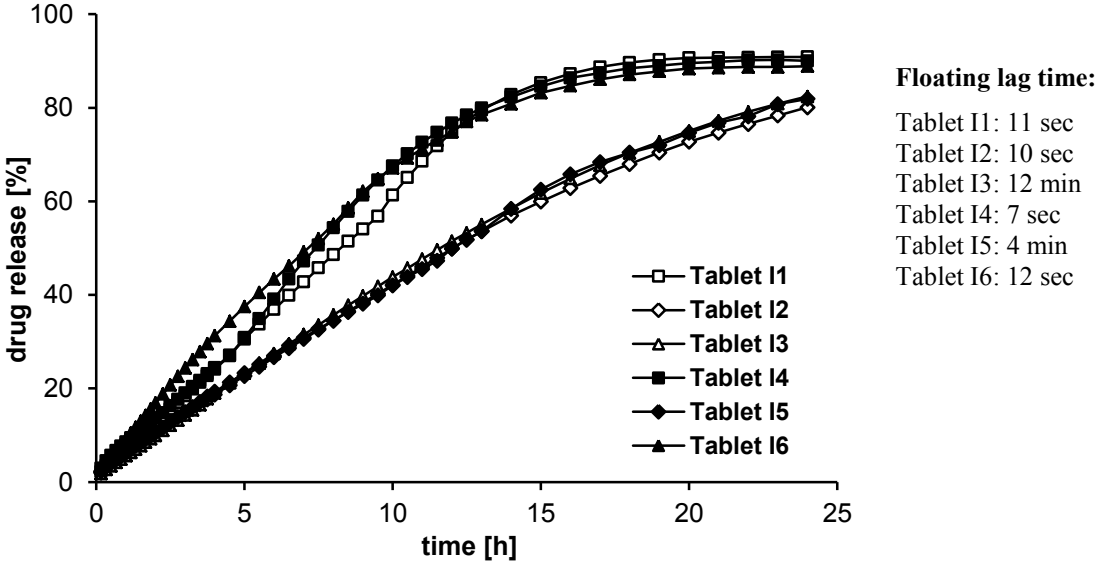


Figure 59 Influence of excipients on Cefdinir release and floating lag time of matrix tablets in simulated gastric fluid pH 1.2. (Tablet I1: matrix formulation; Tablet I2: matrix formulation without Sepitrap 80; Tablet I3: matrix formulation without Na_2HPO_4; Tablet I4: matrix formulation without Eudragit E, Tablet I5: matrix formulation without Eudragit E/ Na_2HPO_4; Tablet I6: matrix formulation using Cefdinir which was granulated with Ryoto sugar ester S1670).

Formulations I2-I6 were developed to analyse the influence of the pH modifiers and the solubilizer of formulation I1 on the release of Cefdinir (see Figure 59). Formulations I3 (without Na_2HPO_4) and I5 (without Eudragit E/ Na_2HPO_4) showed an increase in floating lag time. The formulations without Na_2HPO_4 (formulation I3 and I5) or without Sepitrap 80 (formulation I2) showed a slower, more linear release of Cefdinir compared to formulation I1. Na_2HPO_4 as soluble pH modifier seems to increase the drug release as well as the solubilizer Sepitrap 80. In contrast, the addition of Eudragit E seems to have only a marginal, slowing effect on the drug release of the Cefdinir matrix tablets. When Cefdinir was granulated with Ryoto sugar ester S1670 (see 2.18) before incorporation into the matrix mixture (formulation I6), the drug release of resulting tablets could be slightly accelerated.

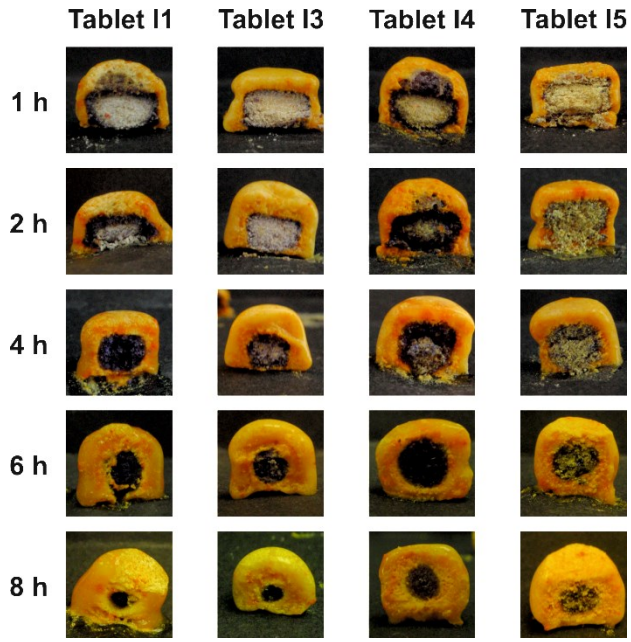


*Figure 60 Cross-sectional images of hydrated matrices of matrix tablets **I1 and I3-I5** with incorporated pH indicator bromcresol purple after different time intervals of contact with simulated gastric fluid pH 1.2. Purple domains indicate a pH >5, yellow domains indicate a pH < 4.5. The dry core appeared white. (Tablet I1: matrix formulation; Tablet I3: matrix formulation without Na_2HPO_4; Tablet I4: matrix formulation without Eudragit E, Tablet I5: matrix formulation without Eudragit E/ Na_2HPO_4).*

To gain deeper insight into the influence of formulation changes on the release behaviour of Cefdinir, the internal pH of tablets I1 and I3-I5 was analysed using pH indicator and EPRI as described before. Figure 60 shows cross-sectional images of hydrated matrices of matrix tablets with incorporated pH indicator bromcresol purple after different time intervals of contact with SGF. Purple domains indicate a pH >5, yellow domains indicate a pH < 4.5. The dry core appeared white. All tablets show a yellow outer layer which is spreading inwards depending on the time of buffer contact. The yellow colour is indicating an acidic pH caused by the pH of the surrounding buffer (SGF, pH 1.2). The tablet core of formulations I1 and I4 appeared purple (hydrated areas) and white (dry areas) indicating a more neutral pH caused by the incorporated Na_2HPO_4. Formulation I1 is completely hydrated after around 4 hours of buffer contact. After 8 hours of buffer contact, only a small purple inner core is visible indicating the almost complete absence of Na_2HPO_4due to neutralizing reactions and release. Formulation I4 showed similar results. Only marginal purple discolouration could be observed in case of formulation I3 (without Na_2HPO_4). A dry core could be detected for more than 4 hours of buffer contact. Eudragit E was hardly able to influence the internal pH of the matrix tablets indicating low buffer capacity. Therefore, Eudragit E showed only marginal influence on the drug release of Cefdinir by slowing down the hydration of tablets and the therewith associated drug release. Formulation I4 showed almost no purple discolouration caused by the absence of pH modifiers (inner core appeared white).

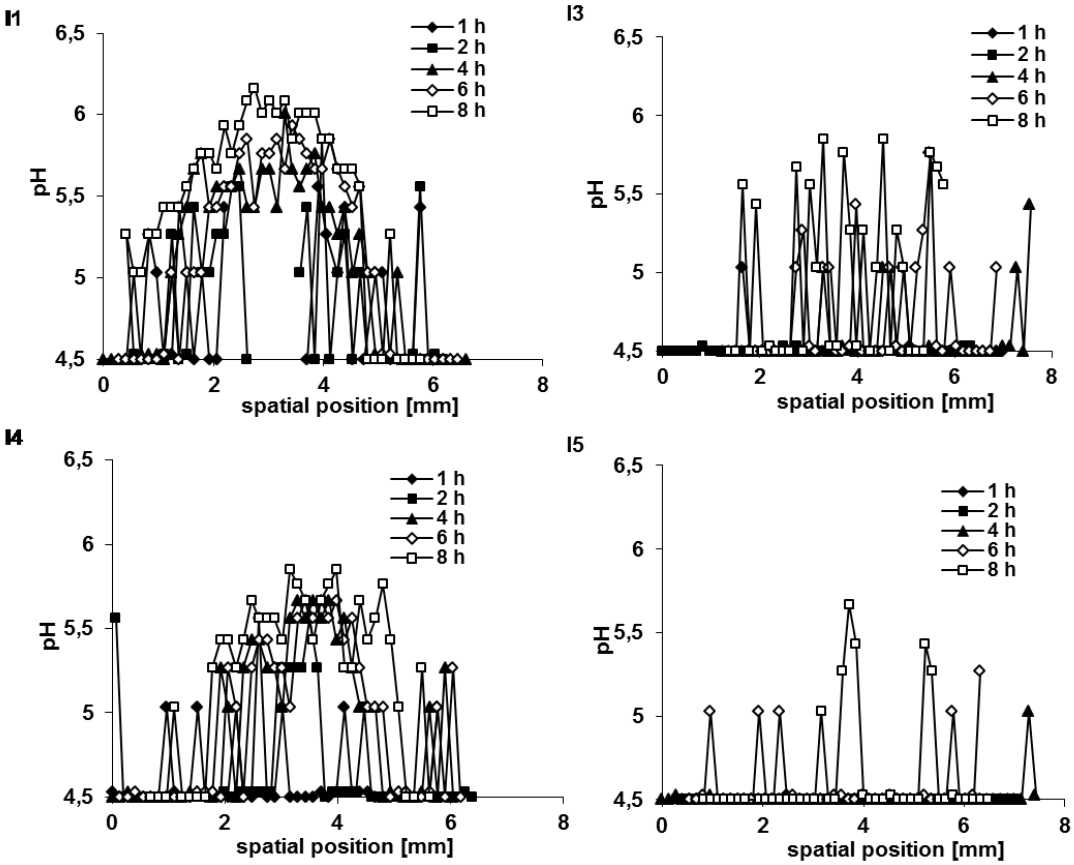


*Figure 61 pH_M averages within matrix tablets **I1 and I3-I5** calculated from EPR images which were generated at different time intervals of contact with SGF. No values could be determined for areas with a $pH_M \leq 4.5$. (I1: matrix formulation; I3: matrix formulation without Na_2HPO_4; I4: matrix formulation without Eudragit E, I5: matrix formulation without Eudragit E/ Na_2HPO_4).*

Figure 61 shows pH_M averages within matrix tablets I1and I3-I5, calculated from EPR images which were generated at different time intervals of contact with SGF. No values could be determined for areas with a $pH_M \leq 4.5$. It should be emphasised that the resulting pH_M describes an average pH_M value of a thin tablet layer, showing a pH_M gradient inside this layer with different pH_M values in the outer regions compared to the centre of the tablet (see Figure 60). Therefore, the pH_M values within the tablet core may be considerably higher than the calculated values of the whole tablet section. Nevertheless, the results were comparable with the results of the pH indicator method. Formulations I1 and I4 (with Na_2HPO_4) showed pH_M values above pH 6 in the middle layers of the tablets for more than 8 hours. In contrast, formulation I3 (with Eudragit E) showed only a marginal, instable and punctual increase of pH_M within the middle tablet layers. The pH_M of formulation I5 was mostly below the evaluation limit of pH_M 4.5. These findings support the assumption, that an increase in pH_M is able to increase the drug release of Cefdinir. Furthermore, it could be stated that pH modifier Na_2HPO_4 is able to modify the internal pH of Cefdinir matrix tablets whereas Eudragit E has only a marginal influence on the pH_M and therefore on the drug release of Cefdinir.

It was possible to analyse the influence of different pH modifiers on the pH_M of the matrix tablets over time of buffer contact with both methods (similar to the coated tablets B). The method establishment for the determination of internal pH gradients (see 3.2) has shown to be successful in gaining information about the average pH_M within solid drug delivery devices. One limitation for the correctness of the calculated pH_M values of the EPRI method was the determination of average values within a cross section of the tablet. One possibility to reduce the development of a pH gradient within a horizontal tablet layer would be the envelopment of the band height of the tablet. Therefore, the hydration of the tablet would only be possible from top and bottom of the tablet which should prevent the formation of horizontal pH gradients. Another possibility would be the determination of pH_M values within a tablet using EPRI with three-dimensional resolution (Kempe et al., 2010).

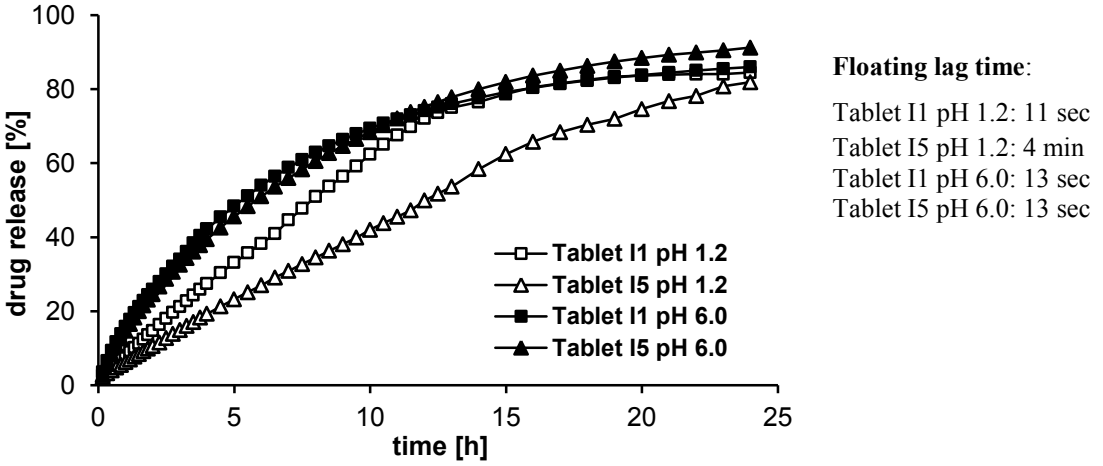


Figure 62 Influence of buffer pH on Cefdinir release of matrix tablets (pH 1.2: simulated gastric fluid pH 1.2; pH 6.0: Phosphate-buffer pH 6.0 R2 Ph. Eur.). (Tablet I1: matrix formulation; Tablet I5: matrix formulation without Eudragit E/ Na_2HPO_4).

The influence of buffer pH on drug release of matrix tablets was analysed to gain insight into the efficiency of the pH modifiers to achieve a pH independent release of Cefdinir. Formulation I1 was able to reduce the difference of the release curves at buffer pH 1.2 and 6.0 in contrast to formulation I5 (see Figure 62). The effect of buffer pH on drug release of Cefdinir could be reduced by modifying the internal pH.

The floating properties Cefdinir matrix tablets I1 were characterised to evaluate the success and security for the potential use as gastroretentive system *in vivo*. Figure 63 shows the floating process of matrix tablets I1 after different time intervals of contact with SGF. These tablets showed a floating lag time below 1 minute and a stable floating duration of more than 6 hours. A swelling process of matrix tablets, caused by the incorporated HPMC, could be observed as well. HPMC also enabled the entrapment of carbon dioxide bubbles which were generated upon hydration. The matrix tablet remained dimensionally stable and consistent upon hydration which

might be caused by the percentage of hardly soluble excipients (especially Cefdinir) within the formulation. Figure 64 shows the floating strength of matrix tablet I1 compared to the floating strength of a coated balloon-forming 2-layer placebo tablet (see 3.1.3). The floating lag time of the matrix formulation is shorter compared to the coated tablet whereas the increase in floating strength is slower and the maximum lower for the matrix formulation. The maximum floating strength values were between 200 and 250 mg. These values were maintained for more than 2 hours with a following slow decrease over more than 6 hours. Floating strength of the coated formulation was higher for the first 2 hours but showed only a marginal difference to the matrix formulation between 2 and 5 hours of buffer contact. The floating duration of coated tablets was more than 24 hours in contrast to the floating duration of the matrix tablets of 6 to 8 hours. Nevertheless, the Cefdinir matrix tablets showed a stable, consistent floating behaviour with a short floating lag time, a sufficient high floating strength and a floating duration which is feasible for its application *in vivo* (prolonged drug release of 6 to 8 hours).

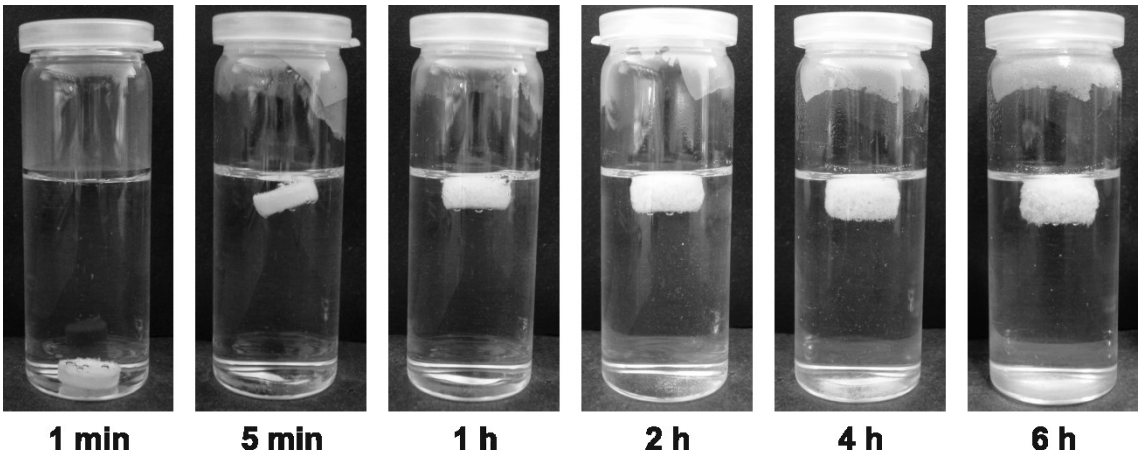


Figure 63 Photographs of matrix tablets I1 after different time intervals of contact with simulated gastric fluid pH 1.2.

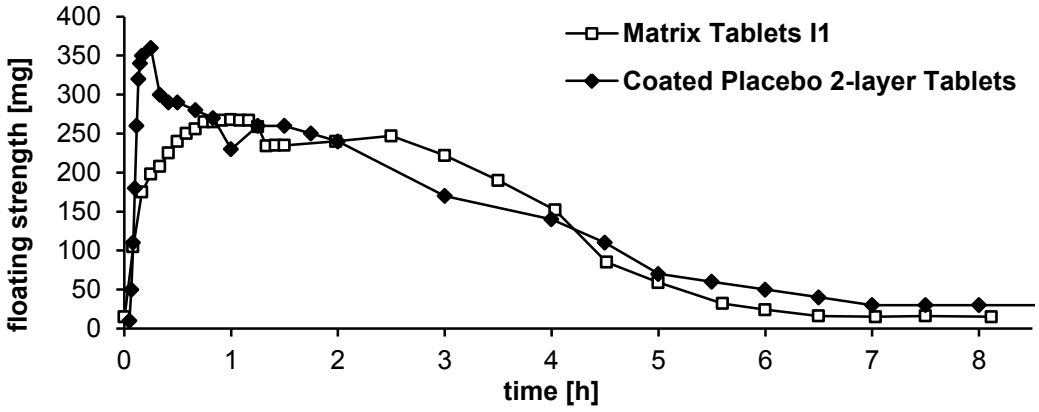


Figure 64 Floating strength of matrix tablets I1 in comparison to coated Placebo-2-layer tablets (see 3.1.3) over time of contact with simulated gastric fluid.

Tablets I7 (2-layer tablets consisting of 379 mg matrix layer I1 and 100 mg floating layer) were coated with Eudragit RL coating to analyse the effect of coating layer on drug release and floating behaviour. The floating lag time of the coated tablets was prolonged (around 3 minutes versus 12 seconds) and the floating duration could not be extended to more than 8 hours. The drug release was changed to a delayed, more linear release of Cefdinir (see Figure 65). In conclusion, an additional coating was not able to significantly improve the floating properties of the Cefdinir matrix tablets while it lead to a more constant release of Cefdinir over 24 hours of buffer contact.

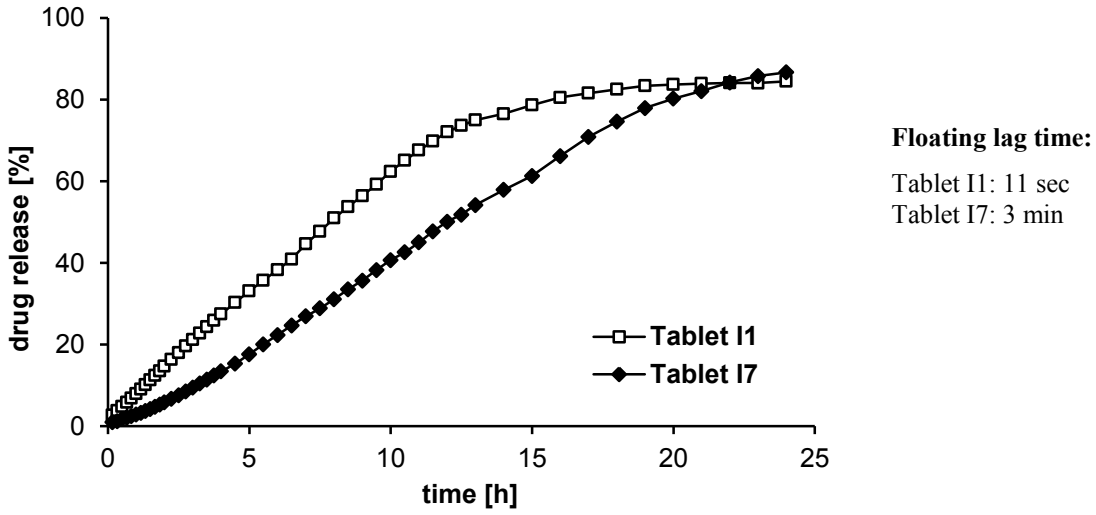


Figure 65 Influence of coating membrane on Cefdinir release and floating lag time of matrix tablets in simulated gastric fluid pH 1.2. (Tablet I1: matrix formulation; Tablet I7: 2-layer tablet (drug layer = matrix formulation I1) with Eudragit RL coating).

4 Summary and Outlook

4.1 Balloon-like floating devices for freely soluble model drug Metformin-HCl

Floating systems are a quite popular approach to achieve gastroretention of drug delivery devices because of the often simple preparation and non-interference with GIT motility. Furthermore, they show a lower risk of occlusion of the oesophagus or pylorus for the patient compared to swelling systems. On the other hand, many FDDS were faced to drawbacks like low floating strength, long FLT and short floating durations. Coated, gas-generating FDDS which were recently published have shown the advantage of high floating strength values, long floating durations and a stable, nearly linear drug release (Strübing et al., 2008a-c).

For this reason, balloon-like floating tablets were developed and characterized for Metformin-HCl as water soluble model drug. The coating of the tablets using poly(vinyl acetate) as insoluble, elastic polymer, was optimized regarding floating characteristics of tablets in aqueous media. When the amount of incorporated hydrophilic plasticizer was increased (Coating 2), the permeability of coating membrane increased as well. Therefore, the tablet surrounding water could penetrate faster which led to an accelerated carbon dioxide generation. A shortened FLT was the result. Furthermore, Metformin-HCl was dissolved faster and could diffuse through the coating more easily which led to a faster drug release. The more lipophilic plasticizer ATEC within Coating 3 showed no advantage concerning floating characteristics and drug release. Goole et al. (2008b) described an increase in drug release and floating strength when ATEC was used instead of the more hydrophilic plasticiser triethyl citrate (TEC) within ammonio methacrylate copolymer containing coating formulation. This finding was attributed to the slower leaching of the lipophilic plasticizer out of the coating membrane which was told to enhance the flexibility of the film for a prolonged period of time. No similar influence could be detected for the poly(vinyl acetate) containing coating formulation.

The tablet core was optimised by incorporation of sodium hydrogen carbonate combined with citric acid to achieve a pH-independent carbon dioxide generation behaviour. This combination led to an independence of FLT from pH of surrounding buffer which is crucial because of the changing pH within the human stomach. The FDDS need to have a short FLT within the fed stomach (around pH 6) as they generally should be taken after meals.

Figure 66 illustrates different tablet preparations, which were analysed within this study. The development of optimised 1-layer tablets, using Coating composition 2 and tablet core Formulation A, led to tablets with a reasonable drug release over 24 hours of buffer contact, a FLT of 11 minutes and a floating duration of more than 24 hours. Nevertheless, to further reduce the FLT and the risk of dose dumping (disintegration of tablet core after coating rupture),

2-and 3-layer tablets with a separation of gas generating excipients and drug were developed (see 2.2). Formulations D (3-layer) and E (2-layer) were found to best meet the expectations (FLTs below 5 minutes, a floating duration of more than 24 hours and a controlled drug release of the core tablet which minimised the risk of dose-dumping by coating defects). Beside these advantages, the drug release of the 2- and 3-layer formulations was somewhat decreased compared to 1-layer tablets A due to the enhanced integrity of the drug containing matrix layer. Another aspect which has to be taken into account was the increase in manufacturing efforts. For commercialisation, a multi-layer tablet press need to be used for tablet core preparation. Therefore, the manufacturing is more time and cost consuming than the manufacturing of 1-layer tablets. Especially 3-layer tablets D were dropped out from further analysis due to the high manufacturing time and effort as well as the higher deviations of drug release compared to 2-layer tablets.

Figure 66 Schematic composition of Metformin-HCl containing FDDS (see 3.1).

Floating strength measurements were carried out on 2-layer tablets E to gain a deeper insight into the floating behaviour of balloon-like floating tablets. The floating strength was found to be influenced by the coating level and the pH and viscosity of surrounding buffer. The floating strength showed higher maximum values and lower FLT at decreasing coating levels which was in accordance with Strübing, 2008c. The optimal coating level was found to be 8-9 mg/cm^2 regarding combination of short FLTs with a reasonable coating stability during time of hydration. High maximum floating strength values could be achieved which enabled the tablets to ascend through highly viscous media. The FLT was increased and the maximum floating strength values were slightly decreased and delayed when a viscous medium was used. Viscous media can be found within the human stomach during ingestion as well (Klein et al., 2004). Therefore, a reasonable floating strength is crucial for the success of the floating principle to prolong gastric retention times. It has to be considered that this kind of coated floating tablets should be administered with a glass of water to facilitate the water penetration through the tablet and therefore to accelerate the carbon dioxide generation and decrease FLT.

Floating and non-floating coated placebo 2-layer tablets were prepared as industrial feasibility study by Piramal. Floating tablets showed a slightly changed floating behaviour compared to the before mentioned 2-layer tablets E but were able to float within 2 minutes of buffer contact for more than 24 hours. Both tablet formulations could be used as clinical samples for a human pilot study. The non-floating tablets should act as control and enable information, if the floating of tablets has an influence on gastric retention times. Therefore, gastroretention times of floating

and non-floating tablets, each of similar size and weight and both non-disintegrating, can be detected by MRI measurements over time of tablet intake for comparison purposes. Black iron oxide was incorporated in the drug layer of both tablet formulations as non-toxic MRI contrast enhancing agent. The iron oxide enables a certain differentiation between clinical samples and possible food components or gas bubbles within the human stomach as described in literature before (Knörgen et al., 2010). To gain a deeper insight into the mechanism of gastric retention, floating matrix tablets (see 3.1.6.1) and swelling systems (see 3.1.6.2) should be analysed for their retention times within the human stomach as well. All studies have to be carried out under same conditions to enable conclusions about the efficiency and safety of different methods to prolong gastric retention within the human stomach compared to an insoluble control. No suitable *in vitro* model, which enables a comparison of the different gastroretentive methods and clarifies their possible success *in vivo,* exists until now. The usage of animal models is not constructive as well because of the huge differences within important physiological characteristics (stomach structure, ingestion behaviour, position: upright walk of humans) which makes the transfer of the results from animal models to humans highly questionable. Food and position (sitting, laying, walking) effects have to be taken into account as well (Waterman, 2007).

The stability testing of Tablets C (2-layer), D (3-layer) and E (optimised 2-layer) demonstrated constant drug release and floating characteristics for more than 12 months when stored under moderate conditions of 20°C and 40 % r.H. A curing process after manufacturing of coated tablets was able to decrease deviations of drug release. An enhanced relative humidity of 75 % showed to be responsible for a premature carbon dioxide formation of the stored tablets which was visible by distortions of the tablet coating. Although no clear influence of this finding on the drug release could be detected, floating tablets should be stored under moisture protection to prevent obvious change in tablet appearance.

Polymer material poly(vinyl acetate) Ph. Eur. (Kollicoat® SR), which was used for the coating of the beformentioned formulations, should be compared to ammonio methacrylate copolymer, type A Ph. Eur. (Eudragit® RL). The two polymer materials, which were already used for the manufacturing of gas-entrapping membranes before (el Samaligy, 2010; Goole et al., 2008a,b; Strübing et al., 2008a,c), were evaluated concerning robustness, release control, pH dependence of drug release and floating characteristics of 2-layer tablets E. Both polymer materials showed the ability to form a coating which was able to withstand the pressure of the generating carbon dioxide but with different characteristics of the coatings.

Ammonium methacrylate copolymer Typ A formed a very flexible coating (Coating 5). Resulting tablets showed short FLTs and a reasonable robustness under normal dissolution conditions *in vitro*. Different paddle speeds had no influence on the drug release. Dissolution

testing with different paddle speeds was discussed in literature before to analyse the robustness regarding mechanical stress of sensible formulation (Abrahamsson et al., 2005). Nevertheless, crack formation could be monitored in some cases, especially under harsher conditions (texture analyser, see Figure 29). The tablets were able to float only until the third cycle of stability testing using texture analyser even when SGF was used. Furthermore, the composition of Coating 5 was not able to control the drug release of the freely soluble drug Metformin-HCl. The coating level showed no influence on the drug release which was similar to the release of the pure core tablet (see Figure 23). The high permeability of this polymer can be advantageous, when a formulation for drugs showing poor solubility needs to be developed. However, the coating formulation has to be modified by incorporation of polymers showing low permeability (e.g. Ammonium methacrylate copolymer Typ B), if the membrane has to be responsible for a controlled drug release. Another possibility would be the control of drug release by an optimized matrix system of the core tablet. The drug release of tablets E/ Coating 5 showed a slight dependence on the pH value of the surrounding buffer showing the fastest release at pH 4.5. Bodmeier et al. (1995) explained this “pH dependence” by ion exchange processes where the anionic buffer species and not the pH showed to have a significant effect on the hydration and release from coated beads.

Poly(vinyl acetate) formed an elastic but robust coating (Coating 2). Resulting tablets showed slightly longer FLTs and a slow, controlled drug release of Metformin-HCl over more than 24 hours. This coating seems to be disadvantageous for drugs showing poor solubility. Although the drug release is depending on the coating level, a certain coating level is needed for a secure floating behaviour. The drug release of tablets with this coating showed to be independent from pH of surrounding buffer. Inflated tablets seemed to be more robust, compared to tablets with Coating 5, especially under harsh conditions. Remarkable is the fast recovery of the inflated tablets after pressure impact of texture analyser (see 3.1.6; Figure 28). The tablets were able to float even after the fourth procedure of stability testing after 8 hours of buffer contact when SGF was used as dissolution medium. No visible cracks within the coating could be observed. When dissolution stress test apparatus (DST, see 2.5.2) was used to further analyse the stability of these tablets, it was shown that the floating behaviour and the drug release were depending on pressure strength and buffer pH (see 3.1.6). Within SGF, tablets did recover after the occurrence of pressure waves and started floating again until the procedure at about 6 hours of buffer contact. A burst release of Metfomin-HCl could be observed during the pressure wave procedure independent from applied pressure strengths and pH of surrounding buffer while the drug release was controlled between the pressure waves (see Figure 30). In SGF buffer, the influence of the pressure waves on the drug release was much less pronounced compared to phosphate buffer pH 4.5. The tablets were optically intact after DST procedure of 12 hours. No loss of tablet core material could be observed. Although the drug release was increased when

the DST method was used compared to USP dissolution method, there was no complete drug dissolution within the pressure wave procedures. These stress tests applied a very high pressure on the tablets which could occur within the fasted human stomach during the so-called "housekeeping waves" (Garbacz et al., 2010). Therefore, it could be shown that even under this high pressure, the tablets showed a reasonable stability concerning drug release and floating behaviour. This finding can be attributed to the embedding of the drug into a polymer matrix where the drug release is controlled even when the tablet coating shows defects in tightness. The fast recovery of the tablets after the pressure procedure might be caused by the self-healing properties of the coating formulation which was described in literature before (Ensslin et al., 2009). Nevertheless, it seems that the stability and elasticity of the coating were pH dependent. Further elasticity analysis of coating membranes, which were hydrated in buffers of different pH, has to be carried out to confirm this assumption for both coating formulations.

The floating strength of tablets E coated with both polymers was comparable. Both formulations showed a pH dependence of floating duration and floating strength although the FLT showed to be independent from pH of surrounding buffer. Osmotic effects could be eliminated as possible explanation for this behaviour by additional release studies using buffers with same pH but different osmotic strength.

To gain further information on the mechanisms of this finding, water uptake behaviour over time of buffer contact of tablets E (Coating 2) in SGF and phosphate buffer pH 4.5 was analysed by weighing and ^{1}H-NMR. If more water would penetrate into the tablet core dependent from pH of surrounding buffer, the density of the tablet would increase which might lead to a sinking of the tablets. No obvious differences in water uptake of tablets in buffers of different pH could be detected independent from used method (see Figure 31). The water permeability of the coating seems to be independent from pH of surrounding buffer.

In another experiment, the amount of carbon dioxide, which was generated upon hydration of tablet cores in buffers of different pH, was analysed. The carbon dioxide formation is a pH dependent process. As more acidic the surrounding pH, as more is the reaction equilibrium shifted to the carbon dioxide formation. This may lead to an uncompleted and retarded carbon dioxide formation when phosphate buffer pH 4.5 is used instead of SGF. The results of this test gave a hint of different amounts of carbon dioxide, which were generated in buffers of different pH (more in SGF than in phosphate buffer pH 4.5, see 3.1.8). Nevertheless, the used method was not suitable to allow a secure and complete determination of generated carbon dioxide amounts. Different analytical settings would be necessary to confirm the assumption of an incomplete carbon dioxide formation in buffers of pH $\geq$ 4.5.

Formulation optimisations of tablet core formulation E were carried out with the goal of pH independent floating duration. The most promising results were obtained, when 10 % of citric acid was incorporated within the drug layer (Tablets I). These tablets showed a floating duration

of more than 24 hours independent from pH of used buffer. This finding supports the theory of pH dependence of the amount of carbon dioxide formation. Nevertheless, further analysis will be necessary to gain more information on the effect of the different internal pH on the elasticity of coating membrane and floating duration of Tablets I as well as on the robustness of the inflated tablets using dissolution stress apparatus and texture analyser. Other topics of interest for tablets I would be the comparison of floating strength in buffers of different pH over time of buffer contact and a carbon dioxide quantification related to the pH of surrounding buffers.

4.2 Monitoring of microenvironmental pH and analytical method establishment

Drugs showing pH dependent solubility/stability are a challenge for formulation development, especially when the physiological pH is inappropriate for drug dissolution at the absorption zone. Furthermore, a pH dependent release shows the disadvantage of inter- and intra-individual differences in bioavailability depending on the physiological pH variations. Cefdinir shows lowest solubility at pH 2 to 4, which is a common pH range within the human stomach. Therefore, Cefdinir is a challenging drug for a gastroretentive formulation where the retention time in the human stomach is prolonged.

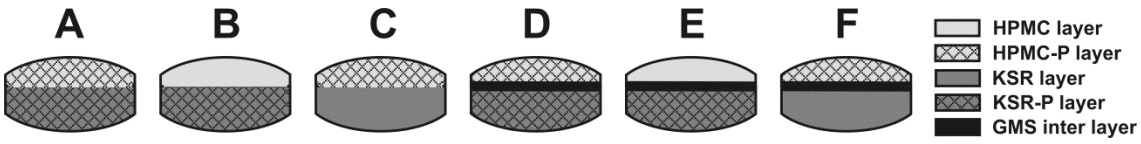


*Figure 67 Tablet compositions of tablets **A-F**, each tablet consisted of 200 mg KSR/-P (Kollidon SR without internal buffer system (IBS)/ Kollidon SR with IBS)- layer and 100 mg of HPMC/-P (HPMC without IBS/ HPMC with IBS)- layer, an additional inter layer of glycerol monostearate (GMS, 50 mg) was included in 3-layer tablets **D-F** (see 3.2) .*

To be able to optimise the drug release of Cefdinir regarding internal pH, methods for investigation of microacidity should be established. Therefore, pH_M gradients within non-floating 2- and 3-layer tablets were investigated using different techniques for comparison purposes. A pH indicator dye was incorporated into tablets **A-F** (see Figure 67**)** which allowed the differentiation between the tablet formulations because of their differences in local pH and therewith associated colour changes. Furthermore, it was possible to monitor the shifting of pH_M within the tablet layers over time of buffer contact and to observe differences in the pH_M shifting of 2- and 3-layer tablets. Nevertheless, this technique allowed only a very rough determination of the pH_M. It was rather difficult to relate a specified pH value to the colour grading of the indicator. Colours indicating same pH appeared different in both matrix forming excipients (HPMC and KSR). In addition, to investigate the pH_M in the interior of the tablet, the tablet had to be cut. It was therefore not possible to analyse the pH_M of one tablet continuously.

Fluorescence imaging gave the opportunity to calculate an average pH_M of an estimated domain of each tablet layer using a fluorescence dye with pH dependent changes in the emission spectra. Similar pH gradients were detected compared to the results of the aforementioned method. However, a different hydration setting had to be used to allow a constant measuring area which changed and delayed the hydration process and made comparison with other results rather difficult. Higher pH_M values were detected within the HPMC-P layer compared to the KSR-P layer of tablet **A** (same amount of IBS in both layers). The usage of different excipients could have an impact on the emission spectrum. The influence of the nature of excipient on the pH_M calculation was therefore analysed by fluorescence imaging. Kollidon SR and HPMC showed no clear trend to enhance or decrease calculated pH_M values. A 10 % Kollidon SR suspension in water generates a pH around 4.6 which also influences the resulting pH_M. Furthermore, the photographs of pH-indicator containing tablets showed a yellow discolouration of the surface of the previously blue KSR-P layer after one to two hours. In contrast, the colour of the HPMC-P layer changed only marginally. With fluorescence imaging, it was only possible to analyse the pH_M of the surface of the tablets because of the limited penetration depth of the excitation and emission light. The pH_M of the surface of the tablet could differ from those of the inner regions which can also contribute to the monitored differences in pH_M.

Therefore, EPR imaging was accomplished to determine the spatial pH_M distribution of the tablets non-invasively. EPR imaging provides the possibility to calculate the average pH_M of hydrated inner and outer regions of different cylindrical layers of the tablet giving a spatial pH_M resolution from top to the bottom of the tablet. Although the analysis with this technique is more time consuming, it gave unique information about the internal pH within analysed tablets and made a continuous measurement of one tablet over time of hydration possible. Furthermore, no influence of the nature of surrounding matrix material on the resulting $2a_N$ values could be detected (comparison of calibration curves of pure HPMC/ Kollidon SR tablets). However, the pH_M calculation is only possible in a limited pH interval of about ± 1.5 pH units depending of the pK_a of the spin probe (pK_a of AT is 6.1). Therefore, no pH_M values could be calculated in tablet regions showing a pH_M below 4.5. It is possible to investigate the pH_M within more acidic regions of the tablets by using a spin probe with a lower pK_a.

The pH of the buffer strongly influenced the internal pH of tablet layers without IBS. Almost no influence could be monitored in the case of tablet layers with IBS. The HPMC layer of tablet **B** (without IBS) showed an acidic pH_M after contact with buffer but started to change to nearly neutral values after 30 minutes. After 2 hours, the complete HPMC layer showed a pH around 6. A possible reason could be the migration of IBS out of the KSR-P layer into the HPMC layer. In contrast, the HPMC layer of tablet **E** remained acidic over 6 hours of buffer contact. The migration of IBS seems to be hindered by the lipophilic inter layer. In the case of the KSR layer of 2- and 3-layer tablet **C** and **F** (without IBS), an obvious pH_M gradient over more than 6 hours

of buffer contact was determined. Especially in the case of tablet **F**, the pH_M of the KSR layer showed an acidic pH value ≤ 4.5 over the analysed time interval of 6 hours, confirming the protective character of the inter layer. This finding could also be valuable to separate drugs with different pH stability optima by the usage of multi-layer tablets with an additional lipophilic inter layer. However, the pH_M of the KSR layer of tablet **C** increased only marginally in the centre region of the tablet as well, which was different from the behaviour of the HPMC layer of tablet **B**. The different behaviour of both matrix-forming excipients might possibly be caused by a faster water exchange within the KSR layer in comparison to the HPMC layer. Furthermore, the acidic behaviour of Kollidon SR seems to have an influence on the pH_M generation as well.

Dissolution studies were carried out to analyse the influence of the pH_M on the drug release. Two model drugs were incorporated into the KSR/ KSR-P layer of tablet **E/F** (with and without IBS). Metformin-HCl shows a pH independent solubility. Therefore, both formulations showed same drug release. In contrast, the release of Ketoprofen could be modified by the incorporation of the IBS. Ketoprofen shows a pH dependent solubility with an improved solubility under neutral conditions. Therefore, the drug release of tablet formulation **E** (with IBS) was faster compared to formulation **F** (without IBS). This finding is in agreement with literature data, where the drug release of weak acids could be improved by the incorporation of alkaline excipients (Doherty and York, 1989; Riis et al., 2007; Tran et al., 2008). Further formulation optimisation would be needed for a reasonable drug release over 12 hours. This issue was beyond the scope of this work as it was intended to keep the formulation of the layers constant for comparability purposes.

Benchtop NMR imaging was accomplished to further analyse the differences in the hydration behaviour of 2- and 3-layer tablets. The MRI signal of the HPMC layer appeared brighter compared to the signal of the KSR layer. The water inside the gel layer of HPMC is not as flexible as in the pores of the KSR matrix leading to a shorter T_1 relaxation time and a brighter signal. This issue could also have an influence on the different behaviour regarding the migration of IBS. Besides, it could be detected that water penetrated between the two layers of the 2-layer tablets which could enable a fast migration of IBS from the KSR-P to the HPMC layer of tablet **B**. Furthermore, a separation of both layers could be facilitated. The water penetration could be prevented by the additional lipophilic inter layer which improved the integrity of the tablets and possibly hindered the migration process of the IBS. In addition, 2- and 3- layer tablets were exposed to two different hydration settings. Tablets exposed to USP dissolution conditions showed a faster water penetration into and erosion of the HPMC layer compared to the unstirred tablets. These findings are consistent with previous work, showing the dependence of erosion and hydration processes of hydrogel-forming HPMC on mechanical stress (Costa and Labo, 2001; Kavanagh and Corrigan, 2004). Further studies have to be carried out to investigate, if mechanical stress could also change the migration behaviour of the IBS.

4.3 Development of floating systems for weakly acidic drug Cefdinir

The aim of the Cefdinir formulation study was to determine the influence of pH-modifiers, solubilizers, filling material characteristics, disintegrants and tablet core preparation on the drug release of Cefdinir as well as the development of FDDSs with suitable microacidity for a stable, pH independent release of the drug. Furthermore, the aspired FDDS should enable short FLT, high floating strength values and long floating duration.

Figure 68 Schematic composition of Cefdinir containing FDDS (see 3.3).

Figure 68 illustrates different tablet preparations, which were analyzed within this study. Drug release of 1-layer formulation A with Metformin-HCl (see 2.2.1) was compared to the release of Cefdinir out of same formulation (A2). Only 30 % of Cefdinir were released in difference to over 90 % of Metformin-HCl over 24 hours of buffer contact which was caused by the low solubility and wettability of Cefdinir in comparison to Metformin-HCl. The results of the determination of Cefdinir solubility at buffers of different pH showed lower solubility values compared to literature data. Nevertheless, the highest solubility of Cefdinir could be achieved in buffer of pH 7.5. Furthermore, sodium hydrogen carbonate (pK_{a1}= 6.46; pK_{a2}= 10.30) is an essential part of gas forming floating formulations. For these two reasons, basic pH modifiers should be analysed for their possibility to enhance the solubility and the therewith associated drug release of Cefdinir. Different pH modifiers were analysed for their effect on drug release and internal pH of coated 2-layer tablets (Formulations B). Na_2HPO_4 and $Ca(OH)_2$ were able to generate pH_M values above pH 6 (mean) within the drug layer for more than 8 hours of buffer contact which was confirmed by indicator method and EPRI. Nevertheless, the release of Cefdinir was low even for formulations showing optimised internal pH within the drug layer (Formulations B3, B4 and B6). Cross-sectional images of Formulation B6 upon time of hydration illustrate that the drug layer showed almost no hydrated regions for more than 4 hours. This finding indicated a slow water penetration inside the drug layer caused by low wettability of excipients. For this reason, Cefdinir was analysed for its wettability (see 3.3.3). It was shown that Cefdinir itself showed very low wettability characteristics which could be improved by granulation of Cefdinir with different solubilizers. However, it was striking that the lowest drug release was observed for Formulation B6, showing the most advantageous internal pH. Cefdinir showed to be stable in buffers of different pH (1.2 – 7.5) over more than 24 hours (see 3.3.2.1). In contrast, only around 50 % of Cefdinir of formulation B6 (with 40% $Ca(OH)_2$) could be recovered in total after 24 hours of buffer contact. Compatibility studies of

Cefdinir with excipients were carried out to gather information about the stability of Cefdinir (see 3.3.2.2). Most excipients showed little influence on the recovering rate of Cefdinir. $Ca(OH)_2$ turned out to show the highest effect on Cefdinir stability. Only about 35 % of Cefdinir could be recovered after 24 hours of compatibility study. A mixture of Cefdinir and $NaHCO_3$ showed a Cefdinir recovery of over 70 % under same conditions followed by Na_2HPO_4 with around 80 % of Cefdinir recovery. Because of its strongly alkaline and possibly complex-forming behaviour, the use of $Ca(OH)_2$ as pH modifier seemed to be not suitable for Cefdinir formulations regarding drug stability as well as coating polymer stability (see 3.3.2.4). Na_2HPO_4 was used as pH modifying substance for further analysis because of its promising effect regarding pH_M adjustment and drug release (Formulation B3) and its acceptable effect on Cefdinir stability. Another pH modifying substance which was analysed more precisely was Eudragit EPO. This polymer was used for internal pH adjustment of weakly acid drugs before (Rao et al., 2003). In case of Cefdinir containing formulations, Eudragit E was able to control the drug release but it seemed to have almost no influence on the internal pH and therewith associated drug solubility (see 3.3.4.4).

To further optimize Cefdinir containing FDDS, different solubilizers were analysed for their ability to fasten and enhance the release of Cefdinir (Formulations C1-C3, D1/2, E2-4, G3/6, H1-3, I1 and I3-I6). Especially formulations with Sepitrap 80 and Ryoto sugar ester D1216 showed an almost complete release within short time of hydration independent of the used type of addition (physically mixed/ granulated). The stability of the tablet coating was influenced by the solubilizers which was visible by the occurrence of cracks/ holes within the coating upon hydration, loss of tablet core material, high deviations in drug release and a floating duration which was considerably below 24 hours. The high ionic strength inside the tablet cores, caused by the addition of inorganic salts, might have a supplementary destabilising effect on the floating properties because of the increased water penetration through the coating layer.

The disintegration behaviour of the drug layer could be optimised by using Mannitol or MCC as filling materials in combination with Kollidon Cl as disintegrant (see 3.3.4.1). These formulation compositions led to a faster water influx into the drug layer which caused a faster dissolution of Cefdinir. Therefore, the release lag time of Formulations D1-3 could be reduced to around one hour of buffer contact in comparison to Formulations C1 and C3 (3 to 4 hours of buffer contact). However, it was not possible to enhance the drug release of the coated 2-layer formulations in total.

The investigated tablet cores showed different advantages and disadvantages regarding drug release and floating characteristics for Cefdinir formulations. 2-layer formulations (Formulations B-D) were advantageous to 1-layer formulations regarding the possibility to optimise floating and release behaviour independently of each other. Furthermore, Cefdinir was separated from $NaHCO_3$ which was positive for stability reasons. Nevertheless, release rates of

2-layer tablets with intact coating were quite low (maximum: Formulation C1 with around 47 % in 24 h). Press coated Formulations E showed higher release rates and Formulation E5 (with Eudrait E) floated for more than 24 hours. Disadvantages of these formulations were the time consuming production followed by an increase of Cefdinir degradation (see 3.3.4.2). This finding might be caused by the increased contact area of the surrounding floating layer with incorporated $NaHCO_3$ and the drug layer, which increased the potential of interaction between Cefdinir and $NaHCO_3$. 1-layer tablets were easy to produce but had the disadvantage of highest interaction potential of Cefdinir and $NaHCO_3$. In conclusion, although many coated formulations were developed and analysed for their ability to release Cefdinir in a controlled, prolonged manner as well as to show sufficient floating properties, no formulation met all expectations. The poor, pH-dependent solubility of Cefdinir were not entirely overcome even with internal pH adjustment, wettability improvement and disintegration optimisation. The Cefdinir diffusion through the coating layer was despite these adjustments quite slow. The most promising coated formulations were press coated Formulation E5 and 1-layer Formulation H3. Formulation H3 coated with Eudragit RL coating achieved best results showing a release of more than 50 % of Cefdinir over 24 hours of buffer contact, a release lag time of about 15 minutes, a floating lag time of 6.5 minutes and a floating duration of more than 24 hours.

To further optimise drug release, floating matrix formulations of Cefdinir were developed and characterised. Matrix formulations are often used to prolong the release of drugs showing poor solubility because of the possibility of drug release through different mechanisms (erosion of the matrix combined with diffusion through the matrix). Matrix formulation I1 showed a constant release of about 80 % of Cefdinir over 12 hours of buffer contact slowing down to only marginal release between 12 and 24 hours of buffer contact (around 15 % of Cefdinir lost through degradation). The floating lag time was very short (around 11 seconds) and the floating duration between 6 and 8 hours. Furthermore, the floating strength of matrix tablets was comparable with coated formulations, especially after the flattening of the floating strengths of the coated formulation after around 2 hours of buffer contact. Internal pH values of different matrix tablets (I1, I3-I5) were determined by indicator method and EPRI. It was possible to analyse the influence of different pH modifiers on the pH_M of the matrix tablets over time of buffer contact with both methods (similar to the coated Tablets B). The method establishment for the determination of internal pH gradients (see 3.2) has shown to be successful in gaining information about the average pH_M within solid drug delivery devices. One limitation for the precision of the calculated pH_M values using the EPRI method was the determination of average values within a cross section of the tablet. These cross sections showed a pH_M gradient with different pH_M values in the outer regions compared to the centre of the tablet. One possibility to reduce the development of a pH gradient within a horizontal tablet layer would be the envelopment of the tablet. Therefore, the hydration of the tablet would only be possible from

top and bottom of the tablet which should prevent the formation of horizontal pH gradients. Another possibility would be the determination of pH_M values within a tablet by EPRI with three-dimensional resolution.

Table 24 Summary of formulation approaches for Cefdinir containing tablet compositions.

Formulation (see 2.2.4)	**Formulation approach**	**Results**
Coated 1-layer tablets A1-A3	Influence of drug solubility	Low release and floating characteristics of Cefdinir containing formulation (A2) compared to Metformin-HCL containing formulation caused by low solubility and wettability characteristics of Cefdinir.
Coated 2-layer tablets B1-B6	Influence of pH-modifiers	Na_2HPO_4 showed highest improvement of drug release (~22 % over 24 h of contact with SGF; B3), drug release of all formulations low and pH dependent
Coated 2-layer tablets C1-C3	Influence of pH-modifiers and solubilizer	Na_2HPO_4 showed highest improvement of drug release, Eudragit E lead to nearly linear release of Cefdinir, solubilizer decreased coating stability (FD < 24 h)
Coated 2-layer tablets D1-D4	Influence of pH-modifiers, solubilizers, filling material and disintegrant	Solubilizer Sepitrap 4000 increased drug release, MCC decreased lag time of drug release compared to mannitol, disintegrant Kollidon Cl decreased lag time of drug release , no influence on total drug release, low FLT, coating instabilities (small cracks, FD < 24 h)
Press-coated tablets E1-E5	Influence of solubilizers and tablet core preparation	Short FLTs, higher release rates, solubilizer caused coating instabilities, Cefdinir degradation enhanced, E5 (Eudragit E) showed a nearly linear release (~46 % over 24 h of contact with SGF) and FD > 24 h
Coated 1-layer tablets G1-G6	Influence of pH-modifiers, solubilizer, filling material, tablet core preparation and coating formulation	Solubilizer caused coating instabilities, Fujicalin as fillig material (G5) led to higher, more controlled drug release compared to MCC (~60 % over 24 h of contact with SGF) and short FLTs, Eudragit RL coating showed higher and faster drug release and decreased FLTs compared to Kollicoat SR coating, FD < 24 h for all formulations
Coated 1-layer tablets H1-H3	Influence ofsolubilizer and filling material	H3(Fujicalin, Eudragit RL coating) showed best results (short FLTs, ~53 % drug release after 24 h of contact with SGF, FD > 24 h)
Matrix tablets I1-I7	Influence of pH-modifier, solubilizer and principle of release control	I1: FD > 8 h, more than 85 % Cefdinir release over 24 h of contact with SGF, very short FLTs, high floating strength values, nearly pH independent release, increased FLTs without Na_2HPO_4, decreased, more linear release without Na_2HPO_4 and Sepitrap 80, nosignificant benefit of Eudragit E, additional coating with Eudragit RL (I7) led to more linear drug release but did not improve the floating properties

Table 24 summarizes the formulation approaches as well as corresponding results for the introduced Cefdinir compositions.

4.4 Conclusions

In conclusion, optimised balloon-like floating tablets were developed in pilot and industrial scale which showed short FLTs, reasonable floating strength values, floating durations of more than 24 hours and a robust, pH independent floating behaviour and Metformin-HCl release. These FDDS can be used as safe once-a day formulation for suitable drugs. Because the drug needs to penetrate a low permeable polymer membrane (Coating 2, Coating polymer poly(vinyl acetate) Ph. Eur./ Kollicoat® SR), this system is suitable for drugs showing high water solubility as Metformin-HCl. Another coating polymer, which has shown to be suitable for balloon-like floating devices as well (Coating 5, Coating polymer ammonio methacrylate copolymer, type A Ph. Eur./ Eudragit® RL), showed a high permeability for active ingredients combined with a decreased robustness of inflated tablets. Robustness studies of different formulations were carried out using dissolution stress test apparatus (see 2.5.2). DST analysis has shown to be a powerful tool to mimic *in vivo* conditions of the stomach. This special dissolution testing is able to indicate possible safety issues of gastroretentive formulations as well as to characterize the robustness of drug release. Further experiments have to be carried out to better understand the pH dependence of floating duration of some tablet core formulations as well as verify the success of these systems regarding elongation of gastric retention times *in vivo*. For this purpose, coated floating and non-floating 2-layer Placebo-tablets were produced in industrial scale and all documents, which are necessary for application of a human pilot study, were created within the scope of this work.

Furthermore, pH_M gradients within multi-layer tablets were analysed using 3 techniques, in particular, a pH indicator dye, fluorescence imaging and EPR imaging. It was possible to gain information on the pH_M with all applied techniques. The qualitative results were similar but the informative value showed major differences. The incorporation of a pH indicator dye turned out to be a simple, fast and inexpensive method to get an overview over proceeding processes. However, no precise pH_M determination was possible and the inner tablet regions could be analysed only invasively. Fluorescence imaging produced calculable results of the pH_M of the tablet surface. A spatial distribution of the surface pH_M could be provided. However, a different hydration setting had to be used, excipient interactions were hard to predict and the inner regions of the tablet can be analysed only by cutting the tablet. In contrast, EPR imaging proved to be a powerful tool for the determination of spatial pH_M information non-invasively. However, it should be emphasised that the resulting pH_M describe an average pH_M value of a thin tablet layer, possibly forming a pH_M gradient inside this layer with different pH_M values in the outer

regions compared to the centre of the tablet. Furthermore, it is a time consuming method which requires expensive equipment. Nevertheless, because of its superior advantages, EPR imaging was used as method of choice for further analysis. The influence of different variables on the pH_M was investigated. The incorporation of an IBS strongly influenced the pH_M as well as the nature of used matrix forming excipient. Kollidon SR generated a more acidic microenvironment compared to HPMC, which was obvious in particular when buffer pH 5.5 was used where the pH_M of the KSR layer underlay the buffer pH. The pH_M of the KSR layer maintained acidic over the analysed time interval. Otherwise, the HPMC layer was able to turn primary acidic pH_M to more neutral values notwithstanding of the acidic properties of the surrounding buffer which may be caused by the migration of IBS from the KSR-P layer. The variation of the buffer pH had an influence on the pH_M especially within tablet layers without IBS. An additional lipophilic inter layer (3-layer tablets D - F) strongly improved the integrity of both layers. Furthermore, it acted as pH neutral region which could decrease diffusion processes between the layers and therefore influence the pH gradient formation. BT-MRI was accomplished to gain a deeper insight on the differences of proceeding processes during hydration of 2-and 3-layer tablets. The protective character of the inter layer was confirmed which could prevent water penetration between the HPMC and the KSR layer, leading to the aforementioned advantages. Mechanical stress influenced the hydration process as well, which was monitored by using different hydration settings. Moreover, an influence of the pH_M on the drug release of the weakly acidic drug Ketoprofen could be demonstrated. In contrast, the drug release of Metformin-HCl, showing pH independent solubility, was not influenced by varied pH_M, as expected.

With this knowledge on microacidity, it was possible to develop different floating drug delivery devices for Cefdinir, a drug showing a pH dependent solubility. The formulation development was challenging due to several additional disadvantageous properties of the drug like low solubility, wettability and stability during dissolution. Floating matrix tablets were found to be the best suitable system for a prolonged release of Cefdinir regarding optimisation of drug release, robustness and floating characteristics of the device. These tablets showed high floating strength values, short FLT and a floating duration of more than 6 hours. The incorporation of alkaline pH modifiers showed to have an impact on internal pH of the tablets which was confirmed by indicator method and EPRI. Furthermore, it was possible to enhance the drug solubility and the therewith associated drug release by adoption of the internal pH with pH modifying substances. The incorporation of solubilizers let to an improved wettability and release of Cefdinir. In vivo trials have to be carried out to further confirm the effectiveness, robustness and benefit of the matrix formulation as gastroretentive drug delivery device for Cefdinir.

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