Floating Gastroretentive Drug Delivery Systems based on Functionalized Calcium Carbonate

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Dekan

Für meine Lieben.

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Abbreviations

API	active pharmaceutical ingredient
AUC	area under the plasma concentration-time curve
$\mathbf{c_{max}}$	maximum plasma concentration of drug
CPP	critical process parameter
CQA	critical quality attribute
FCC	functionalized calcium carbonate
FDA	Food and Drug Administration
FDDS	floating drug delivery systems
GI	gastrointestinal
GMO	glycerol monooleate
GRDDS	gastroretentive drug delivery systems
GRT	gastric residence time
HBS^{TM}	hydrodynamically balanced system
HCl	hydrochloric acid
HPMC	hydroxylpropyl methylcellulose
MMC	migrating myoelectric complex or migrating motor complex
MRI	magnetic resonance imaging
PAT	process analytical technology
PVP	polyvinylpyrrolidone
QbD	Quality by Design
QTTP	quality target product profile
$\mathbf{t_{max}}$	time to reach the maximum plasma concentration
USP	United States Pharmacopoeia

Summary

Orally-administered controlled-release drug delivery systems are associated with the shortcomings of relatively short residence times in the human stomach as well as highly variable gastrointestinal (GI) transit times. Thus, considerable intra-individual and inter-individual differences in the bioavailability of drugs are observable. There are numerous drug substances which may benefit from prolonged and controlled GI passage times. As a solution to the problem, gastroretentive drug delivery systems (GRDDS), which feature an enhanced gastric residence time (GRT), were developed. Several gastric retention approaches, such as flotation, have been proposed and analyzed.

Despite the extensive research performed in the field of GRDDS, the development, the production, and the evaluation of floating devices are still challenging. The aim of the thesis was to come up with a formulation strategy which facilitates the design of innovative floating drug delivery systems (FDDS).

Hydrophilic and lipophilic floating formulations were prepared by wet granulation and melt granulation, respectively. Tablets with an inherent density of less than unity were compacted using porous functionalized calcium carbonate (FCC) as matrix-forming component. For the concurrent assessment of drug release by UV/Vis spectroscopy and floating behavior by visual observation, a custom-built stomach model method was set up. Our *in vitro* evaluation method was combined with *in silico* dissolution simulations to analyze the floating force as a function of drug release. To determine the *in vivo* gastric retention potential of FCC-based FDDS, a study protocol has been proposed for the assessment of the stomach residence time of floating tablets and non-floating references in humans.

The production of tablets and mini-tablets, which met the requirements for immediately floating tablets (i.e. inherently low density accompanied by sufficient hardness), was possible due to the characteristic lamellar structures of the FCC particles. The tablets showed no floating lag time and remained afloat until complete release of the model drug substance caffeine. For the hydrophilic formulation, the drug release was erosion-controlled and the flotation mechanism was a reaction-based erosion mechanism with gelation-layer-forming polymers as imbibition-inhibiting and gas-entrapping components. In the case of the lipophilic formulations, flotation was achieved by slowing-down and/or inhibiting the reaction-based erosion of FCC due to hydrophobization of the particle's stratum layer [215]; the release of the drug was

diffusion-controlled and erosion-controlled.

A FDDS formulation design tool box (including the novel pharmaceutical excipient FCC, an *in vitro* stomach model, an *in silico* tablet dissolution simulation approach, and an *in vivo* clinical study concept) was proposed to assist the future formulation development, the production, and the analysis of innovative FDDS. We introduced and applied a classification system, including an "ideal" floating performance (i.e. no floating lag time, maintaining of the floating force until complete drug release, followed by a decrease of the floating capability) to categorize experimentally observed flotation behavior. It was shown that FCC is an enabling excipient for the manufacture of FDDS and the preparation of formulations with an "ideal" floating behavior was possible. The results of the *in vivo* experiment provided a first evidence for the gastric retention potential of FCC-based floating tablets in humans.

1 Introduction

In the following chapter, the anatomy and the physiology of the human stomach are described in order to illustrate the gastrointestinal (GI) transit of orally-administered pharmaceutical dosage forms. The concept of gastroretentive drug delivery with focus on floating drug delivery systems (FDDS) is explained. Furthermore, the current state of research in the field of gastroretentive drug delivery is summarized and shortcomings associated with the manufacture and the evaluation of floating dosage forms are shown.

1.1 Drug candidates for a gastroretentive delivery approach

The residence time of an orally-administered dosage form in the human stomach and hence of the drug substance is relatively short compared to the transit time through the rest of the GI tract [82]. It is reported that orally-administered drugs pass through the stomach to the intestine within 1 to 2 h [95]; whereas, the residence time in the colon may take 15 up to 48 h [240]. Thus, a reason and a need for a gastroretentive delivery approach are primarily dictated by physiological necessity. By prolonging the stomach residence time of a pharmaceutical dosage form, the total GI transit time of the active pharmaceutical ingredient (API) is extended. Consequently, the bioavailability and the therapeutic efficacy may improve. A reduction of the dose, as well as of the drug administration frequency, may be possible [226].

The gastroretentive delivery approach offers new and important therapeutic options for numerous APIs [168]. An overview of drugs which benefit from a prolonged GI residence time is given below:

(i) Drugs which are **locally active in the stomach**, such as antacids [62], antibiotics for the

eradication therapy of *Helicobacter pylori* infections (e.g. amoxicillin, metronidazole) [10], and misoprostol [161], profit from an extended stomach residence time.

(ii) The gastroretentive drug delivery approach is beneficial for APIs **with a narrow absorption window in the stomach or in the upper part of the small intestine** (e.g. ciprofloxacin [6], cyclosporin [15], furosemide [162], levodopa [94], p-aminobenzoic acid [103, 104], and riboflavin [94]).

(iii) An extended stomach residence time may be favorable for drugs which exhibit a **low solubility at higher pH values** (e.g. chlordiazepoxide [205], diazepam [204], and verapamil HCl [196]).

(iv) Drugs, such as captopril [156], which are **unstable in the intestinal or colonic environment** are possible candidates for a gastroretentive delivery approach.

However, it has to be kept in mind that a prolonged retention in the stomach is not appropriate for drugs which may cause gastric lesions (e.g. non-steroidal anti-inflammatory drugs) [226]. The gastroretentive delivery approach is also not convenient for APIs that are unstable in the acidic stomach environment [220].

1.2 Anatomy and physiology of the stomach

The human stomach is an "J"-shaped organ which is positioned in the left upper part of the abdomen, behind the liver, part of the diaphragm, and the anterior abdominal wall. The pancreas, the left kidney, the left adrenal, the spleen, and the colon are situated behind it. Though, the position, the shape, and the size of the stomach may vary depending on the extent of the gastric contents [120, 240]. The empty stomach has a volume of approx. 50 mL; in the filled state, the stomach volume increases up to a maximum of 1500 mL [207].

1.2.1 Structural organization

FIGURE 1.1 illustrates the structure of the human stomach. The organ is dividable into different anatomical regions, these include the fundus, the body/corpus, and the pylorus (i.e. pyloric antrum and pyloric canal) [89]. The proximal part of the stomach, which is composed of the fundus and the upper one-third of the body, functions as a reservoir for ingested food and liquids [115]. The distal stomach, consisting of the remaining body and the pyloric portion, is the main region responsible for mixing motions, grinding, and homogenization of gastric contents. In addition, the gastric emptying of ingested material is regulated in this part by contraction and propelling actions [122].

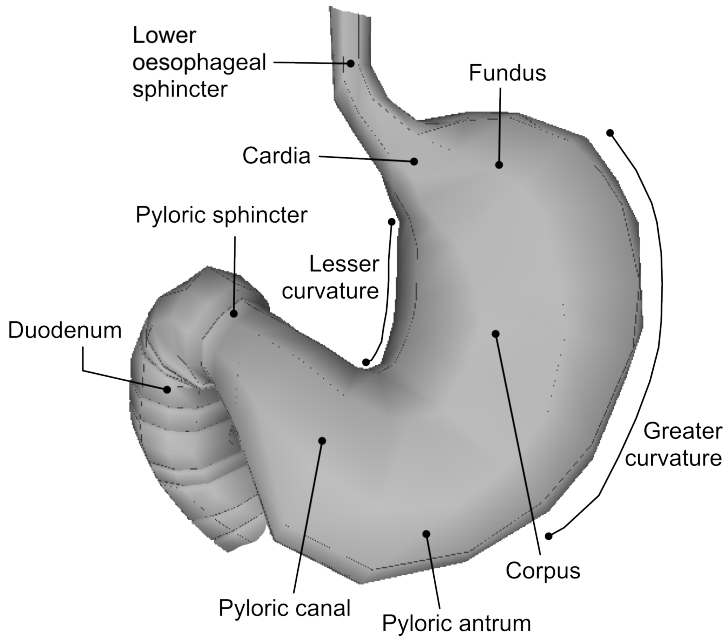

FIGURE 1.1. Structural organization of the human stomach. Adapted from Washington et al. [240].

1.2.2 Gastric pH

In general, the gastric pH for the fasted state is reported to range from 1.5 to 2.0 [27]. It is not uniform within the different regions of the human stomach due to variations in the distribution of the gastric acid-producing parietal cells and due to gastric motility [240]. Dressman et al. measured a median gastric pH of 1.7 in the case of young, healthy men and women. In the fed state, following the ingestion of a standard solid and liquid meal, the gastric pH increased to a median value of 6.7 [55].

Several parameters, including gender and age [187, 240], diseases [139], drugs [27], and composition of meals [240], were investigated regarding their effect on the gastric pH. However, the results of the *in vivo* evaluation in human are often contradictory. Some studies demonstrate an influence of the above-mentioned factors on gastric pH; whereas, other trials do not reveal any effect.

1.2.3 Gastric motility patterns

Two distinct patterns of GI motility, based on fed or fasted state, are distinguished [64]. The gastric emptying process occurs in both conditions [43].

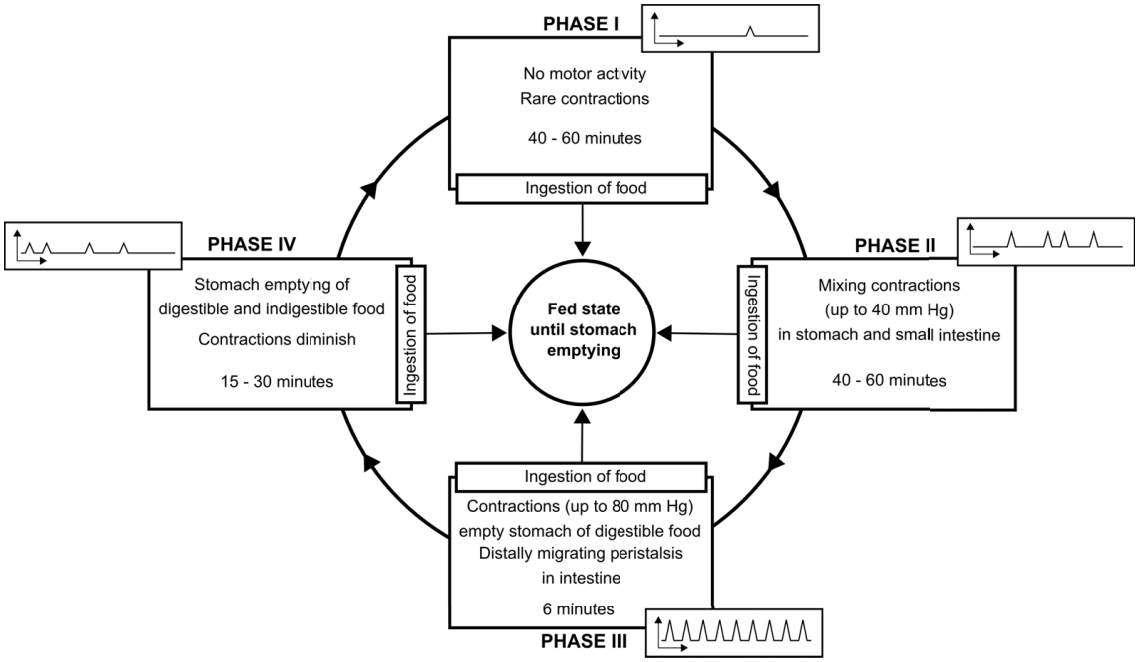

FIGURE 1.2. Overview of the phases of the MMC; it was first described in human in 1977 by Vantrappen et al. [233]. Adapted from Kong and Singh [122], Luiking et al. [133], Minami and McCallum [145], and Washington et al. [240].

1.2.3.1 Fasted state

In the absence of any digestible material, the stomach and the small intestine return to the fasted motility pattern, which is their resting condition [240]. The fasted state is characterized by an interdigestive series of events: the **migrating myoelectric complex** or **migrating motor complex** (MMC) [133]. The contraction pattern cycles through the stomach and the small intestine in 2 to 3 h [64]. Within an individual and between individuals, the MCC activity varies significantly [52]. Differences are observed in the total MMC cycle length, the duration of the individual phases, and the amplitude of the contractions [114].

FIGURE 1.2 displays the four consecutive phases of the MMC which are discriminated by different contractile activities. The MMC starts with a quiescent state (**Phase I**) where no motor activity or only rare contractions take place in the stomach. It is followed by series of irregular mixing contractions (**Phase II**) that begin simultaneously in both the antrum and the duodenum. The intensity and the frequency of the contractile activity increase during this period; a contraction strength up to 40 mm Hg is recorded. **Phase III** is characterized by powerful and regular contractions at their maximum frequency and amplitude (up to 80 mm Hg) against an open pylorus also referred to as "housekeeper waves". Large solid particles are now emptied from the stomach into the small intestine. Then, the motor activity decreases and is followed by a resting period (**Phase IV**).

The cycle repeats until a meal is ingested. The ingestion of food disrupts the fasted state

motility pattern and initiates the digestive phase of motility [122, 240].

1.2.3.2 Fed state

After the ingestion of a meal, the digestible material is processed in the stomach to chyme. The chyme is a slurry composed of separate phases of aqueous solution, fats, and solid material [122, 207]. Both mechanical forces and chemical reactions break down the ingested meal into small food fragments.

The motility pattern of the stomach walls is characterized by two types of contractions [122]. The first type of motor activity is slow and weak, volume-reducing contractions that arise in the upper part of the stomach [163]. The second type of muscle contractions are series of peristaltic waves which originate in the corpus and spread distally towards the duodenum with continuously increasing intensity [65, 240]. The contraction forces are responsible for the mixing and grinding motions in the stomach and push the antral contents towards the pylorus [122]. They are often referred to as antral contraction waves [65]. The antral contractions progress towards the duodenum until simultaneous contraction of antrum and pylorus (i.e. antral systole). After closure of the pylorus, the antral systole mixes solid components with the gastric juice; it grinds and retropels food particles into the proximal antrum. A "sieving effect" occurs as large and dense food fragments get trapped ahead of the constriction [122, 240].

The gastric emptying of meal components (liquids, digestible and indigestible solids) occurs at different rates and not in form of a homogeneous mass. The liquid components empty exponentially (i.e. first order kinetics) according to the pressure gradient between stomach and intestine [26]. The stomach empties solid material in a biphasic pattern. A variable lag time, during which only little material is emptied, is followed by a linear phase of emptying [206]. Solid components are emptied after they were ground, due to grinding and shear forces, to particles sizes smaller than 1 to 2 mm [122]. The duration of the lag time depends on the size of the food particles: larger particles need longer digestion times to be broken down into sizes enabling the emptying through the pylorus.

1.2.4 Gastric emptying process

Numerous factors influence the gastric emptying process and, consequently, the gastric residence time (GRT) of orally-administered drug delivery systems. The characteristics of a dosage form affect its retention in the stomach [151, 240]. The intake of food and the administration of some drug substances are known to modify the gastric motility pattern [22, 153]. Intra-subject and inter-subject variability in stomach emptying may be explained by physiological factors [220].

(i) Properties of dosages forms which influence the gastric emptying

The emptying of delivery systems from the stomach depends on the type of dosage form: the stomach transit time of solutions, capsules, pellets, and tablets varies. Solutions pass

through the stomach into the duodenum within 18 min; the longest stomach residence time is observed for tablets with approx. 2.7 h [168]. In addition, the gastric emptying time of dosage forms is affected by their density and size. In most cases, it applies: the larger the size of the system the longer the GRT. Due to the larger size, the stomach emptying through the pylorus is hindered [5, 35, 75]. Disintegrated tablets are emptied with the digestible phase of a meal; whereas, tablets that remained in shape are emptied with the indigestible material [240].

(ii) Pharmaceutical agents which influence the gastric emptying

Prokinetic drugs enhance the gastric motility and promote the transit through the GI tract [225]. The class of drugs includes, for example: benzamides (e.g. metoclopramide, cisapride), cholinergic agonists (e.g. bethanecol), dopamine antagonists (e.g. domperidone), macrolide antibiotics (e.g. erythromycin), opiate antagonists (e.g. naloxone), and somatostatin analogs (e.g. octreotide) [131].

In contrast, the GI motility is slowed down by anticholinergic agents (e.g. atropin [179], propantheline [152]), opioids [150], and tricyclic antidepressants [247].

The anti-parkinsonian drug levodopa alters the gastric emptying [181]. Adrenergics influence the GI motility: β_2-adrenergic agonists (e.g. isoprenaline) retard, whereas, β_2-adrenergic antagonists (e.g. propanolol) accelerate the gastric emptying process [140].

(iii) Influence of food intake on the gastric emptying

The stomach empties liquids more rapid than solid material [115]. And the gastric emptying of digestible solid meal components occurs faster than of indigestible solids [63]. The size of the ingested meal influences the gastric emptying: the larger the amount of ingested liquid or solid material, the longer the time period which the stomach remains in the fed motility pattern [240]. There is only little evidence provided to support the hypothesis that the meal consistency has an impact [99]. However, the nutritive density and the food composition (carbohydrates, proteins, fat) are reported to influence the gastric emptying rate [235].

(iv) Physiological factors which influence the gastric emptying

The gastric emptying follows the circadian rhythm. The emptying of solids occurs in the morning faster than in the afternoon and evening. In the case of liquids, no differences in the gastric emptying depending on the time of day are observed [79, 240].

The age does not seem to have an effect on the gastric emptying. It was reported to be similar for young and elderly persons; although, the secretion of hydrochloric acid (HCl) and pepsin decreases in elderly people [135]. Contradictory study results were obtained by Moore et al. They reported differences in the stomach emptying of liquids for aged men compared to young subjects [149].

Healthy women exhibit significantly prolonged GRT of solid material compared to men; but, no significant difference is observed in the gastric emptying of liquid meals [14]. In contrast, Datz et al. discovered that females empty both, solids and liquids, slower than men [38]. The menstrual cycle and pregnancy are known to alter the gastric motility patterns [19, 237].

Study results regarding the effect of the body mass index on the gastric motility are contradictory [18]. There are reports providing evidence that obesity is associated with increased gastric emptying rates [109]. However, obese subjects were also found to exhibit similar or depressed stomach emptying rates compared to normal weight subjects [97, 236].

In order to evaluate the influence of the body position on the stomach emptying, subjects were studied in lying, sitting, standing, and combined sitting-standing postures. The lying body position delays the gastric emptying process in comparison to the other body positions [148].

(v) Diseases which influence the gastric emptying

Diseases which alter the stomach emptying process and the gastric motility are primarily disorders of the GI tract [240]. Gastric ulcerations reduce the antral motility; therefore, the stomach emptying is delayed [144]. In contrast, ulcerations in the duodenum are reported to promote the gastric motility [127]. Patients suffering from diseases, such as atrophic gastritis, Crohn's disease, and pernicious anaemia, show delayed emptying of food components [40, 126, 154]. The effect of gastro-esophageal reflux on the emptying process of solid material and liquids has been evaluated. In some patients, gastro-esophageal reflux slowed down the gastric emptying, whereas, in a number of patients the gastric motility patterns remained unaffected [138].

Diabetic patients are known to exhibit altered GI motility patterns and drastically delayed gastric emptying rates [98].

The study data regarding the impact of bulimia nervosa on the GI motility patterns are contradictory. On the one hand, the gastric emptying was found to be unaffected in patients and, on the other hand, abnormal gastric motility patterns and emptying rates were observed. Anorexia nervosa is associated with delayed stomach emptying of liquid and solid meal components [51, 182].

During migraine attacks, the gastric emptying process is depressed in patients [17].

1.3 Gastroretentive drug delivery systems

Oral controlled-release pharmaceutical dosage forms are known to have limitations due to relatively short and unpredictable GI transit times. The interest in innovative pharmaceutical

drug delivery systems which exhibit prolonged GRT has significantly increased during the last decades [176, 195]. Gastroretentive drug delivery systems (GRDDS) were developed to overcome the drawback associated with conventional dosage forms [33]. GRDDS are designed to remain in the stomach for an extended and controlled period of time [168]. Due to a prolonged stomach residence time, the total GI transit time of the drug substance is extended and the bioavailability may improve [5].

1.3.1 Approaches to prolong gastric retention

Researchers have proposed various mechanisms to retain drug delivery systems in the stomach for an extended period of time [168, 226]. An overview of the different techniques is given in FIGURE 1.3.

1.3.1.1 Co-administration of (pharmacologically active) substances

A prolonged GRT of drug delivery systems is achievable by the simultaneous administration of (pharmacologically active) substances which slow down the gastric motility [50]. The passage-controlling excipients may be incorporated in the dosage form and when the substances are released, they delay the GI transit of the drug delivery device.

An *in vivo* study has demonstrated that the GI transit time can be modulated by the administration of drug substances. The pre-treatment with metoclopramide enhances; whereas, the pre-treatment with propantheline delays the gastric emptying process. The effect of the GI-motility-altering APIs has been investigated on the absorption of subsequently-administered metformin in human subjects [136].

Dietary components (e.g. certain amino acids, fats, peptides) are known to prolong the time period that a dosage form remains in the gastric region [42]. For example, the co-administration of fatty acid salts (e.g. salts of myristic acid) delayed the gastric emptying in humans. The effect of ammonium myristate was studied *in vivo* following the administration of a commercially available sustained-release nitrofurantoin capsule formulation. The renal nitrofurantoin excretion was assessed in order to investigate indirectly the influence of ammonium myristate on the absorption of the API. The addition of a GI-passage-controlling agent was found to improve the drug bioavailability and to reduce the inter-individual variations [87, 88].

1.3.1.2 Bioadhesive and mucoadhesive systems

Bioadhesive (i.e. immobilization at intestinal surfaces) and mucoadhesive (i.e. immobilization restricted to the mucus layer) systems prolong the relatively short GRT of orally-administered drug delivery systems by adherence of the dosage form to the mucous membrane of the stomach or the epithelial surface of the remaining GI tract [166, 173, 226]. There are different theories

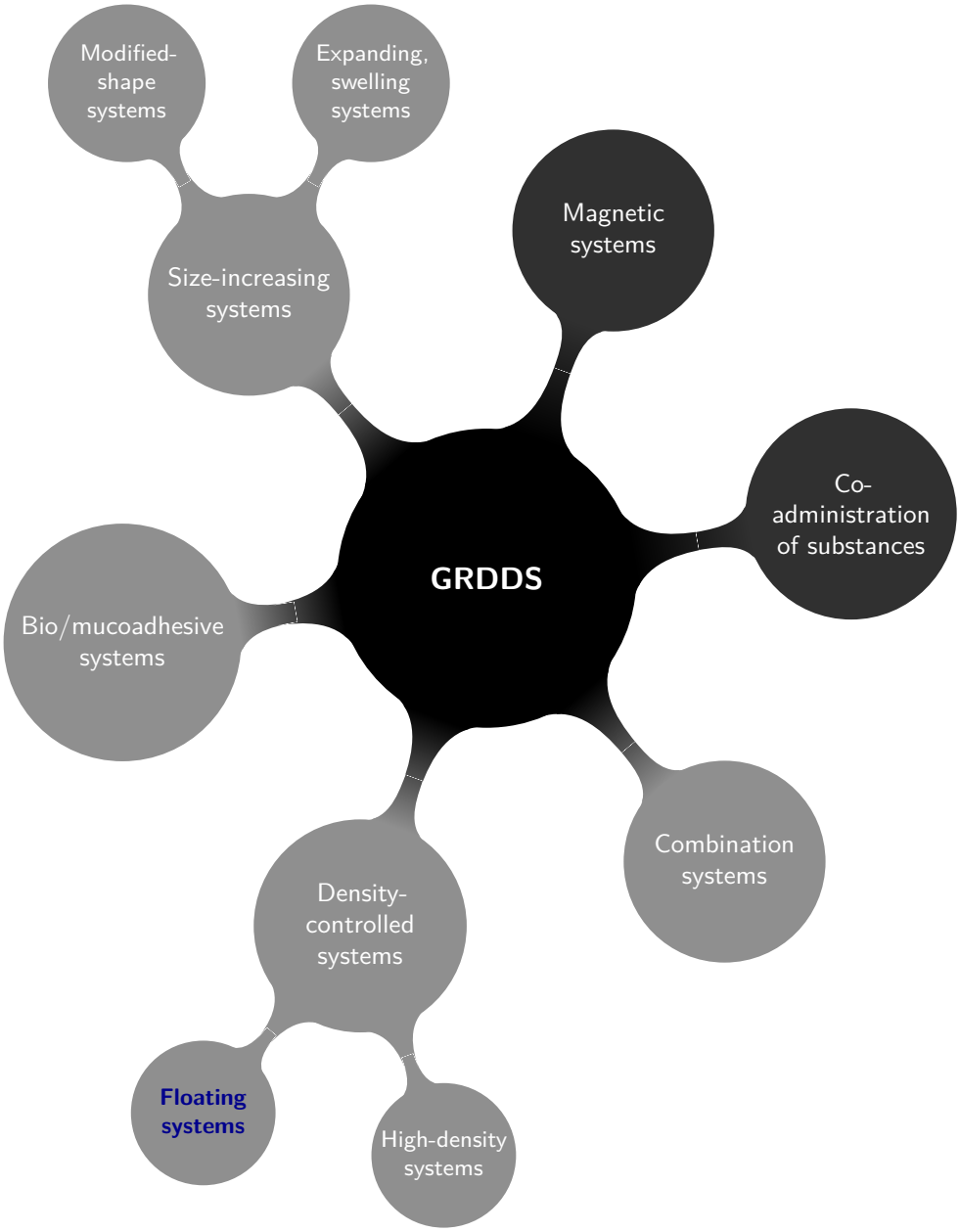

FIGURE 1.3. Overview of different approaches to prolong gastric retention. The most commonly used and the more rarely used mechanisms are colored in light gray and dark gray, respectively [220, 242].

to explain the mechanism of bio/mucoadhesion: the electronic theory, the adsorption theory, the wetting theory, and the diffusion-interlocking theory [10].

Several polymers have been analyzed regarding their bio/mucoadhesive potential. Chitosan, cholestyramine, poly(acrylic acid) (e.g. Carbopol®, polycarbophil), Gantrez® (polymethyl vinyl ether/maleic anhydride copolymers), cross-linked dextran gel (e.g. Sephadex®), dextran, hydroxypropyl methylcellulose (HPMC), polyethylene glycol, sodium alginate, sucralfate, tragacanth, poly(alkyl cyanoacrylate), and polylactic acid are used for preparation of bio/mucoadhesive systems [10, 81, 242].

The gastroretentive potential of bio/mucoadhesive GRDDS has been evaluated *in vivo* in human. Using γ-scintigraphy, the influence of polycarbophil on the GRT of a pellet formulation was investigated in fasted subjects. The pellets were found to be rapidly emptied from the stomach [117].

Akiyama et al. compared the GI transit time of sustained-release adhesive and non-adhesive microspheres in fed and fasted volunteers. The GI transit was pharmacokinetically assessed by analyzing the furosemide plasma concentrations and the riboflavin concentrations in urinary excretions. The microspheres, based on the bioadhesive substance carboxyvinyl polymer, showed an extended gastric retention due to the adherence of the dosage form to the gastric and/or intestinal mucosa [1].

The *in vivo* γ-scintigraphic studies of Säkkinen et al. did not provide a clear evidence whether formulations containing microcrystalline chitosan can be used as gastroretentive delivery platform. In a few volunteers the microcrystalline chitosan granules were retained in the GI tract for an extended time period compared to the reference formulation of lactose granules [188].

It is difficult to target specifically the GI walls. The use of bio/mucoadhesive substances bears the risk of the dosage forms to attach to the esophageal walls. This results in injuries or possible occlusion of the esophagus [168]. Another challenge is the high gastric mucus turnover rate [3]. Due to the regular renewal of the mucosal surface, the adhesion duration is limited [173]. In the stomach and the intestine, the mucus is constantly secreted and digested from the luminal surface. In the human stomach, the turnover time from the production to the removal of the mucus layer is estimated to range from 4 to 5 h [240]. The bio/mucoadhesive drug delivery systems may be encased by a mucus shell. In addition, the efficacy of the delivery approach is influenced by the gastric peristalsis because it may hinder the adhesion of the dosage forms to the GI walls [3].

1.3.1.3 Size-increasing systems

The size-increasing GRDDS are based on the principle of expansion of the pharmaceutical dosage form in the stomach to dimensions larger than the pyloric sphincter [220]. Consequently, the gastric emptying of the drug delivery system through the pylorus is retarded [176].

The size-increasing systems exhibit three configurations. The initial size of the dosage form should be small to facilitate swallowing ("collapsed" configuration) [176]. The delivery approach bears the risk of causing severe injuries or obstruction of the esophagus due to a premature expansion of the dosage form during swallowing [110]. After contact with the gastric juice, the size of the device increases rapidly to prevent uncontrolled stomach emptying through the pylorus [220]. The diameter of the human pyloric sphincter is reported to be 12.8±7 mm [120, 189]. It is thought about establishing a threshold value for the size of dosage forms above which a significant gastric retention may be observable. Researchers have suggested to set a minimum tablet size of 13 mm as cut-off value [120, 220]. The cut-off value is supported by experimental observations: it was discovered that non-disintegrating tablets with a size of 13 mm were retained in the stomach for a prolonged time period compared to 7 mm tablets [118]. The expanded dosage form needs to be rigid enough to withstand the mechanical destruction forces acting in the stomach. On the other hand, the device should not effect the gastric motility, inhibit the gastric emptying, or show local adverse effects (e.g. puncture of the GI walls) [120]. After release of the API, the GRDDS need to be present again in a small configuration to allow clearance from the stomach in order to prevent a permanent stomach retention [168]. The delivery approach has the potential risk of life-threatening complications due to the occlusion of the pylorus or due to the accumulation of dosage forms after multiple administrations.

The size-increase of dosage forms is achievable by different principles. They are explained and illustrated, by means of examples, in the section below:

(i) Expanding, swelling systems

In the stomach, the expanding, swelling systems increase in size to such an extend that their passage through the pyloric sphincter into the intestine is prevented and their GRT is prolonged. Due to their tendency to remain stuck at the pyloric sphincter, the dosage forms are referred to as "plug-type-systems" [200].

Enzyme-digestible hydrogels, based on polyvinylpyrrolidone (PVP) cross-linked with functionalized albumin, have been prepared to extend the GRT of APIs. The swelling and degradation properties of the system were controllable by the albumin cross-linker content and by adjusting the degree of albumin alkylation [198, 199]. The concept of hydrogels has been further investigated and superporous hydrogels, which exhibit gastroretentive properties due to rapid swelling of the delivery system, were developed. The fast swelling of the superporous hydrogels to equilibrium size within minutes is achieved by liquid uptake due to capillary wetting through inter-connected pores. The addition of composite material (e.g. croscarmellose sodium) during the synthesis improves the mechanical properties of the hydrogels [29–32]. Omidian et al. have invented novel superporous hydrogel hybrids with advanced mechanical, elastic, and swelling properties [158, 159].

A GRDDS composed of a swellable tablet core which is coated with a porous membrane

has been investigated. The inner core consisted of the API, the expanding agents (e.g. PVP, Carbopol®), and calcium carbonate. For the permeable tablet coating, different ratios and types of Eudragit® were studied regarding sufficient elasticity to withstand the expansion pressure during swelling and to allow the disintegration of the dosage form after drug release [47, 48].

An expanding system, which exhibits a very high swelling ratio (2 to 50-fold volume increase), has been patented by Theeuwes et al. Due to its large size, the device was, on the one hand, retained in the stomach for an extended time period and, on the other hand, it influenced the gastric motility pattern. The GRDDS are supposed to maintain the stomach in the fed state and thereby delay the onset of the "housekeeper waves" which would empty the dosage form from the stomach. The device consists of tiny, drug-containing pills with a release-controlling wall dispersed within a hydrogel reservoir. The stomach emptying is enabled due to erosion of the device [228].

A complex mechanism of action to increase the dimensions of a drug delivery system and to achieve its gastric retention has been described by Mamajek and Moyer (Figure 1.4). The outer polymer envelope, which is permeable for both, drug and body fluids, contains an expanding agent and a drug metering device. After contact with the gastric contents, the expanding agent causes the expansion of the envelope by osmotic pressure. As a result, the dosage form is retained in the stomach while the drug metering mean releases the API in a controlled manner [134].

Gröning et al. developed compressed collagen sponges which expand after contact with the gastric fluids. The *in vivo* gastric retention capability of the devices has been studied in healthy human subjects following the oral administration of collagen tablets and small sustained-release reference tablets. In the case of the expanding devices, the renal excretion of riboflavin was enhanced; hence, providing evidence for the applicability of the collagen sponges as a drug delivery platform featuring a prolonged GI transit time [85, 86].

(ii) Modified-shape systems

Several unfolding GRDDS with different geometry, size, erodibility, and mechanical properties have been patented. For example, the dosage forms exhibit the following geometries: cloverleaf, planar disc, planar multilobe, pellet/sphere, ring, solid stick, and string (Figure 1.5). For a convenient oral administration, the devices are packed into gelatin capsules. In the stomach, the capsule dissolves and releases the drug delivery device. It unfolds to a sufficiently large size preventing the emptying through the pylorus. The developed GRDDS are claimed to exhibit sufficient resistance to the forces present in the GI tract. After a predetermined period of time, the erosion of the device occurs; thus, enabling the stomach emptying of the dosage form [23–25]. The *in vivo* performance of 2 cm-arms tetrahedrons has been studied in human. In the fasting state, the administered

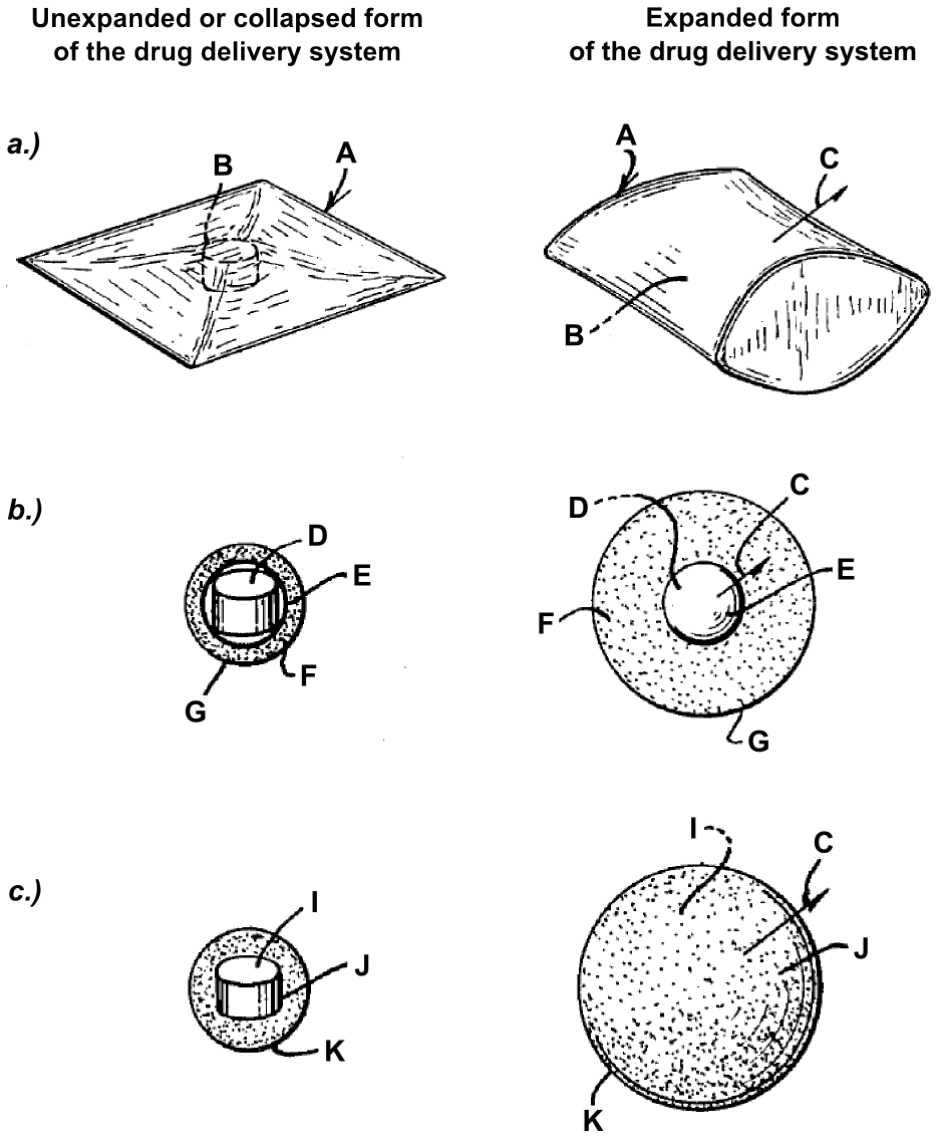

FIGURE 1.4. Schematic representation of expanding delivery devices proposed by Mamajek and Moyer [134]. *(a.)* The dosage form consists of a polymer envelope (**A**) which contains drug and expanding excipients (**B**). *(b.)* The system is based on a drug mixture (**D**) which is enclosed by a first polymer envelope (E), surrounded by expanding excipients (**F**), and packed into another polymer envelope (**G**). *(c.)* The drug delivery device is composed of the drug mixture (**I**) embedded into expanding excipients (**J**), and enclosed by an outer polymer envelope (**K**). Release of the drug substance is indicated by (**C**).

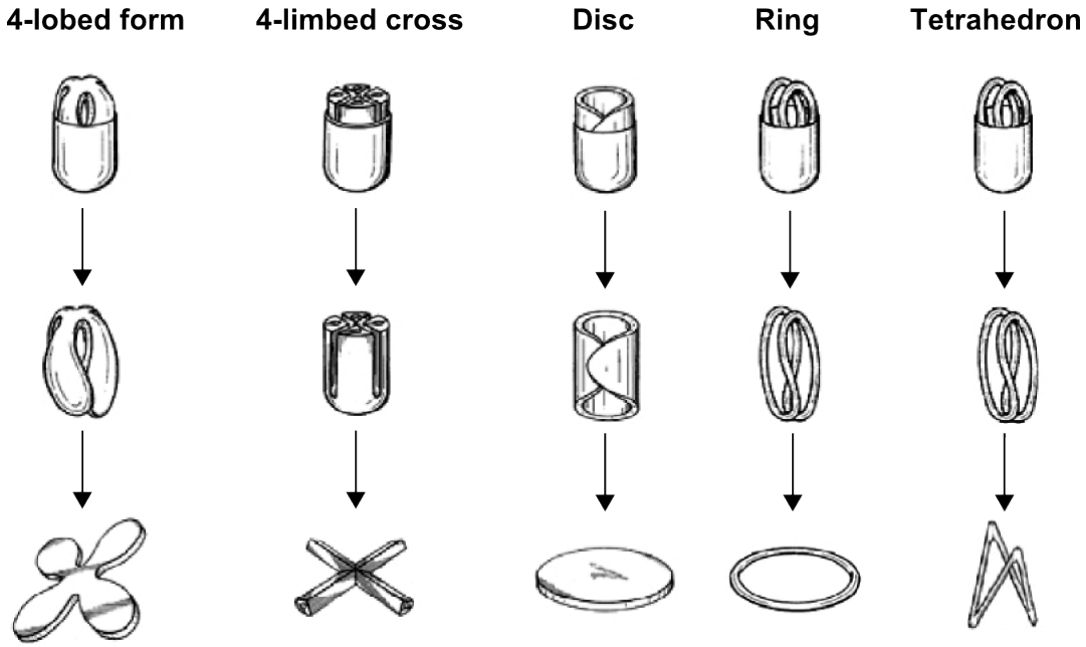

FIGURE 1.5. Schematic representation of unfolding devices proposed by Caldwell et al. The carrier gelatin capsule contains a drug delivery system in the compressed state. In the stomach, the delivery device unfolds. Adapted from Bardonnet et al. [10].

tetrahedrons exhibited a median GRT of 3 h. But, the stomach residence time was found to be highly variable, ranging from 0.5 to 6 h. Under fed conditions, the median GRT increased to 6.5 h. The retention time of the dosage form in the human stomach, after the regular ingestion of meals, varied from 3.5 to 12 h [67].

The unfolding GRDDS are often associated with the disadvantages that the devices are complex and expensive from the manufacturing point of view. Another problem of the above-described modified-shape systems is the degradation of their elastic and mechanical properties after relatively short time. Long storage times and the stress thereby applied to the dosage forms affect negatively the ability of the devices to expand in the stomach [120, 168]. This drawback was addressed by Pogany and Zentner. They invented bioerodible, thermoset, covalently-crosslinked, elastomeric poly (ortho esters). The material, being referred to as "prolonged mechanical shape memory material", extends the time period after which the dosage forms start loosing their unfolding capability [172].

In order to extend the GRT of drug substances, Sonobe et al. developed modified-shape systems composed of at least three coplanar limbs which extend from the center of the device (FIGURE 1.6). The GRDDS are prepared of a molding of "prolonged shape memory material" combined with eroding excipients. The API is mixed with the erodible material; it defines the stomach residence time of the dosage form by its degradation rate [211].

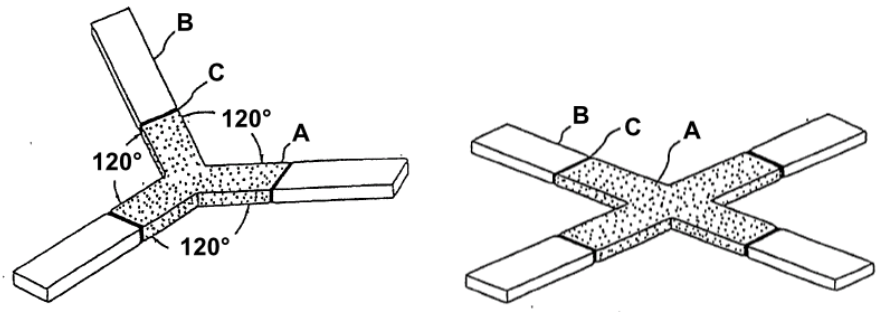

FIGURE 1.6. Schematic representation of unfolding dosage forms proposed by Sonobe et al [211]. The devices (e.g. Y-shape, cruciform) are constructed of so-called "shape memory material" (**A**), erodible material serving as drug reservoir (**B**), and connection pieces (**C**).

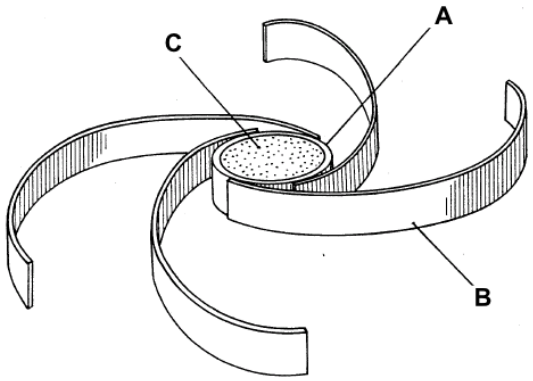

FIGURE 1.7. Schematic representation of a gastroretentive dosage form proposed by Curatolo and Lo [37]. The device is composed of four retention arms (**B**) connected to a receptacle (**A**) which contains a controlled-release tablet (**C**).

An unfolding spiral or coil configuration was proposed by Curatolo and Lo to delay the GI transit time of drug substances (FIGURE 1.7). It consists of a drug reservoir in form of a capsule or tablet and at least one retention arm attached to the drug container. In the stomach, the fiber-shaped or ribbon-shaped retention arms should unfold, uncoil or unroll to reach cross-sections of at minimum 3 cm. After complete API release, the gastric emptying of the receptacle is enabled due to softening, disintegration, dissolution or detachment of the retention arms [37].

The successful *in vivo* performance of an unfolding multilayer ("sandwich-type") polymeric GRDDS was demonstrated by Klausner et al. After oral administration of the drug delivery device to healthy subjects, a significant prolongation of the absorption phase was observed for drugs with a narrow absorption window in the GI tract (e.g. furosemide, levodopa) [71, 119, 121].

1.3.1.4 Magnetic systems

The magnetic systems are composed of a dosage form, containing a small internal magnet or a mass of magnetic material, and an extra-corporal magnet to control the GI transit of the dosage form [72, 84].

The concept of magnetic drug delivery systems has been evaluated in human. By using a magnetic model dosage form which consists of small magnets attached to a pH-telemetring capsule (Heidelberg capsule), it was demonstrated that due to an external magnet the GRT of the model dosage form could be significantly extended [83]. In addition, magnetic depot tablets have been analyzed. They were retained in the stomach region for a prolonged period of time; hence, an extension of the acyclovir absorption after peroral administration of a sustained-release magnetic drug delivery platform was achieved [84].

Despite the promising results of the *in vivo* studies, the magnetic drug delivery systems exhibit a major shortcoming: the external magnet needs to be placed with a high degree of precision; therefore, a good patient compliance is required.

1.3.1.5 High-density systems

Orally-administered pharmaceutical dosage forms with a density higher than the density of the gastric contents (1.004-1.01 g/cm^3 [174]) sink down to the bottom of the greater curvature of the stomach, in case the patient is in an upright position, and get entrapped in the folds of the antrum. The devices are located on a level lower than the pylorus away from the antral mixing. Consequently, the gastric emptying is supposed to be delayed [13]. High-density systems are prepared by the incorporation of heavy inert material, such as barium sulfate, iron powder, titanium dioxide, and zinc oxide [10, 184].

Contradictory results were obtained regarding the influence of density on the GI passage time of dosage forms. The *in vivo* gastric emptying rates of pellets with densities of 0.94 g/cm^3 and 1.96 g/cm^3 did not differ significantly in γ-scintigraphy studies [44]. The observation is supported by the finding that pellets with densities of 1.29 g/cm^3 and 1.92 g/cm^3 did not vary in gastric emptying times [35].

In contrast, Bechgaard and Ladefoged have reported prolonged average GI transit times in ileostomy subjects after increasing the density of a multiparticulate formulation from 1 g/cm^3 to 1.6 g/cm^3 [13]. The clinical study of Simoni et al. showed that the administration of an enteric-coated sinking ursodeoxycholic acid tablet formulation (density>1 g/cm^3) to healthy subjects resulted in a better bioavailability of ursodeoxycholic acid compared to an enteric-coated floating tablet and a hard gelatin capsule [208].

Above a threshold value of 2.4-2.8 g/cm^3, the high-density delivery systems are reported to be retained in the rugae at the bottom of the stomach [36]. A significantly prolonged stomach residence time was found for pellets with a density of 2.6 g/cm^3 [36] and 2.8 g/cm^3 [49] in comparison to control pellets with a density of 1.5 g/cm^3.

Up to now, there is no high-density GRDDS available on the market. A drawback of the dosage forms is the limited drug loading capacity. High amounts of heavy inert material need to be added to the formulations in order to achieve and maintain a sufficiently high density. The porosity of high-density devices is low, resulting in a slow drug release speed and in difficulties controlling the drug release kinetics.

1.3.1.6 Floating systems

The concept of tablets which have a density less than unity was first described in 1968 by Davis. His invention was aimed to solve the problem of gagging and choking experienced by some people when swallowing a pharmaceutical dosage form. Due to a density less than unity, the medicinal pill floats on liquid surfaces. The intake with a certain volume of water is supposed to facilitate swallowing of the dosage form [41].

FDDS are pharmaceutical dosage forms exhibiting a density lower than the gastric fluids (1.004-1.01 g/cm^3) [201]. Due to its density less than unity, the dosage form floats on the gastric contents and is retained in the stomach while releasing the API [168]. FDDS offer the advantage that they do not influence the gastric emptying process [209]. But, the filling state of the stomach is important; a certain amount of liquid is required for floating delivery platforms.

Single-unit FDDS (e.g. tablets, capsules) are associated with the problem of "all-or-nothing" gastric emptying [10]. Therefore, high inter-subject and intra-subject variability in GI transit time and in bioavailability are observed. However, most floating devices described in literature are single-unit dosage forms [209]. The design of multiple-unit FDDS offers the possibility to overcome the shortcomings of single-unit devices [212]. Multiple-unit floating dosage forms spread over the gastric contents and they are gradually emptied from the stomach. The drug release profiles are supposed to be more predictable and inter-individual as well as intra-individual differences in bioavailability are claimed to be reduced [168].

Different mechanisms are known to achieve flotation: **floating systems due to swelling of excipients** [205], **non-effervescent systems with an inherently low density** [220], and **effervescent systems which float due to the generation and entrapment of gas** [8].

(i) Non-effervescent drug delivery systems with flotation due to swelling

One of the first floating GRDDS described in literature is the so-called hydrodynamically balanced system (HBS^{TM}). It is a single-unit floating gelatin capsule which contains a mixture of drug substance and one (or more) gel-forming hydrophilic polymers [205]. For example, agar, alginic acid, carrageenans, hydroxyethylcellulose, HPMC, hydroxypropylcellulose, and sodium carboxymethylcellulose have been studied as gelation-layer-forming excipients [168]. Upon contact with the gastric fluids, the gelatin capsule shell dissolves; hydration and swelling of the polymers occur. A buoyant mucus body with a density of less than unity is formed. At the surface, the gelatinous barrier erodes constantly and a

new hydrated layer is generated. The API release is controlled by diffusion and by erosion of the hydrated gel barrier. The principle of HBS^{TM} is also applied for the preparation of floating gastroretentive tablets [202, 203] and mini-tablets [185].

Kumar et al. has studied the use of glycerol monooleate (GMO) matrices for the manufacture of floating, swelling GRDDS. The API was added to molten GMO under stirring. Then, the molten mass was transferred into cylindrical molds and frozen. The swelling and flotation performance of the devices has been evaluated *in vitro*. The authors concluded that GMO matrices are suitable for oral controlled-release floating GRDDS [125].

(ii) Non-effervescent floating drug delivery systems with inherently low density

The preparation of FDDS featuring an inherently low density (i.e. the devices are immediately floating on the gastric contents) is favored. The systems have a reduced risk of unpredictable, premature gastric emptying because the flotation mechanism does not need to be activated in the stomach [220]. Long floating lag times increase the possibility of premature gastric emptying of the dosage forms by the "housekeeper waves" before flotation starts. An inherently low density may be achieved by the entrapment of air and/or the incorporation of low-density material [220]. Such kind of low-density material includes, for example, fatty components or oils [213], porous material [57], and foamed powders [217].

Krögel and Bodmeier proposed HPMC tablets in combination with a hollow, impermeable cylinder. Each HPMC tablet closes one of the ends of the cylinder in a way that an air-filled compartment is created providing an inherently low density to the delivery system. But, the flotation of the device is terminated as soon as at least one of the tablets has dissolved [124].

A delivery platform (Dome Matrix®) based on hydrophilic matrices which are prepared by "release modules assemblage" technology has been presented by Losi et al. The device is constructed of units having the shape of a disc with one convex and one concave base. For FDDS, two different base-shaped matrices (i.e. "male" and "female" module) are interlocked in "void configuration". The internal void space provides an inherently low density to the dosage form [132, 157, 221, 222]. Strusi et al. evaluated the *in vivo* performance of a FDDS based on the Dome matrix® technology in humans. The γ-scintigraphy proofed a significantly-prolonged GRT for the floating device compared to the non-floating control system [222].

A single-unit floating delivery device with an inherently low density was developed by Watananbe et al. The system consists of a hollow core (e.g. empty hard gelatin capsule, polystyrene foam, pop rice grain) coated subsequently with two layers: a subcoat of cellulose acetate phtalate and an outer API-containing coating of ethylcellulose/HPMC [241]. FDDS based on highly porous foamed powder, which provides an inherently low density, have

been proposed. Tablets were compacted of propylene foamed powder, matrix-forming polymers, API, and optional a filler material [218]. The highly porous foamed powder was also used for the preparation of multiparticulate FDDS [217, 219].

Multiple-unit hollow microspheres (microballoons; size ranging from 1 up to 1000 µm) consisting of enteric polymers, combined optionally with hydrophilic or hydrophobic polymers, and containing the API in the outer polymeric shell were prepared by emulsion-solvent diffusion method [60, 112, 113, 192]. Lee et al. introduced a non-volatile oil as core material to optimize the drug release kinetics from the devices [128]. The drug delivery platform has been investigated following oral administration of riboflavin-containing microballoons and non-floating controls to healthy human volunteers. The GI behavior was studied by γ-scintigraphy and by urinary excretion of riboflavin. In the fed state, the floating microspheres were dispersed in the upper part of the stomach and were retained for a prolonged period of time (up to 5 h) compared to the non-floating reference formulation. Based on the *in vivo* results, the authors concluded that floating microballons are suitable for improving the drug bioavailability and for sustaining the pharmacological action [193].

An alternative technique for the design of multiple-unit FDDS featuring an inherently low density was proposed by Iannucelli et al. [100, 101]. The individual units with a size of 4-7 mm consist of a calcium alginate core and a calcium alginate (or calcium alginate/polyvinyl alcohol) membrane with an air compartment between core and outer layer. The authors reported excellent *in vitro* buoyancy properties of the FDDS. The behavior of the air-compartment multiple-unit GRDDS was also investigated in human subjects. In the fasted state, the floating and non-floating dosage forms did not differ in their gastric emptying time. In contrast, the GI passage time was found to vary under fed conditions: the FDDS were retained in the stomach for a prolonged time period [102]. The findings were supported by the study results of Whitehead et al. In the case of floating calcium alginate beads, the γ-scintigraphic evaluation in humans in the fed state showed extended gastric transit times compared to the non-floating controls [245].

(iii) Effervescent drug delivery systems with flotation due to gas generation and entrapment

The flotation of dosage forms may be achieved by gas generation, upon contact with body fluids, and entrapment of the gas bubbles in a swollen matrix [220]. For example, carbon dioxide is generated by carbonates or bicarbonates reacting with acidic components (i.e. gastric acid, citric or tartaric acid added to the formulation) [10]. Effervescent floating devices have been prepared by intermixing carbon-dioxide-producing excipients with matrix components and compacting the mixture into tablets [39, 106, 107]. Rouge et al. selected the approach for the preparation of floating mini-tablets containing

sodium bicarbonate as gas-generating agent [186].

As they offer the possibility to formulate and optimize the API and the flotation-promoting excipients individually, bilayer [105, 178] and multilayer [248, 249] floating tablets have been proposed. The gas-generating layer contains effervescent substances and, maybe in addition, acidic excipients. Upon contact with the acidic gastric fluids, carbon dioxide is generated and gets entrapped within a gelling hydrocolloid; thus, providing buoyancy to the dosage form. Additionally, capsules that are based on the same flotation mechanism were evaluated [129, 130]. For example, Umezawa et al. patented floating mini-capsules with a diameter in the range of 0.1-2.0 mm. The mini-capsules consisted of a sodium bicarbonate core coated with an inner HPMC layer and an outer pepstatin layer [232].

A balloon-like, multiple-unit dosage form which floated due to carbon dioxide generation was developed and evaluated by Ichikawa et al. The system is constructed of a core-shell structure, i.e. the sustained-release core is coated with two subsequent layers: an inner effervescent (e.g. sodium bicarbonate and tartaric acid) layer and an outer swellable membrane containing polyvinyl acetate and shellac [104].

The applicability of ion-exchange resin beads for the preparation of effervescent FDDS was studied *in vitro* and *in vivo* by Atyabi et al. The resin beads are loaded with bicarbonate which, upon exposure to acidic gastric fluids, releases carbon dioxide. The delivery system floats due to entrapment of the gas within a semipermeable membrane that surrounds the resin beads. The γ-scintigraphic evaluation in human volunteers showed a significantly-prolonged GRT of the coated resin beads compared to non-coated controls [7, 8].

An alternative approach to provide flotation to dosage forms by gas formation is the use of matrices containing a gas with a boiling point below 37 °C (e.g. cyclopentane, diethyl ether) [220]. The gas is incorporated in the device in solid or liquid form at ambient temperature. It evaporates at physiological temperature and inflates the dosage form. Several drug delivery systems have been patented using this floating mechanism [11, 12, 142, 143, 171]. Though, the approach is mainly interesting from scientific point of view as the manufacture of the complex devices is expected to be challenging [220].

Buoyancy due to gas generation and entrapment is associated with the disadvantage of floating lag times because the gas needs to be produced first. Therefore, the delivery device may undergo a premature stomach emptying before it starts floating on the gastric contents [168].

1.3.1.7 Combination systems

This kind of system combines different gastroretentive approaches to extend the GRT of drug delivery platforms; thus, is allows to overcome the drawbacks of the individual concepts. It is common to combine the working principles of flotation and bio/mucoadhesion [108, 210,

231, 234, 250]. The joint application of swelling and bio/mucoadhesion for gastroretentive drug delivery was also investigated [28].

The introduction section illustrates that various techniques have been invented to prolong the GI transit time of drug delivery systems. But, the summary reveals that the manufacturability of GRDDS is challenging and some of the gastroretentive approaches cannot be generally considered as "safe" for administration to humans.

1.3.2 Marketed gastroretentive drug delivery systems

During the last decades, considerable research has been done in the field of GRDDS: a number of patents were filed and a few products were launched. An overview of commercially available gastroretentive dosage forms is provided in Table 1.1.

TABLE 1.1. Marketed formulations in the past and nowadays [164, 168].

Product	**Technology**	**API**	**Company**	
Madopar HBS®	HBS™ (floating capsule)	Levodopa, benserazide	Roche, USA	[61]
Valrelease®	HBS™ (floating capsule)	Diazepam	Roche, USA	[239]
—	GIRES® (controlled-release device in a gas-generating inflatable pouch placed into a capsule)	—	Merrion Pharma	
Cytotec®	Bilayer floating capsule	Misoprostol	Pharmacia Limited, UK	[70]
Cafeclor LP®	Minextab® Floating technology (tablet of active phase and inactive floating phase (i.e. gas-generating agents and hydrophilic polymers or porous minerals))	Cefaclor	Galenix, France	[16, 73]
Metformin Hcl LP®	Minextab® Floating technology	Metformin HCl	Galenix, France	[73]
Tramadol LP®	Minextab® Floating technology	Tramadol	Galenix, France	[73]
Cifran OD®	Effervescent floating system	Ciprofloxacin	Ranbaxy, India	[6]
Riomet OD®	Effervescent floating system	Metformin HCl	Ranbaxy, India	
Zanocin OD®	Effervescent floating system	Ofloxacin	Ranbaxy, India	[28]
Inon® Ace Tablets	Foam-based floating system	Siméthicone	Sato Pharma, Japan	[194]
Topalkan®	Floating liquid alginate	Aluminum hydroxide, magnesium carbonate	Pierre Fabre Medicament, France	[45]
Conviron®	Colloidal-gel-forming floating system	Ferrous sulfate	Ranbaxy, India	
Almagate floatcoat®	Floating liquid form	Aluminum magnesium sulphate	Almirall	[62]

TABLE 1.1. Marketed formulations in the past and nowadays [164, 168].

Product	**Technology**	**API**	**Company**	
Liquid gaviscon®	Effervescent floating liquid alginate preparation	Alginic acid and sodium bicarbonate	Reckitt Benckiser Healthcare	[91]
Prazopress XL®	Effervescent and swelling-based floating system	Prazosin HCl	Sun Pharma, Japan	[223]
Gabapentin® GR	AcuForm™ (polymer-based swelling technology)	Gabapentin	Depomed, USA	[46]
proQuin XR®	AcuForm™	Ciprofloxacin	Depomed, USA	[46]
Glumetza®	AcuForm™	Metformin HCl	Depomed, USA	[46, 197]
Metformin GR®	AcuForm™	Metformin HCl	Depomed, USA	[46]
Kadian®	Capsule with polymer-coated extended-release pellets	Morphine sulfate	Sumitomo Pharma, Japan	[183]
Cipro XR®	Erodible matrix-based system	Ciprofloxacin HCl, betaine	Bayer, USA	
—	Accordion Pill® (expandable film in a capsule)	—	Intec Pharma	[71]
Baclofen GRS®	GRID® (coated multilayer floating and swelling system)	Baclofen	Sun Pharma, India	[190, 224]
Coreg CR®	Gastroretention with osmotic system	Carvedilol	GlaxoSmithKline	
—	Micropump® (multiple-particulate gastroretention device with osmotic system)	—	Flamel	[68]

The overview of marketed formulations shows that there is no instantly floating GRDDS commercially available.

1.3.3 Methods for the analysis of floating systems

1.3.3.1 *In vitro* techniques for the analysis of flotation

The **density**, the **floating lag time** (i.e. time period which a dosage form requires to rise to the surface of the dissolution medium after being immersed into the liquid [164]), the **floating duration** (i.e. time period which the dosage form floats constantly in the experimental setup [201]), and the **floating kinetics** (i.e. resultant force) are considered as parameters that are essential for the characterization of FDDS.

A simple measurement approach to study the flotation of FDDS was applied by Jimenez et al. They placed the dosage forms in individual flasks containing 400 mL 0.1 N HCl. The floating lag time and the total buoyancy time were visually assessed [108]. The described method brings the disadvantages along that the test setup is non-dynamic and it does not mimic the motility of the GI tract.

To take into account the gastric motility, El-Gibaly used a water bath shaker (shaking speed: 100 oscillations per minute) for the evaluation of microparticles. The floating lag time and the floating duration were visually determined by soaking 50 microparticles in 100 mL dissolution medium at 37 °C [59].

Numerous researchers combine drug release measurements with floating time measurements: they observe visually the flotation characteristics of FDDS during United States Pharmacopoeia (USP) II (paddle) dissolution testing [164]. However, the approach is associated with several problems. For example, the floating device may stick to the paddle shaft; hence, incorrect results for drug release and flotation are obtained [170].

The above-described techniques do not enable a quantification of the floating capability of FDDS. Additionally, they are restricted in terms of floating behavior comparison of different formulations. To overcome the drawbacks, Moës and Timmermans have invented an apparatus to monitor the resultant force which acts vertically on an object being immersed into liquid (i.e. resultant-weight of an object). The direction and magnitude of the resultant force is used to quantify floating and non-floating performance of FDDS. The proposed evaluation method allows studying the floating capability of a dosage form as a function of time [147, 230]. Some researchers applied the resultant-weight measurement apparatus for the formulation design and optimization of FDDS [53, 80, 90, 129].

1.3.3.2 *In vitro* techniques for the analysis of drug release

The USP dissolution apparatus I (basket) and II (paddle), depending on the type of floating dosage form, are commonly used for the assessment of drug release. The measurements are performed in 0.1 N HCl with/without enzymes and surfactants or in simulated gastric fluids to mimic the *in vivo* GI conditions [164]. The volume of dissolution liquid, required for the conventional USP I and II dissolution tests (approx. 900-1000 mL), is relatively large compared

to the volume of gastric fluids available in the GI tract (20-30 mL mucus in the fasted state stomach [54]).

The USP methods exhibit limitations regarding the evaluation of drug release from floating devices and the correlation between *in vitro* and *in vivo* data is often poor [78].

The USP apparatus I offers the advantage that the FDDS is entirely immersed into the dissolution medium. But, the device may stick to the mesh of the basket; or in case of a heavily swelling system, the device may completely occupy the basket [164]. Consequently, the correct analysis of swelling properties and drug release may not be feasible.

In case the dissolution tests are performed using the USP paddle apparatus, the tablets tend to float on the surface of the medium. The incomplete exposure of the dosage form to the dissolution liquid affects drug release and floating kinetics [57]. The position of the drug delivery system in the dissolution vessel plays an important role as the complex hydrodynamics and the three-dimensional fluid flow pattern, generated by the UPS paddle, vary significantly within the different parts of the vessel. A dosage form floating on the liquid surface is less affected by the paddle rotation and there is a potential risk of non-homogeneous distribution of the API [170]. To overcome the shortcoming, Burns et al. modified the conventional USP apparatus II by positioning the paddle blades in the upper part of the dissolution vessel [20, 21]. The United States Pharmacopeial Convention recommends the attachment of a helical wire sinker to dosage forms, that tend to float, in order to immerse them completely into the dissolution medium [229]. However, a sinker may influence or prevent the swelling process of heavily swelling dosage units and eroding or disintegrating devices are assumed to escape the wire sinker.

Various modifications of the USP methods have been proposed and innovative measurement systems were invented in order to achieve more reliable and reproducible *in vitro* dissolution data for FDDS.

For example, different ring mesh assemblies have been introduced to entirely submerge the floating dosage form into the liquid of the dissolution vessel [20, 56, 170]. Aoki et al. stated that mechanical destruction forces or frictional forces are necessary elements of the *in vitro* dissolution test setup. Therefore, they developed the so-called "paddle-beads" method: it describes a USP II method with polystyrene beads which are added to the dissolution liquid [4].

As the conventional USP dissolution methods and the above-described modifications do not take into account the gastric emptying process and the gastric acid secretion rate, novel methods to analyze the behavior of FDDS under conditions closer to the *in vivo* situation have been proposed. Bajpai and Dubey as well as Gohel et al. introduced test systems to study the performance of floating dosage forms based on the Rossett-Rice apparatus [9, 78]. Further optimization of the experimental setup has been done by Parikh et al.: they came up with a multi-compartment dissolution apparatus which is supposed to mimic *in vivo* stomach and intestine conditions [165].

And finally, there exist several complex model systems for the human GI tract [146, 246].

Kong and Singh proposed a "Human Gastric Simulator". The apparatus is designed in a way that it mimics the physiological conditions of the GI tract, including the continuous peristaltic contractions of the stomach walls, the gastric acid secretion, and the gastric emptying process [123].

1.3.3.3 *In vivo* techniques for the analysis of gastric retention

Although, animal studies may proof the *in vivo* gastric retention potential of a drug delivery system; the clinical evaluation in human often fails to confirm the results [242]. A reason for the different outcomes is the significant species differentiation between humans and common laboratory animals, which includes: metabolic differences, as well as anatomical, physiological, and biochemical differences in the GI tract [111]. For example, the *in vivo* analysis of FDDS is associated with the drawback that quadrupeds do not maintain a floating dosage form in the stomach at a level higher than the pyloric sphincter. Animal experiments may be used for a screening approach and they may provide a first evidence for the gastric retention capability of dosage forms; but, in order to assess adequately the *in vivo* performance of FDDS, the evaluation in human is required [242].

Independent of the species, an appropriate reference system (i.e. non-buoyant, controlled-release formulation) has to be selected. In some clinical trials, the *in vivo* behavior of GRDDS was compared with immediate-release formulations; hence, suggesting an extended GRT of the investigated GRDDS in comparison to the selected controls [93, 137, 196].

Another important point to be considered is whether the evaluation of the GRT is performed under fed or fasted conditions. *In vivo* studies are often carried out in fed state, though, the GRT of non-disintegrating tablets shows a linear correlation with the caloric content of food. The intake of high-caloric meals with 850 kcal results in a significantly-prolonged GRT of approx. 7 h [242].

Different analytical methods are used to track the GI passage of orally-administered pharmaceutical dosage forms and to determine their GRT:

(i) For **γ-scintigraphy**, a stable γ-emitting radioisotope (e.g. ^{111}Indium, ^{99m}Technetium) is co-formulated in a low amount within the delivery system. In comparison to other marker-based methods, the γ-scintigraphic evaluation requires only small changes of the formulation [164]. Nonetheless, it is associated with the shortcomings of low resolution, limited topographic information, ionization radiation, as well as complicated and expansive manufacture [168]. The highly-sensitive technique is considered as "gold standard" for the assessment of GI transit [169].

(ii) **Radiology** is a more simple and cost effective method with an excellent spatial resolution. High amounts ($\geq$40%) of contrasting agent, such as barium sulfate, need to be incorporated into the delivery device for an optimum evaluation. Hence, the formulations are modified

and the GI passage of the systems may be affected. Due to x-ray exposure of the study subjects the application of this analytical technique is not favored (average effective dose for computed tomography of the abdomen: 8 mSv [141]). For GI transit studies, the health risk increases as series of images are recorded [164, 244].

(iii) In recent years, the interest in **magnetic resonance imaging** (**MRI**) techniques has increased. The non-invasive imaging method is shown to be a valuable analytical tool for the investigation of the *in vivo* behavior of dosage forms. To label the delivery device, the contrast agents Fe_3O_4 and Gd-DOTA (gandoteric acid) are feasible as MRI markers. MRI features the advantages of high soft tissue contrast, high temporal and spatial resolution, as well as the absence of x-ray radiation [214].

(iv) It is possible to mark magnetically dosage forms by the incorporation of small amounts of ferromagnetic material into the formulations and to acquire images by biomagentic measurement systems. The addition of high-density iron powder may affect the GI behavior of the delivery device. In comparison to the above-described techniques, the **magnetic marker monitoring system** is less hazardous because it does not employ any radiation [243].

(v) Another visual observation method is **gastroscopy**: an endoscope is used to assess the behavior of dosage forms in the GI tract. The approach features the advantages that is does not require a modification of the formulation (e.g. addition of marker substances) and that the dosage form can be withdrawn from the stomach during the measurement. However, food particles remaining in the gastric region may complicate the assessment of the GRT. At predetermined time points, the endoscope has to be administered to the study subject; the inconvenient procedure limits the application of gastroscopy to assess stomach residence times [168].

(vi) As an alternative imaging technique, which is not yet routinely used for the *in vivo* evaluation of GRDDS, the application of **ultrasonography** is discussed [168].

(vii) The **^{13}C-labeled octanoic acid breath test** offers a non-invasive measurement approach to assess the stomach residence time of dosage forms. The ^{13}C-labeled octanoic acid, a medium chain fatty acid, is co-formulated within the dosage form. The substance is absorbed in the upper part of the small intestine and transported to the liver. Due to mitochondrial oxidation, carbon dioxide is generated and exhaled in the breath. It indicates the transit of the dosage form through the small intestine and marks the gastric emptying of the delivery device from the stomach. The presence of ^{13}C-labeled carbon dioxide in the expired air is measured by isotope-ratio mass spectrometry [164].

(viii) **Pharmacokinetic parameters**, such as the maximum plasma concentration of drug (c_{max}), the time to reach the maximum plasma concentration (t_{max}), and the area

under the plasma concentration-time curve (AUC) are evaluated. Based on the results, conclusions are drawn regarding the GI transit behavior: some researchers assume that an improved bioavailability of the API is linked with a prolonged GRT of the dosage form [242]. However, the pharmacokinetik analysis does not enable the direct assessment of the stomach residence time of a drug delivery system.

2

Aim of the thesis

Following the analysis above, the interest in drug delivery systems which are retained in the GI tract for a predictable and prolonged period of time persists. As it was shown, various approaches for the design of GRDDS have been proposed and analyzed. The mechanism of flotation is considered as the most straightforward approach. Despite considerable research, the development, the manufacture, as well as the *in vitro* and *in vivo* evaluation of FDDS remains challenging.

The main aim of the thesis was to address the shortcomings associated with gastroretentive FDDS and to propose a strategy which facilitates the formulation development.

(i) **Preparation and *in vitro* evaluation of gastroretentive FDDS**

Until recently, there was no pharmaceutical excipient commercially available that allowed the compaction of floating tablets with an inherently low density and a sufficient hardness. Functionalized calcium carbonate (FCC), which was originally developed for the use in paper industry [74], was identified as a material that may be suitable for the manufacture of tablets featuring the above-mentioned characteristics. FCC was invented and patented by OMYA Development AG (Oftringen, Switzerland). The material is prepared by decomposition under acidic conditions and re-crystallization. The starting material, ground natural calcium carbonate, is treated with one or more water-soluble acids (e.g. phosphoric acid) and gaseous carbon dioxide is provided [76, 77]. Depending on the reaction conditions, different particle shapes and particle size distributions are obtained [216].

The objective of the thesis was to investigate the applicability of FCC for the preparation of instantly floating GRDDS in form of floating tablets and floating mini-tablets. The *in vitro* USP dissolution methods exhibit limitations regarding the assessment of drug release

and flotation behavior of FDDS. Therefore, it was important to introduce a custom-built stomach model method for the analysis of floating dosage forms.

(**ii**) ***In vitro* and *in silico* evaluation of gastroretentive FDDS**

Up to now, it does not exist an *in vitro* evaluation method to determine simultaneously drug release and floating force of FDDS; thus, complicating the preparation, the optimization, and the comparison of floating formulations. The objective was to propose a formulation strategy for the development of floating tablets with desired drug release and flotation performance using a combination of *in vitro* and *in silico* techniques. The *in silico* tablet dissolution simulations provided a tool to assess tablet density and resultant force during drug release.

(**iii**) ***In vivo* evaluation of gastroretentive FDDS**

The objective was to analyze the gastric retention capability of FCC-based FDDS in human volunteers. Therefore, the stomach residence time of FCC-based floating tablets was compared to the residence time of non-floating reference tablets.

3

Publications

3.1 Design and *in vitro* evaluation of hydrophilic floating systems

Floating gastroretentive drug delivery systems: Comparison of experimental and simulated dissolution profiles and floatation behavior

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Floating gastroretentive drug delivery systems: Comparison of experimental and simulated dissolution profiles and floatation behavior

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ABSTRACT

Introduction: Gastroretentive drug delivery systems (GRDDS) play an important role in the delivery of drug substances to the upper part of the gastrointestinal tract; they offer a possibility to overcome the limited gastric residence time of conventional dosage forms.
Aims: The aim of the study was to understand drug-release and floatation mechanisms of a floating GRDDS based on functionalized calcium carbonate (FCC). The inherently low apparent density of the excipient (approx. 0.6 g/cm^3) enabled a mechanism of floatation. The higher specific surface of FCC (approx. 70 m^2) allowed sufficient hardness of resulting compacts. The floating mechanism of GRDDS was simulated *in silico* under simulated acidic and neutral conditions, and the results were compared to those obtained *in vitro*.
Methods: United States Pharmacopeia (USP) dissolution methods are of limited usefulness for evaluating floating behavior and drug release of floating dosage forms. Therefore, we developed a custom-built stomach model to simultaneously analyze floating characteristics and drug release. *In silico* dissolution and floatation profiles of the FCC-based tablet were simulated using a three-dimensional cellular automata-based model.
Results: In simulated gastric fluid, the FCC-based tablets showed instant floatation. The compacts stayed afloat during the measurement in 0.1 N HCl and eroded completely while releasing the model drug substance. When water was used as dissolution medium, the tablets had no floating lag time and sank down during the measurement, resulting in a change of release kinetics.
Conclusions: Floating dosage forms based on FCC appear promising. It was possible to manufacture floating tablets featuring a density of less than unity and sufficient hardness for further processing. *In silico* dissolution simulation offered a possibility to understand floating behavior and drug-release mechanism.

1. Introduction

Compared to conventional dosage forms, gastroretentive drug delivery systems (GRDDS) are designed to remain in the stomach for a prolonged, predictable time. Consequently, gastric residence time of drug substances is extended and bioavailability improved (Arora et al., 2005). GRDDS are suitable for a number of drugs, including substances whose sites of action are in the stomach (Bardonnet et al., 2006) (e.g. antibiotics such as metronidazole used for the eradication of *Helicobacter pylori* (Adebisi and Conway, 2013)) and drugs that exhibit a narrow absorption window in the stomach or the upper part of the small intestine (Streubel et al., 2006a) (e.g. simvastatin (Jagdale et al., 2013) and norfloxacin (Guguloth et al., 2011)). Moreover, GRDDS are suited for drugs degraded in the intestinal or colonic environment (e.g. captopril (Nur and Zhang, 2000)), as well as substances that are poorly soluble in alkaline media (e.g. diazepam (Sheth and Tossounian, 1984)).

Various approaches have been proposed to achieve gastric retention and avoid unpredictable gastric emptying of dosage forms. These approaches include co-administration of drugs or pharmaceutical excipients that influence the gastric motility pattern and thereby delay gastric emptying (Gröning and Heun, 1989, 1984), magnetic systems (Fujimori et al., 1995), muco-adhesive systems

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(Dhaliwal et al., 2008), systems that increase in size due to swelling (Deshpande et al., 1997) or unfolding (Michaels, 1974), density-controlled systems that either float on gastric contents (Baumgartner et al., 2000; Stops et al., 2008) or sediment (Devereux et al., 1990), and combination systems (Jiménez-Castellanos et al., 1994). However, despite the multitude of options, the broad application of GRDDS remains an unsatisfied need.

Pawar et al. considered floating drug delivery systems (FDDS) a logical approach developing GRDDS (Pawar et al., 2011). FDDS are low-density systems with a density less than that of gastric fluids (approx. 1.004 g/cm^3) (Pawar et al., 2011). Therefore, dosage forms float on gastric contents and are retained in the stomach while releasing drug (Singh and Kim, 2000).

According to literature data, enhanced gastric residence times of floating pharmaceutical dosage forms are achievable under fasted conditions (Babu and Khar, 1990; Desai and Bolton, 1993; Xu et al., 1991). Since the introduction of the concept of floating tablets by Davis (1968), many research groups have invented varying strategies to prepare FDDS. Floatation is achieved by incorporating low-density materials (Streubel et al., 2002), by swelling (Sheth and Tossounian, 1978), or by generation and entrapment of gas (Atyabi et al., 1996). Because excipients with a density <1 provide immediate floatation of the delivery device, their use is highly favored for formulation development (Streubel et al., 2006b). However, design of floating dosage forms is technically demanding. First, traditional *in vitro* dissolution methods are not able to predict *in vivo* behavior with a sufficiently high accuracy (Pawar et al., 2012). Neither the European Pharmacopeia nor the American Food and Drug Administration (FDA) describe any specific methods to assess dissolution behavior and floating characteristics of FDDS. Second, methods for preparation of FDDS are often cumbersome and expensive. Third, cost-effective large-scale production of FDDS remains a challenge.

Optimal floating tablets must feature two, often self-excluding characteristics: high porosity to promote floatation on stomach contents, but also sufficient hardness to withstand destruction by gastric peristalsis. A novel pharmaceutical excipient that exhibits a highly porous meshwork with a lamellar surface structure to interlock particles tightly was identified in the paper industry (Stirnimann et al., 2013). Due to its unique properties, functionalized calcium carbonate (FCC) holds promise in the preparation of FDDS. It offers the possibility to compact tablets that can be further processed at a relative density <1.

The objective of this work was to design an FDDS using the novel excipient FCC and the model drug caffeine. To overcome the drawbacks of existing dissolution methods, we introduced a custom-built stomach model to simultaneously evaluate drug release and floating characteristics of dosage forms. Using a 3D cellular automata-based computational model, an attempt was made to evaluate *in silico* the floating characteristics and drug release. The theoretical background of the cellular automata-based software is described in the next section.

2. Mathematical model: cellular automata-based dissolution model for floating tablets

Use of cellular automata (CA) for modeling drug release profiles from solid dosage forms has previously been described for polymer-containing formulations (Zygourakis and Markenscoff, 1996). In this study, the standard three-dimensional CA dissolution model (Kimura, 2013; Puchkov et al., 2013) with extended rule set was used to account for medium absorption kinetics by porous materials. In addition, output statistics were collected to obtain information about every automaton state at every sampling interval. This allowed calculation of tablet density during *in silico* experimentation and thus assessment of tablet floatation. Tablet densities >1 g/cm^3 indicated that the dissolving tablet sank. General automata rules used in this study can be split into 3 main categories: rules for active pharmaceutical ingredients (API), rules for polymers, and rules for porous FCC material.

2.1. CA rules for active pharmaceutical ingredients

Fig. 1a displays the dissolution of non-hydrophobic API cells. Solvation of the solid is controlled by a C_1 constant of an automaton. This primary constant defines the number of iterations needed to change the "solid" state of the API cell into a "liquid" state. Each "liquid" cell in the 3D Moore neighborhood (Kari, 2005) of an API cell subtracts one unity at a time from the C_1 value of the API cell. Automaton changes its state at reaching the C_1 value of zero and irreversibly converts itself into a "liquid" cell. Physical meaning of the C_1 value is the reciprocal of the product of solid–liquid interface surface and *diffusion* coefficient divided by the thickness of the boundary layer. In other words, the C_1 value is reciprocal to the constant term of the Noyes–Whitney equation (Noyes and Whitney, 1897). This basic rule applies to all automaton states except the "liquid" state.

2.2. CA rules for polymer component

Spatial changes of the hydrated materials, i.e. swelling, require separate governing rules and control parameters. In this study, the C_2 constant was used for polymer materials to control the degree of swelling.

The swelling cell state mimics the properties of a component which shows an increase in volume after contact with the dissolution medium (see Fig. 1b). The "liquid" cells in the 3D Moore neighborhood of the swelling compound are converted into "hydrated" polymer cells and obtain a C_1 value which is calculated by dividing C_1 by the C_2 value. Therefore, the higher the C_2 value, the lower is the swelling capacity of a component. From the physical point of view, the relationship between C_1 and C_2 constants of the swelling polymer component can be expressed as the logarithm of C_1 of base C_2 (Eq. (1)):

$$q = 1 + \log_{C_2} C_1 \tag{1}$$

where q is the volumetric swelling ratio $\left(q = \frac{\text{Volume of swollen gel}}{\text{Volume of dry gel}}\right)$.

Solving Eq. (1) for C_2 yields the following relationship:

$$C_2 = C_1^{\frac{1}{q-1}} \tag{2}$$

When applying Eq. (2), the values for C_2 can be obtained experimentally for different polymers or gels in different media.

2.3. CA rules for porous materials such as FCC

Unlike swelling, liquid sorption into porous particles does not result in spatial changes but requires dedicated governing rules and a control parameter. In this case, C_2 is the constant responsible for the rate of liquid sorption into porous particle meshwork.

Fig. 1c and d shows the behavior of porous state cells after contact with dissolution medium. Division of the C_2 value by the number of surrounding "liquid" cells gives the number of iterations needed to change a porous "dry" state cell into a "wet" state, respecting the 3D Moore neighborhood. Considering the physical meaning of the value for C_2, it is possible to experimentally obtain this constant for different materials and media by liquid sorption measurements.

To obtain experimental values for the C_1 constant of the polymer components and C_2 constant of porous FCC, the liquid sorption kinetics have to be determined. The sorption rate is the slope

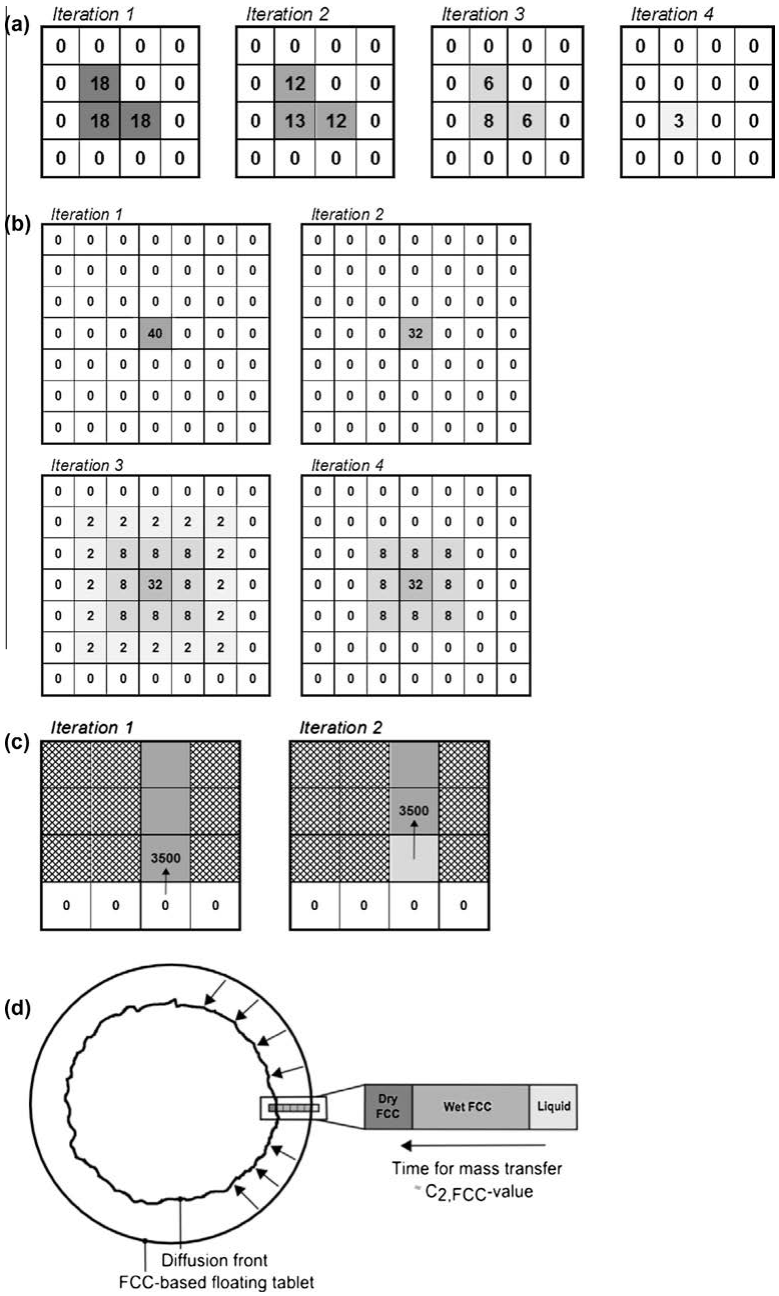

Fig. 1. (a) Dissolution of non-hydrophobic API cells with $C_1 = 18$. (b) Behavior of a hydrophilic swelling cell with $C_1 = 40$ and $C_2 = 4$. (c and d) Liquid absorption of FCC with $C_2 = 3500$.

coefficient of the linear part of a sorption curve, which is measured in gram per second. To determine the time in seconds needed to fill a volume which is equal to the volume of one automaton cell (i.e. 3.94×10^5 μm^3 for the cell volume used in this study), the volume of one cell layer (i.e. 6.95×10^9 μm^3 in this study) at the surface of the virtual tablet has to be divided by the rate of sorption. It is

important to note that water density of 1.00 g/cm^3 is assumed for this calculation. Another assumption is that the skeleton volume of the porous material is significantly smaller than the volume of the voids in the particles; hence it is neglected.

To assess the number of neighbor cells with assigned state of "liquid" or "liquid-filled porous material" per "wet" polymer or "wet" FCC cell, the average number of "liquid" neighbors per cell has to be calculated. Therefore, the total number of "liquid" and "liquid-filled" cells as well as the number of "wet" polymer cells was recorded after every iteration during *in silico* dissolution. In 3D Moore neighborhood of a "wet" polymer component, an average of 13 cells had a state of "liquid" or "liquid-containing" material. This implies a necessity of multiplying the time needed for one cell to occupy the polymer or FCC cell by a factor of 13. The resulting product is the C_1 or C_2 constant for the polymer compound or the porous material, respectively.

3. Materials and methods

3.1. Materials

FCC (VP-DP141 S04, Omya, Oftringen, Switzerland) (Stirnimann et al., 2013) was used as the matrix to prepare the floating tablets. Water-soluble polyethylene oxide (Polyox™ WSR 301, The Dow Chemical Company, Midland, Michigan) and hydroxypropyl methylcellulose (Methocel® K100 Premium LV, Sandoz Pharma AG, Basel, Switzerland) were selected as gelation-layer forming polymers. Citric acid (Acid citricum monohydr. pulvis, Hänseler AG, Herisau, Switzerland) was chosen as the effervescent excipient. For wet-granulation, ethanol 96% (Schweizerhall Chemie AG, Flawil, Switzerland) was used. Caffeine (Coffeinum WSF, Böhringer-Ingelheim, Ingelheim, Germany) served as the model drug.

3.2. Methods

3.2.1. Preparation of FCC-based floating formulation

The floating formulation used for the study was prepared according to Table 1. It contained highly porous FCC, which allowed manufacture of tablets with an inherently low density. The gelation-layer forming polymers, Polyox™ WSR 301 and Methocel® K100 Premium LV, were included in the formulation to slow down penetration of liquid into the tablet during dissolution; entrapped air in the porous FCC particles should ensure low density of the tablet and provide floatation of the dosage form. Moreover, the swelling polymers should retard the release of the model substance (caffeine) from the tablet.

The required amounts of FCC, Polyox™ WSR 301, Methocel® K100 Premium LV, citric acid, and caffeine were weighed and mixed in a tumbling mixer (Turbula type T2C, Willy A. Bachofen, Switzerland) for 10 min. The speed of the tumbling mixer was kept at the default value of 30 rpm. Afterwards, ethanol 96% was added to the mixture to form a paste. The obtained slurry was dried and extruded through a sieve (1000 μm).

3.2.2. Preparation of FCC-based floating tablets

Floating tablets of 400 mg were compacted using a single-punch eccentric press (EK0, Korsch, Germany) equipped with 11 mm round flat tooling. The resulting tablet height of 5 mm was calculated to yield a tablet density of 0.8 g/cm^3. For the compaction process, the punch gap was set to the calculated value.

3.2.3. Characterization of FCC-based floating tablets

Mean tablet weight ($n = 30$) was determined with an electronic balance (AX204 Delta Range, Mettler Toledo, Switzerland). Determination of tablet diameter ($n = 30$) and tablet thickness ($n = 30$) was done using a dial indicator (CD-15CPX, Mitutoyo, Japan). Helium pycnometry (AccuPyc 1330, Micromeritics, USA) was performed to measure the apparent true density. Porosity ε of flat-faced tablets was calculated according to Eq. (3):

$$\varepsilon = 1 - \frac{m}{\rho} \cdot \frac{1}{V} \tag{3}$$

where volume V is $V = \pi \cdot r^2 \cdot h$, m is tablet weight (g), ρ is true density of the powder mixture (g/cm^3), r is tablet radius (mm), and h is tablet height (mm).

A hardness tester (Tablet Tester 8 M, Dr. Schleuniger Pharmatron, Switzerland) was used to analyze tablet breaking strength ($n = 10$). Afterwards, tablet tensile strength σ_t was calculated according to Eq. (4):

$$\sigma_t = \frac{2 \cdot F}{\pi \cdot d \cdot h} \tag{4}$$

where F is diametrical crushing force (N), d is tablet diameter (mm), and h is tablet height (mm).

3.2.4. Evaluation of in vitro floating behavior and drug release

To simultaneously assess the *in vitro* floating characteristics and drug release of tablets ($n = 12$), a modified dissolution apparatus (AT7smart, Sotax, Switzerland) was used. The experimental setup (Fig. 2) consisted of four polycarbonate Erlenmeyer flasks (500 ml) fixed to the carriage of a water-bath shaker (TB VS-02, Heto InterMed, Germany; Kobrin scientific precision centigrade temperature processor 345, Switzerland). The carriage moved horizontally at a rotation speed of 75 rpm and an amplitude of 50 mm. The tests were carried out in 400 ml 0.1 N HCl and distilled water as the media at a temperature of 37 °C.

For comparison, floating behavior and drug release ($n = 15$) were also analyzed using the USP dissolution apparatus II (AT7smart, Sotax, Switzerland) in 900 ml 0.1 N HCl with a paddle rotation of 100 rpm and a temperature of 37 °C.

Drug content in the dissolution media was analyzed at predetermined time intervals using a UV/Vis spectrophotometer (Lambda 25, Perkin Elmer, USA) at 272 nm. Floating lag time, defined as the time a tablet required to rise to the surface of the test medium after being placed in the medium, and floating duration were visually inspected.

Table 1
Composition of the FCC-based floating formulation.

Component	Apparent true density (g/cm^3)	Tablet composition				
		Experimental (%, w/w)	Experimental (mg)	*In silico* (%, w/w)	*In silico* (%, v/v)	*In silico* (mg)
Caffeine	1.4489	25.000	100.000	25.013	14.510	100.000
FCC	0.6350 (2.9090[a])	56.250	225.000	56.227	74.425	224.792
Polyox™ WSR-301	1.2332	7.500	30.000	7.504	5.114	30.000
Methocel® K100 Premium LV	1.5901	10.875	43.500	10.881	5.751	43.500
Citric acid	1.5827	0.375	1.500	0.375	0.199	1.500

[a] For crystalline material (skeletal density).

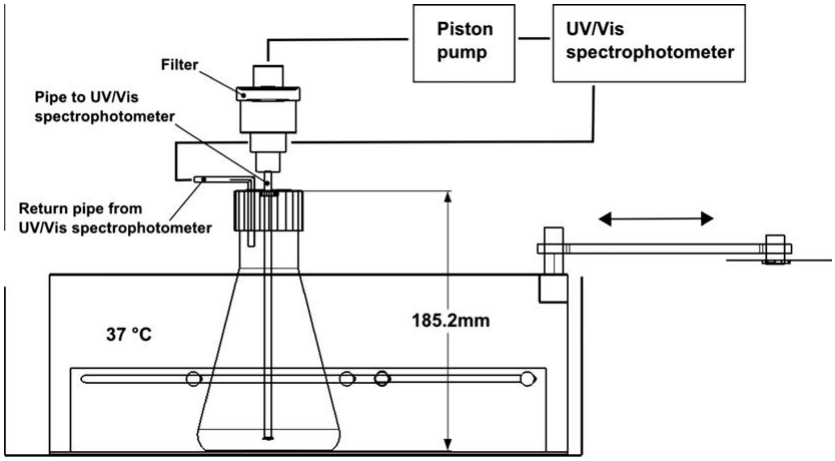

Fig. 2. Schematic representation of a single unit of the proposed stomach model to evaluate *in vitro* floating behavior and drug release.

3.2.5. Evaluation of mechanical stability of FCC-based floating tablets after incubation in dissolution media

A texture analyzer (FMT-310 Force Tester, Alluris, Germany) was used in order to evaluate the mechanical properties of the FCC-based tablets. The floating tablets were placed in the Erlenmeyer flasks of the custom-built stomach model for 30 min using distilled water ($n = 3$) and 0.1 N HCl ($n = 3$) as dissolution media. Afterwards, the required force to break the tablets at a certain displacement of the force gauge was assessed.

3.2.6. Kinetics of liquid absorption

A tensiometer (Krüss Processor Tensiometer K100MK2) was used to characterize liquid sorption kinetics. Powder samples were filled in a glass tube which had a ceramic filter bottom. The tubes were sealed at the top to prevent mass loss due to evaporation. The sample holder was attached to the microbalance of the tensiometer and immersed to a depth of 4 mm into a beaker with distilled water thermostated at 37 °C. The beaker was covered with a plastic paraffin film to minimize evaporation. The tensiometer software plotted mass gain against time. During the measurement, the glass tube contributed to the recorded mass gain. Therefore, the mass gain of the empty glass tube was subtracted from the recoded data of the powder samples at every time point. The slope coefficient of the linear part of the water sorption curves was calculated; values for the sampling points at 200–600 s (20–60 s in the case of FCC powder) were included.

3.2.7. Cellular automata-based tablet model setup and parameters

The cellular automata-based dissolution model was used from software package F-CAD v.2.0 (CINCAP GmbH, Switzerland) (Puchkov et al., 2013). For computer simulation, a flat-faced tablet with a diameter of 11 mm and a thickness of 5 mm was defined as a geometric object which consists of unit cubes with an individual unit cube side length of 73.3 μm. This transformation is done using the ray-casting discretization algorithm. In brief, the rays penetrate the cubic matrix in *x*- and *y*-direction and the coordinates of the intersection points of the rays and the tablet matrix are detected. The matrix around the virtual tablet is filled with unit cubes, while the tablet remains as hollow space. Then, the matrix is inverted, resulting in a discrete cubic grid in a shape of a tablet. This grid was filled at random with components in the particle arrangement and compaction (PAC) module. The resulting 3D tablet matrix (Fig. 3a and b) contained the components of the floating formulation (Table 1).

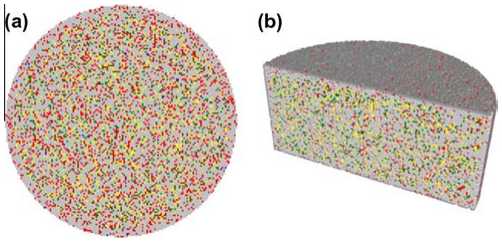

Fig. 3. (a) Cross-section of the prepared 3D tablet matrix. The outer rim (5 units thick) was kept free of cells with swelling properties to account for the initial "burst"-effect. (b) 3D tablet matrix.

3.2.8. Evaluation of in silico floating behavior and drug release

Floating characteristics and drug release from the virtual tablet were investigated *in silico* using the dissolution simulation module of the F-CAD software. Table 2 shows the component types and codes, as well as the parameters used for caffeine release simulation. At predetermined time points, the number of remaining unit cubes of each component type in the tablet matrix was recorded in order to calculate the density of the virtual tablet and drug release.

Density of the simulated tablet was calculated as the total sum of individual weights of the cells, divided by the total volume of the cells assuming no disintegration of the tablet. The density of "hydrated" polymer cells was assumed to be = 1, and the density of the "liquid-containing" FCC particles was assumed to be 1.6 g/cm^3.

4. Results

4.1. Characterization of FCC-based floating tablets

Table 3 summarizes the properties of the prepared tablets. Tablet height was set to achieve tablet densities <1 g/cm^3 in order to ensure floatation on the gastric fluids. Despite their high porosity of approx. 60%, FCC-based floating compacts were hard enough

Table 2
F-CAD component types, codes, and constants used for simulation of the dissolution runs. C_1 and C_2 values of caffeine and citric acid were taken from the F-CAD database.

Component	Type ID	Component code	Dissolution run in HCl		Dissolution run in water	
			C_1 value	C_2 value	C_1 value	C_2 value
Caffeine	1	API	800	–	800	–
Citric acid	12	Non-swelling soluble filler	10	–	10	–
Polyox™ WSR-301	41	Hydrophilic swelling matrix	2500	4	2500	4
Methocel® K100 Premium LV	42	Hydrophilic swelling matrix	5000	12	5000	12
FCC	80	Porous material	1800	3500	4000	3500

Table 3
Properties of the experimental and simulated FCC-based floating tablets. Discrepancies between virtual and experimental parameters were explained by discretization error. Mechanical stability of tablets cannot be simulated by the current version of the software.

Tablet formulation	Weight (mg)	Diameter (mm)	Thickness (mm)	Tensile strength (N/mm^2)	Porosity (%, v/v)	Tablet density (g/cm^3)	Apparent true density of formulation (g/cm^3)
Experimental	399.65 ± 0.59	11.00	4.99	0.5924 ± 0.0419	58	0.84	2.0101
In silico	399.79	11.07	4.98	–	0	0.99	0.9909

to be processed further. For computer simulation, the tablet had a porosity of 0% and a density <1 g/cm^3.

4.2. In vitro evaluation of floating behavior and drug release in 0.1 N HCl

Fig. 4a compares caffeine release from floating tablets measured in 0.1 N HCl using the custom-built stomach model with that obtained with the conventional USP dissolution apparatus II. The tablets floated immediately when introduced into liquid. In the stomach model, the compacts stayed afloat for approx. 300 min. Within this period, they eroded completely while releasing caffeine. Caffeine was entirely released after 295 min, and the drug release mechanism was classified as erosion-controlled.

Dissolution testing by the USP paddle method resulted in a slowdown of caffeine release: 100% of caffeine was released after 500 min. During dissolution measurement, the FCC-based tablets floated on the surface of the test medium and rotated around the paddle shaft. In the stomach model, the floating tablets were fully immersed in the dissolution medium throughout the test. Due to the horizontal movements of the water-bath shaker, drying of the tablets' surfaces was prevented.

4.3. Experimental determination of simulation constants

Table 4 displays the obtained water sorption rates of polymer components, FCC, and floating formulation. In line with the

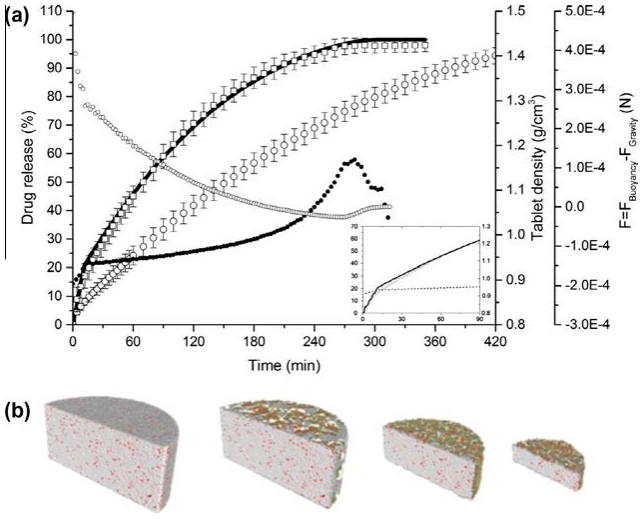

Fig. 4. (a) *In vitro* drug release profiles of FCC-based floating tablets in 0.1 N HCl tested using the stomach model (□, $n = 12$) and the USP dissolution apparatus II (○, $n = 15$). Each data point is the mean ± standard deviations. *In silico* caffeine release profile (–) and densities (●) of floating tablet were obtained using dissolution simulation. The buoyancy of the tablets F (○) is displayed as the vectorial sum of the gravity $F_{Gravity}$ and buoyancy $F_{Buoyancy}$ forces. It was calculated as follows: $F = \rho_f \cdot V \cdot g - \rho_t \cdot g \cdot V$, where ρ_f is the density of the fluid (g/cm^3), ρ_t is the tablet density (g/cm^3), V is the volume of the displaced object (cm^3), and g is the gravitational acceleration (m/s^2) (Sauzet et al., 2009). (b) Hydrophilic floating tablet after 0, 10, 100, and 200 min *in silico* dissolution simulation in 0.1 N HCl. Caffeine and "dry" material are displayed in red and light gray, respectively. "Wet" material is shown in dark gray and the formed gel-layer in yellow. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 4
Calculated C_1 and C_2 constants based on water sorption measurements.

Component	Liquid sorption rate (g/s)	C_1 value	C_2 value
Polyox™ WSR-301	4.48×10^{-5}	2015	–
Methocel® K100 Premium LV	1.23×10^{-5}	7340	–
FCC	2.45×10^{-3}	–	37
Floating formulation	2.32×10^{-5}	–	3883

method described in the theoretical section, the C_1 value of the two polymer components and the C_2 value of FCC were determined using the results of the tensiometer measurements.

4.4. In silico evaluation of floating behavior and drug release in 0.1 N HCl

Table 2 shows the selected parameters for dissolution simulation of the FCC-based floating tablet under acidic conditions. Fig. 4a displays the resulting *in silico* caffeine release profile and tablet densities during dissolution. The virtual compact eroded completely (as shown in Fig. 4b) while releasing caffeine, and complete drug release was obtained after 308 min. Maximum tablet density of approx. 1.17 g/cm^3 was observed after 279 min.

4.5. In vitro evaluation of floating behavior and drug release in distilled water

Additionally, caffeine release and floatation were analyzed in distilled water to provide additional data for *in silico* simulation and elucidation of the floatation mechanism. Fig. 5a shows drug release from floating tablets in distilled water using the custom-built stomach model. The FCC-based tablets exhibited no floating lag time, similar to the behavior in simulated gastric fluid. However, unlike in HCl, the compacts sank to the bottom of the Erlenmeyer flasks at approx. 90 min. The drug release profile showed a significant change in the speed of caffeine release at this time point. Complete caffeine release was measured after approx. 18 h, and tablet matrices remained at the bottom of the flasks after 100% drug release.

4.6. In silico evaluation of floating behavior and drug release in distilled water

The solid line in Fig. 5a displays the *in silico* caffeine release from the FCC-based tablet in distilled water. The simulated profile was obtained using the automaton constants given in Table 2. Caffeine was entirely released after 533 min. A linear increase in tablet density up to 1.47 g/cm^3 at 288 min was calculated. After 64 min of simulated release, the density of the FCC-based compact had reached values higher than 1.004 g/cm^3, which implied that a real tablet would sink to the bottom. The change in experimental release profile (Fig. 5a) was observed at a similar time point and was associated with tablet sinking, which occurred at approx. 90 min and was visually confirmed.

4.7. Evaluation of mechanical stability of FCC-based floating tablets after incubation in dissolution media

After incubation in 0.1 N HCl, a force of 7 ± 2 N was detected by the texture analyzer in order to break the tablets. At the same displacement of 0.9 mm, a force of 8 ± 2 N was recorded for the tablets immersed into distilled water. FCC-based floating tablets which soaked dissolution medium did not lose their stability.

5. Discussion

The concept of FDDS is not well established, as animal studies and clinical trials often fail to prove significant gastric retention

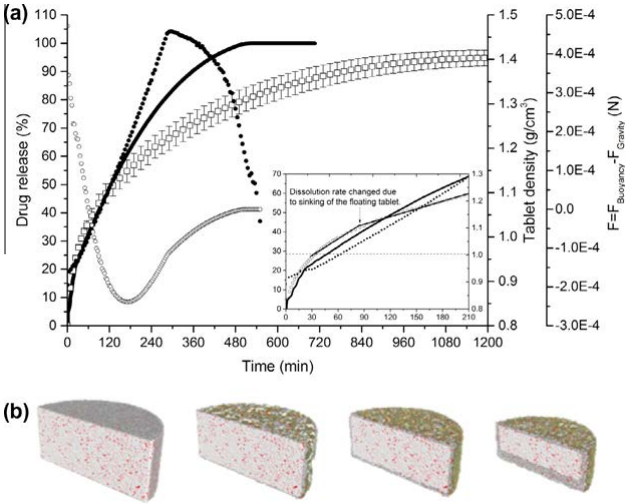

Fig. 5. (a) *In vitro* caffeine release profiles of floating tablets in distilled water tested using the stomach model (□, n = 12). Each data point is the mean ± standard deviations. Drug release profile (–) and densities (●) of the virtual tablet obtained using dissolution simulation. The buoyancy of the tablets F (○) is displayed as the vectorial sum of the gravity $F_{Gravity}$ and buoyancy $F_{Buoyancy}$ forces. It was calculated as follows: $F = \rho_f \cdot V \cdot g - \rho_t \cdot g \cdot V$, where ρ_f is the density of the fluid (g/cm^3), ρ_t is the tablet density (g/cm^3), V is the volume of the displaced object (cm^3), and g is the gravitational acceleration (m/s^2) (Sauzet et al., 2009). In the magnification of the initial part of the release profile linear regression lines and the density of the gastric fluid (approximately 1.004 g/cm^3) were added. (b) Hydrophilic floating tablet after 0, 20, 60, and 120 min *in silico* dissolution simulation in distilled water. Caffeine and "dry" material is displayed in red and light gray, respectively. "Wet" material is shown in dark gray and the formed gel-layer in yellow. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(Waterman, 2007). Although considerable research on floating systems has been done, only a few products are on the market (Pawar et al., 2012). One factor contributing to this unsatisfactory situation is the lack of predictive *in vitro* test systems to evaluate the performance of FDDS. Most scientists carry out *in vitro* floating tests and drug release studies of gastroretentive dosage forms without taking into account anatomical and physiological parameters such as volume of gastric fluids or stomach pH, gastric motility pattern, or the gastric emptying process. Research groups primarily use USP dissolution apparatus II to analyze FDDS drug release, although this traditional method has a number of limitations. First, the floating tablet surface dries during experiments because it is not immersed in test media. Drying out of the compact surface artificially prolongs the floating times and slows the release rate due to constant exposure of the upper part of the tablet to air. Compared to conventional dosage forms, floating devices are less exposed to rotational forces during dissolution measurement using the USP paddle method because the floating tablets rotate around or may stick to the paddle shaft. Sinkers added to ensure that the floating device is fully submerged in the dissolution medium were not considered suitable because floating tablets may undergo erosion or disintegration during the release experiment. Neither USP I/IV dissolution apparatuses nor a meshwork to prevent floatation to the surface were used because the floating dosage forms tend to stick to the mesh structures.

To overcome the drawbacks of USP dissolution methods, we introduced a custom-built stomach model in the present study to simultaneously evaluate drug release and floating characteristics of dosage forms. This method has clear advantages over the USP dissolution methods. Drying of the floating compact surface was prevented by the continuous shaker movement and complete immersion of tablets into medium throughout the test. In addition, there was no need to force the tablets underneath the liquid surface, hence simplifying the construction of the stomach model. The volume of test medium was only 400 ml, compared to 900 ml necessary for the USP II dissolution method. Thus, higher impact forces may act on the floating tablets. As a general observation, dissolution speed of floating tablets in 0.1 N HCl was higher in the stomach model than the conventional USP paddle apparatus.

Devices such as the TIM gastrointestinal model (Minekus and Havenaar, 1996), the human gastric simulator (Kong and Singh, 2010), and the dynamic gastric model (Wickham et al., 2012) provide realistic and complex simulations of the human stomach. They mimic continuous peristaltic movements of the stomach walls, take into account the secretion of gastric acid and enzymes, and provide a tool to study gastric emptying processes. In contrast, the custom-built stomach model method is not aimed to evaluate digestion and gastric emptying of floating dosage forms. It mainly offers a simplified system to assess *in vitro* floatation and drug release of floating tablets. Additionally, due to continuous horizontal movement of the Erlenmeyer flasks a constant stress to simulate gastric motility is applied to the floating tablets.

In the case of an "ideal" human stomach simulation device, the evaluation of the behavior of floating tablets during the complete interdigestive migrating myoelectric complex (Washington et al., 2001) including gastric emptying waves would be possible. Additionally, the effect of the density and the viscosity of the chime on floatation behavior and the ability of dosage forms to be retained in the stomach could be studied. A minimum required filling state of the human stomach might be determined which would be necessary to retain the floating tablet in the stomach without being emptied through the pylorus by the gastric emptying wave. These features have been implemented at least in part in other stomach models (Table 5). If needed, our custom-built stomach model could be adapted accordingly. However, this was not considered to be necessary for the present study.

Table 5
Features and overview of available stomach models.

	Custom-built stomach model	Available devices to simulate the human gastrointestinal tract[a]
Evaluation of floatation behavior (e.g. floating lag time, floating duration)	Implemented	Not possible
Evaluation of drug dissolution	Implemented	Implemented
Simulation of acid and enzyme secretion	Possible	Implemented
Simulation of different prandial states	Possible	Implemented
Simulation of gastric emptying	Not possible	Implemented
pH range	1.1–7.0	1.1–9.0

[a] Kong and Singh (2010), Minekus and Havenaar (1996) and Wickham et al. (2012).

In vitro floating behavior of FCC-based compacts heavily depended on the pH of the dissolution medium. Two pH conditions were studied: pH 1.1 and pH 7.0. In 0.1 N HCl, the tablets were floating during the entire dissolution measurement while eroding. However, in water the floating tablets sank to the bottom of the Erlenmeyer flasks after approx. 90 min. Erosion of the FCC-based tablet was observed *in vitro* when using HCl as dissolution medium. After contact with liquid, swelling of the polymers and formation of a gelation layer took place; thus penetration of the test medium into the porous structure of the floating tablet was limited. After erosion of the outer tablet layer due to formation of soluble $CaCl_2$, the dissolution medium penetrated further into the tablet, and a new gel layer was generated around the tablet. This process was visualized using a computer simulation. A corresponding video file is provided as Supplementary material. After contact with water, the polymers also swelled, and a gel layer formed around the tablet. Thus, liquid penetration into the compact was slowed down in a manner similar to that seen when using simulated gastric fluid as the medium. However, the porous FCC did not react with water to form a soluble salt. Thus, the floating tablets did not erode but gained weight, and floatation was stopped. This process was as well visualized using a computer simulation. A corresponding video file is provided as Supplementary material. Thereafter, dissolution continued, however at much lower rate. This was clearly observed after 90 min of drug release (Fig. 5a). The slowed release rate was associated with a reduction of tablet surface exposed to the dissolution medium. Thus, it can be expected that in the case of neutral pH of the gastric content the gastric retention due to floatation of the dosage form might not be sufficient.

The evaluation of the mechanical properties of the floating tablets showed that the tablets after incubation in both dissolution media still exhibited sufficient hardness and might withstand destruction due to gastric peristalsis. The contraction forces in the stomach range between 0.2 and 1.89 N depending on the fasting or fed state (Kong and Singh, 2010).

These hypothesized floating mechanisms and drug release properties were tested in *in silico* dissolution simulation. The virtual tablet was designed with an outer layer devoid of any swelling, gelation-layer forming polymer particles. Thus, simulation of initial, rapid caffeine release ("burst" effect) as observed in the *in vitro* dissolution profiles was possible. The *in silico* model simulated drug release from a tablet completely immersed in the dissolution medium. Thus, *in silico* dissolution results were in better agreement with the *in vitro* profiles obtained in the stomach model than those obtained in the USP test.

By varying the C_1 value, the different behavior of FCC in HCl and water was taken into account during dissolution simulation. The primary constant C_1 defines the number of iterations necessary to convert a cell occupied by a solid into a liquid cell. For *in silico*

dissolution of the tablet in acidic medium, a low C_1 value was selected, as FCC reacted with HCl. Because the tablet did not erode when using distilled water as dissolution medium, the $C_{1,FCC}$ value was increased for the *in silico* evaluation. The calculated tablet densities obtained from *in silico* dissolution simulation support the *in vitro* observations. Compact density increased to slightly higher than 1 g/cm^3 during dissolution simulation in HCl, while the experimental tablets floated during the entire *in vitro* measurement. Time difference between the visually observed sinking of the floating tablets during *in vitro* evaluation and the calculated time point according to *in silico* data might be due to incomplete assumptions of densities for "hydrated" swollen components and "wet" FCC used to calculate simulation profiles of tablet densities.

Water sorption measurement of powder samples of the floating formulation (powder blend) resulted in a secondary constant for *in silico* dissolution modeling. In the case of pure FCC, a low C_2 constant (implying high porosity of the material and thus a fast mass transfer) was obtained compared to the powder blend constant. Penetration of liquid into porous FCC particles was slowed down due to gelation-layer formation of the polymer substances after contact with water.

Summing up the experimental and simulated data, the concept of floatation of FCC-based tablets can be defined as a competition between rates of erosion and imbibition. The different erosion kinetics (i.e., fast erosion in simulated gastric fluid and infinitely slow erosion in a neutral medium) govern the mechanism of floatation: prevalence of imbibition induced the sinking of the tablet after a certain time. Such description of the observed phenomenon of sinking and reduction of dissolution speed in the case of distilled water as test medium is well supported by the computer-based calculations. During the computer experiments, imbibition front thickness was significantly larger in neutral (Fig. 5b) than acidic (Fig. 4b) media.

It has to be kept in mind that conventional modeling of such propagation kinetic is cumbersome and yields non-linear dynamic models; such models are often difficult to analyze. The modeling technique used in the presented study allows simulation of the mass-balance dynamics in the dissolving tablet and assessment of tablet densities during the dissolution experiment (which is not possible in reality), avoiding the complexity of conventional modeling yet providing higher correlation with the data obtained experimentally.

In this respect, it can be concluded that floating tablet formulation for different APIs, drug loads, formulation components, and tablet shapes can be optimized on the basis of our findings for the mechanism of floating behavior. Understanding the behavior of the key component of the studied formulation, i.e., FCC, is necessary to keep the tablets afloat throughout the desired drug release time frame. The mathematical model based on 3D cellular automata used in the presented study allows taking into account the key properties of FCC and their influence on the formulation; therefore, further optimization is possible and can be carried out *in silico*.

6. Conclusions

FCC is a promising pharmaceutical excipient suitable for the preparation of floating tablets. Due to its highly porous structure and lamellar surface, manufacture of compacts that feature a density <1 and sufficient hardness is feasible. The prepared floating tablets exhibited no floating lag time, thus lowering the risk of unpredictable, premature gastric emptying. Furthermore, FCC-based floating tablets exhibited sufficient hardness to resist destruction by gastric peristalsis.

Simulated drug release profiles using F-CAD software matched the experimental data of caffeine release from floating tablets in the custom-built stomach model. Moreover, calculated tablet densities based on *in silico* data were in accordance with the observations made during *in vitro* dissolution testing. Measurement of liquid sorption kinetics allows determining F-CAD constants of polymer compounds and porous FCC material based on experimental data. The *in silico* drug release and floatation simulations supported the hypothesis of floating mechanism, i.e. a reaction-based erosion mechanism with polymers as imbibition-inhibiting components.

The strategy used in the present work facilitates rational design, *in vitro* testing, and *in silico* analysis of floating tablet formulations. This will be instrumental for future development and optimization of innovative FDDS.

Acknowledgements

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejps.2014.03.001.

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3.2 *In silico* evaluation of multiple-unit lipophilic floating systems

In silico and *in vitro* methods to optimize the performance of experimental gastroretentive floating mini-tablets

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RESEARCH ARTICLE

In silico and *in vitro* methods to optimize the performance of experimental gastroretentive floating mini-tablets

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Abstract

Context: Development of floating drug delivery systems (FDDS) is challenging. To facilitate this task, an evaluation method was proposed, which allows for a combined investigation of drug release and flotation.
Objective: It was the aim of the study to use functionalized calcium carbonate (FCC)-based lipophilic mini-tablet formulations as a model system to design FDDS with a floating behavior characterized by no floating lag time, prolonged flotation and loss of floating capability after complete drug release.
Materials and methods: Release of the model drug caffeine from the mini-tablets was assessed *in vitro* by a custom-built stomach model. A cellular automata-based model was used to simulate tablet dissolution. Based on the *in silico* data, floating forces were calculated and analyzed as a function of caffeine release.
Results and discussion: Two floating behaviors were identified for mini-tablets: linear decrease of the floating force and maintaining of the floating capability until complete caffeine release. An optimal mini-tablet formulation with desired drug release time and floating behavior was developed and tested.
Conclusion: A classification system for a range of varied floating behavior of FDDS was proposed. The FCC-based mini-tablets had an ideal floating behavior: duration of flotation is defined and floating capability decreases after completion of drug release.

Keywords

Drug release, floating force, flotation, functionalized calcium carbonate, mini-tablet formulations

History

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Introduction

During the last decades, the interest in novel pharmaceutical dosage forms which are retained in the stomach has increased significantly, as conventional oral controlled-release dosage forms are known to exhibit limitations due to relatively short gastrointestinal transit times[1]. The gastroretentive delivery approach offers new and important therapeutic options for numerous drug substances[2]. Various mechanisms were investigated in order to enhance the stomach residence time of pharmaceutical dosage forms[3,4]. The development of floating drug delivery systems (FDDS) is favored: they do not influence the motility pattern of the gastrointestinal tract, and immediately floating dosage forms, due to an inherent low density, reduce the risk of uncontrolled and premature gastric emptying as no activation mechanism is needed[5,6].

Most floating gastroretentive drug delivery systems (GRDDSs) reported in the literature are single-unit drug delivery systems (e.g. tablets and capsules)[7]. Single-unit delivery devices have a major drawback: they feature the risk of unpredictable ''all-or-nothing'' gastric emptying[8,9]. Consequently, high inter- and intra-subject variability in gastrointestinal transit time and, therefore, in bioavailability is observed[2].

A possibility to overcome the problem is the development of multiple-unit drug delivery systems[9,10]. Multiple-unit FDDS are evenly spread over the stomach contents due to their density lower than the gastric fluids (i.e. 1.004–1.01 g/cm^3)[11] and are gradually emptied from the gastric region. Consequently, they have more predictable drug release profiles and inter- as well as intra-individual differences in drug bioavailability are reduced[2]. In addition, multiple-unit dosage forms feature the advantage that combinations of subunits with different drug release kinetics may be administered[12]. Various multiple-unit FDDS, comprising powder formulations[13], granules[14,15], microspheres[16,17] and mini-tablets[18,19], have been described in literature.

Numerous researchers still use the density of a dosage form and the visually observed floating behavior (i.e. floating lag time and floating duration) as the main parameters to characterize, compare and optimize the *in vitro* floating capabilities of FDDS[20,21]. On the one hand, determination of the density of the ''dry'' dosage form alone is not a predictor for the changes in the resulting floating forces acting on the tablet occurring during the release of the drug substance[22]. To observe the actual floating

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visually, on the other hand, does not provide any information about the magnitude of the floating forces and their effect on the floating kinetics. Therefore, when using these traditional approaches the comparison of different FDDS formulations is limited[23].

In order to evaluate the *in vitro* floating capabilities of buoyant dosage forms as a function of time more precisely, an apparatus to measure the resultant-weight of floating systems was proposed[24]. The instrument monitors the total resultant force acting vertically on an immersed object which results from the difference between the flotation force, i.e. buoyancy (=displacement volume of liquid × liquid density), and the force on the object due to gravity. This force characterizes the resultant-weight of the immersed object, hence, allows quantification of floating and non-floating capabilities of drug delivery systems. The resultant-weight method was used to provide an overview of the floating behavior of some typical floating formulations[22]. The development of FDDS requires the *in vitro* assessment of drug release profiles as well as the assessment of the floating behavior of the dosage forms[25]. However, it is common to evaluate and optimize these parameters separately due to the formidable obstacles to simultaneously investigate floating properties and drug release. For example, the measurement conditions of the resultant-weight method are not comparable to the conditions of the *in vitro* USP 1 and 2 dissolution measurements, as mechanically stirred hydrodynamics will prevent accurate resultant-weight registration. The measuring principle of the resultant-weight recording apparatus was also used by Sauzet et al[26]. They developed a custom-built apparatus to assess floating capabilities of drug delivery systems; however, this method does not allow for the determination of drug release and floating simultaneously.

The general approach for the analysis of dissolution behavior and floating capabilities of FDDS is to plot drug release and buoyancy forces separately versus time. However, in order to develop floating formulations successfully a combined evaluation of *in vitro* drug release and floating capabilities is needed[27]. The objective of the study was to propose such a combined evaluation method and investigate its applicability to find a formulation which has no floating lag time and maintains its floating capabilities while releasing the drug substance. After complete drug release, the delivery systems should lose their floating capability. The loss of floating capability allows gastric emptying of the FDDS and prevents possible accumulation of tablet remains in the stomach after multiple administering. Termination of flotation after complete drug release is supposed to be ideal for FDDS regarding safe administration in humans. In this study, functionalized calcium carbonate (FCC)-based lipophilic mini-tablet formulations were used as a model system to optimize the final dosage form based on the findings derived from the above described concepts. Mini-tablets were selected as model dosage forms as their manufacture is associated with some difficulties: good flowability of the powder mixtures is required in order to obtain uniform filling of the die and consequently the preparation of mini-tablets with acceptable properties (i.e. tablet weight and content uniformity)[28]. Larger particle size generally enhances flowability, however, powder particles are limited in their maximum size to prevent blockage of the die entry opening during the compaction process. In the case where mini-tablets are intended for subsequent coating, they should exhibit sufficient hardness and friability[29].

Materials and methods

Materials

Functionalized calcium carbonate (FCC VP-OM2501 S02, Omya, Switzerland)[30] served as matrix-forming excipient for the preparation of mini-tablets. For hot-melt granulation, Lubritab® (JRS Pharma, Germany), a hydrogenated cottonseed oil, was selected as lipophilic substance. Polyethylene oxide Polyox™ WSR-Coagulant (approximate molecular weight 5 000 000) (Cimex AG, Switzerland) was added to the formulations as gelation-layer forming polymer. As a model drug substance, caffeine (BASF, Ludwigshafen, Germany) was used.

Methods

Preparation of mini-tablet formulations

Table 1 shows the Box–Behnken experimental design generated by STAVEX 5.0 (Aicos, Switzerland). A Box–Behnken design was selected as a screening approach that provides sufficient coverage for the design space. Three mixture factors – concentrations of FCC, Lubritab® and Polyox™ WSR-Coagulant – were specified (mixture equation: FCC + Lubritab® + Polyox™ = 0.83. For FCC, the factor levels were set to 15, 23, 31, 37, 45, 53 and 59% (w/w). Lubritab® levels and Polyox™ WSR-Coagulant levels were 1, 8, 15, 23, 30, 37 and 45% (w/w).

In cycle 2, a formulation $F_{optimal}$ was prepared. The criteria set for the optimization were a caffeine release time of 12 h and the highest tablet hardness possible for this drug release time. The composition of $F_{optimal}$ is displayed in Table 1.

The required amounts of each excipient were weighed. Caffeine, FCC, Lubritab® and Polyox™ WSR-Coagulant were then mixed in a tumble-action mixer (Turbula type T2C, Willy A. Bachofen, Switzerland) for 10 min. Granulation of the prepared mixtures was performed using a twin-screw hot-melt extruder (ZE9, Three Tec, Switzerland). The co-rotating screws had a diameter of 9 mm and a length to diameter (*L*/*D*) ratio of 30 D. During the granulation process, the die plate of the hot-melt extruder was removed to obtain granules directly.

Prior to compaction, the granules obtained by hot-melt granulation were sieved. Afterwards, 1% (w/w) Aerosil® 200 and 1% (w/w) magnesium stearate were added. The formulations were mixed in a Turbula mixer (Turbula type T2C, Willy A. Bachofen, Switzerland) for 15 and 3 min, respectively. For the preparation of round, convex mini-tablets, a single punch tablet press (STYL'One, Medel'Pharm, France) equipped with 2 mm (diameter), r1.4 (cap radius 1.4 mm) Euro-B multiple tooling (multiple-tip punch with 12 tips) was used. The mini-tablet weight was set to 6 mg. Mini-tablets were compacted using a mechanically-assisted feed shoe.

Computer simulation parameters for mini-tablet formulations

The computer simulations of drug release and flotation kinetics were performed using the three-dimensional cellular automata-based dissolution model from the software package F-CAD v.2.0 (CINCAP GmbH, Switzerland)[31]. For the *in silico* dissolution experiments ($n = 1$), concave-shaped tablet matrices with a diameter of 2 mm and a cap radius of 1.4 mm were generated. The virtual tablet matrices consisted of a discrete cubic grid with an individual voxel side length of 35.43 µm. Discrepancies between the experimental and the simulated mini-tablet properties are due to the discretization error. The absolute average error of the tablet weight was 0.58 mg. The absolute average deviation of *in silico* tablet thickness and diameter from the experimental parameters were 0.02 and 0.14 mm, respectively.

Using the particle arrangement and compaction (PAC) module, the *in silico* generated grid was filled with the components of the mini-tablet formulations to 0% simulated tablet porosity. To assess the deviation in composition of the *in silico* packed tablet matrices from the experimentally prepared formulations, the absolute average errors were calculated for every component.

Table 1. Composition of the experimental FCC-based mini-tablet formulations according to the generated Box–Behnken design.

		Mixture factors					
Formulation	Caffeine (%, w/w)	FCC (%, w/w)	Lubritab® (%, w/w)	Polyox™ WSR-Coagulant (%, w/w)	FCC	Lubritab®	Polyox™ WSR-Coagulant
F1	17.00	53.00	15.00	15.00	+2	−1	−1
F2	17.00	37.00	1.00	45.00	0	−3	+3
F3	17.00	37.00	45.00	1.00	0	+3	−3
F4	17.00	23.00	30.00	30.00	−2	+1	+1
F5	17.00	31.00	37.00	15.00	−1	+2	−1
F6	17.00	15.00	23.00	45.00	−3	0	+3
F7	17.00	59.00	23.00	1.00	+3	0	−3
F8	17.00	45.00	8.00	30.00	+1	−2	+1
F9	17.00	31.00	15.00	37.00	−1	−1	+2
F10	17.00	15.00	45.00	23.00	−3	+3	0
F11	17.00	59.00	1.00	23.00	+3	−3	0
F12	17.00	45.00	30.00	8.00	+1	+1	−2
F13	17.00	37.00	23.00	23.00	0	0	0
$F_{optimal}$*	17.00	40.00	43.00	0.00			

The experimental design matrix is displayed in uncoded and coded form.
*Preparation of the optimal mini-tablet formulation was done in cycle 2.

Table 2. Composition of the simulated FCC-based mini-tablet formulations and *in silico* tablet matrix properties.

Formulation	Caffeine (%, w/w)	FCC (%, w/w)	Lubritab® (%, w/w)	Polyox™ WSR-Coagulant (%, w/w)	Tablet weight (mg)	Tablet height (mm)	Tablet density (g/cm^3)	Calculated inherent resultant force $\vec{F}_r$ ($\cdot 10^{-5}$ N)
Simulated F1	19.58	45.10	17.66	17.66	5.36	2.84	0.6858	2.408
Simulated F2	18.14	32.77	1.09	48.02	5.62	2.59	0.7985	1.392
Simulated F3	19.54	28.50	51.18	0.78	5.37	2.56	0.7751	1.529
Simulated F4	17.31	19.11	31.79	31.79	5.79	2.42	0.8917	0.689
Simulated F5	18.23	23.71	41.64	16.42	5.76	2.52	0.8299	1.158
Simulated F6	15.90	21.35	21.12	41.63	6.60	2.73	0.8821	0.865
Simulated F7	22.25	47.56	28.90	1.29	4.73	2.62	0.6614	2.375
Simulated F8	18.80	39.31	8.77	33.12	5.59	2.77	0.7356	1.969
Simulated F10	17.40	13.95	45.61	23.04	6.03	2.45	0.9131	0.563
Simulated F11	20.80	50.85	0.79	27.53	5.05	2.77	0.6648	2.497
Simulated F12	21.18	31.94	36.86	10.01	4.96	2.42	0.7643	1.500
Simulated F13	18.15	33.79	24.03	24.03	5.78	2.77	0.7619	1.774
Simulated $F_{optimal}$	20.64	27.48	51.89	0.00	5.09	2.42	0.7839	1.376

The diameter of the *in silico* mini-tablet matrices was 2 mm for all formulations. Mechanical stability of tablets cannot be simulated by the current version of the software.

The absolute average errors for Polyox™ WSR-Coagulant, caffeine, Lubritab® and FCC were found to be 1.81% (w/w), 2.24% (w/w), 3.19% (w/w) and 7.17% (w/w), respectively. The high absolute average error for the FCC component can be explained by the highly porous structure of the FCC particles and their ability to accommodate relatively large amounts of other components within the lamellar structures of the particles. The computer simulation model accounts only for components with rigid volumes and the filling of formulation components into porous FCC cannot be simulated *in silico*.

Tablet density was less than 1 g/cm^3 for all virtual mini-tablet matrices and the absolute average deviation from the experimental values was 0.04 g/cm^3. The properties of the *in silico* mini-tablets are shown in Table 2.

Characterization of experimental mini-tablets

Weight, diameter and height. The weight of the mini-tablets, using a sample number $n = 20$, was determined using an electronic balance (AX 204 Delta Range, Mettler Toledo, Switzerland). Tablet diameter ($n = 10$) and height ($n = 10$) were assessed by a microscope (Projectina, Switzerland). Use of a slide caliper gauge was not possible, as the mini-tablets would be compressed during the measurement resulting in wrong tablet diameter and thickness values.

True density and porosity. According to Equation (1), the porosity ε of the tablets was calculated

$$\varepsilon = \left(1 - \frac{m}{V \cdot \rho}\right) \cdot 100 \quad (1)$$

where ε is the tablet porosity (%), m is the mass of the mini-tablet (mg), ρ is the true density of the formulation (g/cm^3) and V is the tablet volume (cm^3).

Tensile strength. A texture analyzer (FMT-310, Force Tester, Alluris GmbH & Co. KG, Germany) was used in order to evaluate the hardness ($n = 10$) of the mini-tablets. The mini-tablet was placed under the sensor and the zero point of force was determined. Afterwards, the sensor was moved downwards 0.4 mm and a path–force diagram was recorded. The peak value of the path–force diagram was taken as the hardness of the

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mini-tablet. The tensile strength σ_t of the mini-tablets was calculated according to Equation (2)[32]

$$\sigma_t = \frac{10P}{\pi \cdot D^2 \cdot \left(2.84 \cdot \frac{t}{D} - 0.126 \cdot \frac{t}{W} + 3.15 \cdot \frac{W}{D} + 0.01\right)} \quad (2)$$

where σ_t is the tensile strength (MPa), P the fracture load (N), D the tablet diameter (mm), t the tablet thickness (mm) and W the wall height (mm).

Drug content. Caffeine content of the mini-tablets was measured for each formulation in triplicate. Each mini-tablet was ground in a mortar and dissolved in 100 ml 0.1 N HCl while stirring. The solution was filtered and the UV/Vis spectrophotometric absorbance was determined (UV/Vis-spectrophotometer, Jasco V-630, Brechbühler AG, Switzerland) at 272 nm. For the drug content analysis, a calibration curve ($A = 50.88 - 0.0074$; $R^2 = 0.9997$, where A is the absorbance and c the concentration (mg/ml)) was prepared with five measurement points in the concentration range from 0.005 to 0.015 mg/ml.

In vitro *evaluation of drug release*

A custom-built stomach model was used to assess *in vitro* drug release behavior of mini-tablet formulations[27]. In brief, dissolution was measured in a volume of 400 ml of 0.1 N HCl on a horizontally shaking platform. For simultaneous and precise placement into the Erlenmeyer flasks of the stomach model, 20 mini-tablets were packed into a gelatin capsule size 2. The capsule dissolves upon contact with 0.1 N HCl and releases the mini-tablets into the assay medium. Drug release was monitored continuously by UV-spectroscopy. In combination with visual inspection and *in silico* modeling, tablet flotation could be monitored. Dissolution profiles were thereby used to calibrate the *in silico* dissolution model and to derive from these computer models estimates of the forces acting on the immersed tablets as described below.

In silico *evaluation of dissolution and floating behavior*

To assess *in silico* tablet dissolution and floating behavior, the three-dimensional cellular automata-based dissolution model from the software package F-CAD v.2.0 (CINCAP GmbH, Switzerland) was used. The F-CAD component types, codes and constants set for the computer simulations[27] are detailed in Table 3. The general cellular automata rules used in the present study are the following: rules for active pharmaceutical ingredients, rules for polymer components, rules for hydrophobic excipients and rules for porous FCC material. The primary constant C_1 of an automaton, independent of its component type, controls the solvation of the solid; i.e. it defines the number of iterations needed to change the ''solid'' state of a voxel into a ''liquid'' state. Each ''liquid'' voxel in the 3D Moore neighborhood[33] of a ''solid'' state voxel subtracts one unity at a time from the C_1 value of the ''solid'' state voxel. When reaching the C_1 value of zero, the ''solid'' state voxel converts into a ''liquid'' voxel. The function of the C_2 value depends on the component type. In the case of polymer components, the C_2 value defines the degree of swelling of the hydrated polymer voxel. In order to mimic a volume increase after contact with the dissolution liquid, the ''liquid'' voxels in the three-dimensional Moore neighborhood of the swelling material are converted into ''hydrated'' polymer voxels. The C_1 value of these ''hydrated'' polymer voxels is obtained by integer division of C_1 by C_2 value. The C_2 constant of FCC controls the rate of liquid sorption into porous FCC particle meshwork: division of the C_2 value by the number of liquid voxels in the three-dimensional Moore neighborhood defines the number of iterations which are needed to change a ''dry'' into a ''wet'' state voxel[27].

In addition to the FCC, a second FCC type – hydrophobized FCC – was introduced for the computer simulations. The new FCC type was generated to take into account the hydrophobization of FCC due to melting of Lubritab® during the hot-melt granulation process. Hydrophobized FCC was assumed to have a C_1 value of 100 000, which indicates a low solubility material, and a C_2 value of 3500[27]. Hence, *in silico* dissolution of the hydrophobized FCC was slowed down and penetration of dissolution liquid into FCC particles was decelerated. Lubritab® was assumed to have a C_1 value of 7 000 000 to indicate completely insoluble material.

Density of the virtual tablets was assessed as described in Eberle et al[27]. The density value of hydrated polymer voxels was assumed to be 1 g/cm^3. Based on the results of liquid sorption measurements (data not shown), the density of ''wetted'' FCC was set to 0.45 g/cm^3.

The resultant force $\vec{F}_r$ acting on an immersed dosage form was calculated according to Equation (3)[22]

$$\begin{aligned} \vec{F}_r &= \vec{F}_{\text{buoyancy}} - \vec{F}_{\text{gravity}} \\ \vec{F} &= (\rho_f - \rho_t) \cdot \vec{g} \cdot V \end{aligned} \quad (3)$$

where $\vec{F}_r$ is the total vertical force acting on an immersed object (N), ρ_f the fluid density (g/cm^3), ρ_t the density of the tablet (g/cm^3), V the tablet volume (mm^3) and $\vec{g}$ the acceleration of gravity (m/s^2). In order to evaluate the floating behavior of the mini-tablet formulations, the resulting force $\vec{F}_r$ is plotted versus the *in silico* caffeine release data.

Evaluation of the adequacy of the simulation model

In order to evaluate the adequacy of the simulation model, the *in silico* dissolution profiles were compared to the experimentally obtained drug release profiles. A model-independent approach calculating a difference (f_1) and similarity factor (f_2) was used[34]. The difference factor f_1 was calculated according to Equation (4)

$$f_1 = \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \cdot 100 \quad (4)$$

Table 3. Summary of the parameters used for *in silico* dissolution simulation.

Component	True density (g/cm^3)	Type ID	Component code	C_1 constant	C_2 constant
Caffeine	1.4489	1	API	700	Not applicable
Polyox™ WSR-Coagulant	1.2372	41	Hydrophilic swelling matrix	1300	4
Lubritab®	0.9926	71	Hydrophobic ingredient	>7 000 000	Not applicable
FCC	0.45* (2.7525†)	81	Porous material	500	15
Hydrophobized FCC	0.45	81	Porous material	100 000	3500

*Bulk density of FCC[44].
†For crystalline material (skeletal density).

where n is the number of time points, R_t the dissolution value of the experimental tablet at time t and T_t the dissolution value of the simulated tablet at time t. A difference factor f_1 in the range from 0 to 15 ensures equivalence of two dissolution curves[34].

According to Equation (5) the similarity factor f_2 is determined as follows:

$$f_2 = 50 \cdot \log\left(\frac{1}{\sqrt{1+\frac{1}{n}\cdot\sum_{t=1}^{n}(R_t - T_t)^2}}\cdot 100\right) \quad (5)$$

where, once again, n is the number of time points, R_t the dissolution value of the experimental tablet at time t and T_t the dissolution value of the simulated tablet at time t. A similarity factor f_2 in the range from 50 to 100 implies sameness of two drug release profiles[34].

In addition, Pearson correlation coefficients[35] were calculated to compare *in vitro* and *in silico* drug release profiles.

Results

Characterization of experimental mini-tablets

The properties of the experimentally prepared tablets are summarized in Table 4. It was possible to compact mini-tablets featuring a tablet density less than 1 g/cm^3. In the case of formulation F9, no mini-tablets were obtained due to sticking of the tablets to the punches of the tablet press during the ejection process. The contraction forces acting in the human stomach have been reported to range between 0.2 and 1.89 N depending on the fasting or fed state and the used investigation method[36]. In the case of formulations F1, F3, F8 and F13, the measured hardness values were below 1.89 N; however, all mini-tablet formulations exhibited sufficient hardness for further processing. The other tablet characteristics shown in Table 4 are within acceptable or expected ranges.

In vitro *evaluation of drug release and floating behavior, and simulation model adequacy proof*

The visual observation of the floating behavior (i.e. floating lag time and floating duration) revealed that the mini-tablets were floating immediately after being placed in the Erlenmeyer flasks of the custom-built stomach model. All tablets stayed afloat during the caffeine release measurement. In the case of formulations F3, F6, F7 and F10, a lipophilic matrix remained after complete drug release. In contrast, all other mini-tablet formulations dissolved entirely. In Table 5, the coefficients of first-order fitting of the *in vitro* drug release profiles are summarized. Fastest caffeine release within 75 min was obtained for formulation F1. In the case of formulation F3, 100% caffeine release was observed after about 27 h.

Flotation and drug release of a reference mini-tablet formulation consisting of 17% (w/w) caffeine and 83% (w/w) Lubritab® were analyzed only *in vitro*: within 66 h only 24% caffeine was released from the dosage forms. Tablet density was 0.94 g/cm^3 before immersion into the dissolution liquid; hence, the tablets were floating immediately. Due to tablet density very close to unity, floating behavior was unstable; most of the mini-tablets sank down during the caffeine release measurement.

In Table 5, the results of the comparison of simulated and experimental caffeine release curves are shown. The f_1-factors were found to be smaller than 15 and the f_2-factors were higher than 50, hence equivalence of the *in silico* and *in vitro* drug release profiles was assumed. The calculated Pearson correlation coefficients also confirmed this result.

Statistical analysis

Statistical analysis using the p value, expressing the probability of obtaining the observed sample results when the null hypothesis is actually true, showed that the excipients Lubritab® ($p < 0.05$) and FCC ($p < 0.05$) significantly influenced the caffeine release speed. The lipophilic excipient Lubritab® slowed down the drug release, whereas FCC was found to increase the rate of caffeine release. In addition, the interaction of Polyox™ WSR-Coagulant and FCC ($p < 0.05$) had an effect on the drug release from the mini-tablets.

Evaluation of mini-tablet formulation $F_{optimal}$

In Table 4, the properties of mini-tablet formulation $F_{optimal}$ are given. The tablet hardness calculated from response surface methodology for $F_{optimal}$ was 2.13 N; a hardness of 2.62 ± 0.70 N was experimentally observed. *In vitro* and *in silico* caffeine release profiles of the formulation are displayed in Figure 1. The targeted drug release time of $F_{optimal}$ was 12 h. Complete caffeine release was experimentally observed after 13 h. *In vitro* evaluation of the floating behavior showed that the mini-tablets had no floating lag time and stayed afloat during the entire drug release measurement. After complete caffeine release, lipophilic tablet matrices remained in the dissolution vessels. The experimental and simulated caffeine release curves of $F_{optimal}$ showed good correlation (Pearson correlation coefficient: 0.9875).

Table 4. Properties of the experimental mini-tablet formulations.

Formulation	True density (g/cm^3)	Weight (mg)	Diameter (mm)	Thickness (mm)	Drug content (mg)	Porosity (%)	Tablet density (g/cm^3)	Calculated inherent resultant force $\vec{F}_r$ (10^{-5} N)	Hardness (N)	Tensile strength (MPa)
F1	1.7004	5.98 ± 0.23	2.10 ± 0.02	2.85 ± 0.07	0.92 ± 0.06	58.58	0.7044	2.462	1.65 ± 0.26	0.1800 ± 0.0284
F2	1.5706	5.50 ± 0.39	2.13 ± 0.01	2.59 ± 0.13	0.93 ± 0.10	54.40	0.7161	2.139	1.37 ± 0.47	0.1681 ± 0.0582
F3	1.3987	6.31 ± 0.58	2.08 ± 0.03	2.57 ± 0.11	1.10 ± 0.13	41.79	0.8142	1.413	2.07 ± 0.96	0.2521 ± 0.1171
F4	1.3267	6.66 ± 0.60	2.09 ± 0.01	2.46 ± 0.06	1.02 ± 0.02	31.70	0.9061	0.677	2.10 ± 0.93	0.2725 ± 0.1200
F5	1.3691	6.39 ± 0.30	2.10 ± 0.01	2.55 ± 0.07	0.99 ± 0.02	38.51	0.8419	1.177	2.13 ± 0.62	0.2647 ± 0.0772
F6	1.2862	6.70 ± 0.44	2.10 ± 0.02	2.75 ± 0.06	1.08 ± 0.04	36.63	0.8151	1.491	2.06 ± 0.50	0.2340 ± 0.0567
F7	1.7570	5.91 ± 0.15	2.11 ± 0.01	2.62 ± 0.06	0.86 ± 0.01	57.20	0.7519	1.913	2.49 ± 0.41	0.3012 ± 0.5010
F8	1.6427	5.83 ± 0.46	2.13 ± 0.01	2.76 ± 0.03	0.97 ± 0.05	58.20	0.7398	2.010	1.40 ± 0.38	0.1561 ± 0.0422
F10	1.2284	6.21 ± 0.29	2.09 ± 0.01	2.44 ± 0.09	0.85 ± 0.11	27.78	0.8871	0.775	2.21 ± 0.67	0.2934 ± 0.0890
F11	1.9089	5.82 ± 0.39	2.11 ± 0.01	2.76 ± 0.10	0.93 ± 0.06	63.66	0.6937	2.521	2.01 ± 0.75	0.2272 ± 0.0847
F12	1.5387	5.90 ± 0.52	2.10 ± 0.01	2.45 ± 0.12	0.94 ± 0.17	48.11	0.7984	1.462	1.99 ± 1.09	0.2565 ± 0.1409
F13	1.4975	5.93 ± 0.45	2.10 ± 0.01	2.74 ± 0.13	0.90 ± 0.05	51.17	0.7312	2.139	1.68 ± 0.49	0.1928 ± 0.0561
$F_{optimal}$*	1.4341	5.95 ± 0.26	2.10 ± 0.02	2.45 ± 0.06	1.02 ± 0.03	44.08	0.8019	1.442	2.62 ± 0.70	0.3385 ± 0.0901

*Preparation of the optimal mini-tablet formulation was done in cycle 2.

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Table 5. Experimental and simulated data of the mini-tablet formulations and comparison of *in silico* to *in vitro* caffeine release profiles.

	Experimental data		Simulated data				
Formulation	Coefficient of first-order dissolution curve fitting	Quantification of the fit	Coefficient of first-order dissolution curve fitting	Quantification of the fit	Difference factor (f_1)	Similarity factor (f_2)	Pearson correlation coefficient
F1	0.0384	0.9994	0.0413	0.9966	8.85	64.70	0.9963
F2	0.0252	0.9987	0.2565	0.9989	2.57	83.26	0.9986
F3	0.0019	1.0000	0.0028	0.9999	8.46	65.24	0.9950
F4	0.0152	0.9982	0.0175	0.9993	7.02	67.63	0.9973
F5	0.0142	0.9998	0.0175	0.9997	7.80	69.32	0.9976
F6	0.0221	0.9996	0.0217	0.9988	7.94	69.03	0.9996
F7	0.0346	0.9997	0.0431	0.9996	10.45	59.07	0.9939
F8	0.0391	0.9991	0.0319	0.9976	7.54	67.43	0.9999
F10	0.0158	0.9999	0.0244	0.9999	4.56	62.44	0.9899
F11	0.0476	1.0000	0.0410	0.9984	11.76	56.34	0.9908
F12	0.0344	0.9995	0.0327	0.9989	3.46	81.55	0.9985
F13	0.0256	0.9984	0.0268	0.9990	7.21	68.66	0.9997

Difference factors (f_1) from 0 to 15 and similarity factors (f_2) greater than 50 ensure equivalence of two dissolution curves[35].

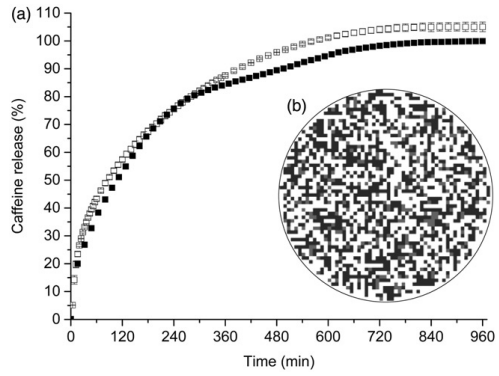

Figure 1. (a) Experimental (□) and simulated (■) caffeine release profiles of mini-tablet formulation $F_{optimal}$. (b) Cross-section of the *in silico* mini-tablet matrix of $F_{optimal}$, where caffeine, FCC, and Lubritab® are displayed in light grey, white and dark grey, respectively.

The difference (f_1) and similarity (f_2) factors were 8.25 and 65.61, respectively. As the values were within the factor limits (i.e. f_1-factor smaller than 15; f_2-factor higher than 50) equivalence of the *in vitro* and *in silico* drug release curves was concluded.

In silico evaluation of drug release and floating behavior

Figures 2(a) and 3 display the resulting force $\vec{F}_r$ of the mini-tablet formulations as a function of the percentage of caffeine released. The initial resulting force at time zero acting vertically on the virtual tablets was positive for all formulations. This means that all mini-tablet formulations had no floating lag time. The magnitude of $\vec{F}_r$ at 0% caffeine release depended on the amount of FCC in the mini-tablet formulations: the higher the amount of FCC in the formulation, the higher the floating capability of the mini-tablets (Figure 2b). According to Figure 2(b), a minimum amount of 2.75% (w/w) FCC would be needed to reach a positive resulting force acting on the tablet. Two different floating behavior types were observed. The formulations in Figure 2(a) exhibited an almost linear decrease in floating capability while the drug substance was released. In the case of mini-tablet formulation F7, an initial drop in floating force was observed. Despite this observation for formulation F7, the calculated floating forces did not reach negative values, i.e. the tablets did not sink down. Due to positive floating forces, it was concluded that the simulated mini-tablet was floating during the entire *in silico* drug release measurements. Figure 2(c) illustrates the slope of the floating force curves, obtained by linear regression, versus the FCC content of the mini-tablet formulations. The higher the amount of FCC in the formulations, the faster the resulting force $\vec{F}_r$ was decreased while releasing caffeine.

The floating behavior of formulations F3, F10 and $F_{optimal}$ is shown in Figure 3. The mini-tablets maintained their floating forces up to 70% caffeine released from tablet formulations. Afterwards, their floating capabilities were declining to zero floating force (i.e. unit density) when 100% of the drug was released from the simulated mini-tablets. The described floating behavior was indeed observed for mini-tablet formulations with Lubritab® contents of approximately 42% (w/w). It was hypothesized that in the case of these formulations enough of Lubritab® was available to result in a hydrophobization of the FCC particles during hot-melt granulation process. This assumption was supported by the fact that for the *in silico* dissolution simulations of F3, F10 and $F_{optimal}$, the F-CAD component ''hydrophobized FCC'' with increased C_1- and C_2-values had to be used. The decrease in floating forces of the simulated mini-tablets was a result of the declining number of FCC voxels during tablet dissolution simulations.

Discussion

Experimental mini-tablet formulations

As it was visually observed, the experimental mini-tablets exhibited no floating lag times due to tablet densities less than unity. The inherent calculated floating force of the tablets depended on the amount of FCC in the formulations. High amounts of FCC due to its inherently high porosity resulted in high initial floating forces of the mini-tablets.

The resultant floating force values of the mini-tablets could not be experimentally assessed by using the custom-built stomach model approach. However, it was visually observed that the floating tablets did not sink to the bottom during the *in vitro* evaluation. This implies that the experimental tablets maintained a positive resultant floating force while the drug substance was released. In addition, it is assumed that the resultant force value of the experimental mini-tablets was close to zero after complete

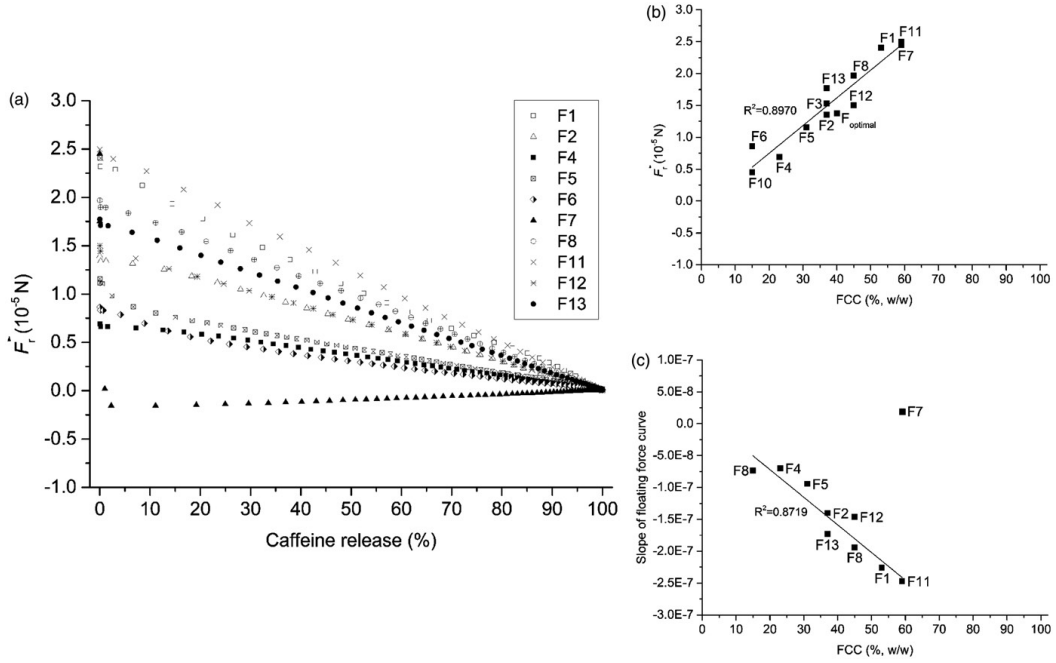

Figure 2. (a) Resulting force curves of simulated mini-tablet formulations. (b) Initial floating forces of the mini-tablets plotted against the amount of FCC in the formulations. (c) Slope of the resulting force curves plotted versus the amount of FCC in the formulations. The slope of formulation F7 was almost zero, implying that the mini-tablets were prone to sink while releasing the drug substance.

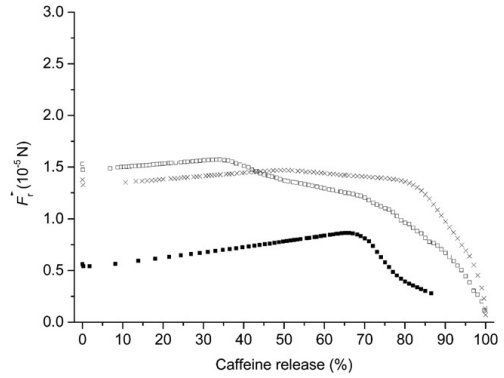

Figure 3. Resulting force curves of simulated mini-tablet formulations. Formulations F3 (□), F10 (■) and $F_{optimal}$ (x) exhibited no floating lag time as the initial values were positive. Mini-tablets maintained their floating capabilities while releasing caffeine followed by a decrease in floating force.

caffeine release, as flotation-promoting FCC reacts in acidic dissolution medium and the only formulation component which remained in the dissolution test set-up was Lubritab® featuring a density of 0.99 g/cm^3. Taking into account these considerations and the visual observation of flotation behavior, it was concluded that the floating capability of the experimental mini-tablets decreased, compared to their inherent floating potential, while caffeine was released.

In silico mini-tablet formulations and simulation model adequacy proof

The data suggest that floating forces of dosage forms should be analyzed as a function of drug release instead of a function of time. For example, it was then possible to evaluate if a dosage form stayed afloat while releasing the drug and if it was still floating after complete drug release. Plotting the resulting force versus the amount of drug released offers the possibility to compare the floating capabilities of different formulations against each other. The proposed method is advantageous for formulation development of FDDS, as formulations with unstable floating properties (i.e. floating lag time or the risk of sinking) can be identified. Good correlation ($f_2 > 56$) between simulated and experimental caffeine release profiles was obtained, hence, providing a proof for the correct design of the virtual mini-tablet matrices and the simulation parameters set for the computer calculations of floating forces. Consequently, it can be assumed that the floating force curves were in accordance with the real floating capabilities of the tablets.

For formulations with a linear decrease in floating capability, it was observed that the higher the amount of FCC in the formulation the faster the decrease in floating force during *in silico* caffeine release simulation. This observation might be explained by the fact that FCC, which promotes flotation of the dosage form, reacted with the acidic dissolution medium and, hence, the resultant floating force was reduced. At 100% caffeine released, the calculated resultant floating force value was approx. 0 N for all mini-tablets. In addition, tablet formulations containing high amounts of FCC were found to be prone to have unstable flotation properties (e.g. in the case of formulation F7 an abrupt decrease in resulting force occurred).

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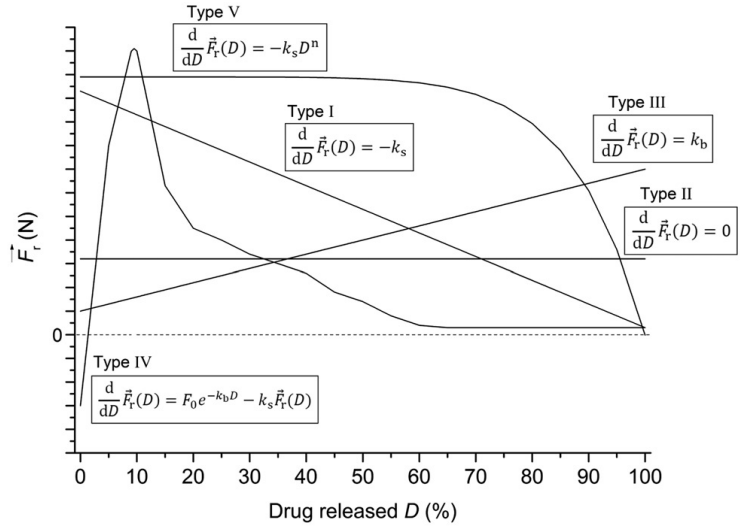

Figure 4. Model floating behavior of FDDS, where $\vec{F}_r$ is the resulting force, D is the drug release, k_b is the buoyancy constant and k_s is the constant of dosage form sinking. The proposed model behavior is for illustrative purpose and more complex behavior may be observed.

Table 6. Categories of model floating behavior of FDDS.

	Characteristics			
Category	Floating lag time	Behavior while drug substance is released	Potential danger of permanent retention	Example floating formulation
Type I	No	Resultant floating force decreases	No	Eroding, hydrophilic drug delivery system
Type II	No	Resultant floating force is maintained	Yes	Constantly buoyant inert fillers
Type III	No	Resultant floating force increases	Yes	Constantly buoyant inert fillers
Type IV	Yes	Resultant floating force first increases and is followed by a decrease	No	Drug delivery system with flotation due to effervescence
Type V	No	Resultant floating force is maintained with subsequent decrease	No	Hydrodynamically balanced system; lipophilic FCC-based drug delivery system

The experimental and simulation data indicate that the preparation of FCC-based lipophilic mini-tablet formulations with targeted floating and drug release kinetics was possible. Mini-tablets with immediate flotation, which retained their floating capability while releasing the drug substance, were produced. After complete drug release, the mini-tablets had lost their floating capability. However, porous FCC or similar porous materials were necessary as matrix-forming excipients to achieve stable floating behavior (i.e. no risk of the tablets sinking) and desired drug release.

Classification system for types of floating behavior

Figure 4 shows five different model behavior types for FDDS. Each model floating behavior is for illustrative purpose and obtained by summing up experimental, simulation and literature data. The FDDS are floating immediately, except for the system of type IV. Type I shows the floating characteristics of hydrophilic eroding systems, where the floating force is decreasing due to predominant dissolution of the tablet components. Type I floating kinetics were experimentally obtained for matrix capsules filled with a hydrophilic formulation[22]. Floating behavior type II illustrates the idealized *in vitro* floating characteristics of dosage forms whose floating capabilities do not change while releasing the drug. Type II is a model for systems where the drug density is equal to the density of the surrounding liquid. Mass exchange between the drug and liquid is steady and monotonic; hence, the floating capability of the dosage form is maintained. As displayed in Figure 4, FDDS can gain in floating force during drug release. This kind of floating model behavior (type III) can be obtained in the case of constantly buoyant inert fillers, such as hollow cores[37]. The release of the drug substance results in a decrease in gravity force due to decreasing mass. A type III floating behavior was measured for bilayer floating tablets composed of drug-loaded and floating granules[38]. However, types II and III floating systems might possess a risk of being accumulated in the human stomach after multiple administering.

The problem of permanent retention in the human stomach is especially associated with large single-unit floating gastroretentive dosage forms in particular for patients with bowel obstruction, gastropathy or a constricted pyloric opening. It may lead to local irritations in the stomach[39,40]. For multiple-unit dosage forms, such as mini-tablets, this risk is negligible following a single administration; however, the potential risk for aggregation and accumulation of drug-depleted mini-tablets in the human stomach increases after multiple, sequential administrations.

Floating behavior type IV shows the *in vitro* floating behavior of a FDDS exhibiting a floating mechanism which needs to be activated first[41,42]. The initial density of the system is higher than unity, implying that the delivery device is not floating. Upon contact with an acidic medium, carbon-dioxide is being generated and entrapped in a hydrated polymer layer forcing the dosage form to float[43]. The buoyancy capability of the system decreases during drug release as carbon-dioxide is escaping from the gel layer. A floating behavior considered to be ideal for floating gastroretentive drug delivery systems is type V. This system, due to its inherent low density, is immediately floating and maintains its floating force while releasing the drug substance. The tablet matrix sinks down after complete drug release followed by gastric emptying. Type V floating behavior was experimentally obtained in the case of hydrodynamically balanced systems like Valrelease® and Valium® CR[22]. A summary of the defined flotation behavior types and their characteristics is given in Table 6.

Conclusions

The proposed strategy of combining the analysis of drug release and flotation behavior offers the possibility to design FDDS with desired drug release and floating kinetics, and, hence, safer gastroretentive floating dosage forms. A classification system to characterize the performance of FDDS was introduced in the present study and applied to describe floating behavior of FCC-based lipophilic mini-tablet formulations.

Mini-tablets exhibiting a type V floating behavior were prepared and are considered desirable for gastroretentive FDDS. Pharmaceutical dosage forms with a type V behavior start floating in the stomach immediately after administration. The risk for uncontrolled and premature stomach emptying of the FDDS is therefore reduced as no floating mechanism needs to be activated first. The floating force curve of model behavior type V looks simplistic: the drug delivery system is supposed to have no floating lag time and it should maintain its floating capability while releasing the drug substance. The floating force should decrease after complete drug release to allow gastric emptying of the dosage form in order to prevent accumulation in the stomach. But, in fact, the floating behavior is a result of complex interactions of different formulation components.

The present study shows that porous materials with an inherent porosity-driven low density, like FCC, are ideal candidates for the preparation of gastroretentive floating dosage forms. However, in order to activate the flotation promoting role of FCC, additional excipients (e.g. lipophilic components) are needed. Proper combination of the components is required to design FDDS exhibiting controlled floating dynamics. The proposed classification system and measurement approach (i.e. combination of *in vitro* and *in silico* methods) help to identify ideal flotation characteristics of solid dosage forms and assist thereby in the development of such advanced drug delivery strategies.

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Declaration of interest

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3.3 Formulation development of hydrophobic matrix systems

Designing a paraffin wax functionalized calcium carbonate matrix for gastroretentive floating tablet formulations

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Manuscript ready for submission.

Abstract

Hydrophobic matrix systems are used to design delivery platforms with sustained release kinetics; but, they are associated with the shortcoming of incomplete drug release.

The aim of the present study was to identify the key factors influencing the desired drug release and the statistics of the design space for hydrophobic matrix formulations. A floating drug delivery system (FDDS) was used as a model system.

Hydrophobic matrix formulations, containing paraffin wax and functionalized calcium carbonate (FCC) as release-modulating agents, were produced my melt granulation in a twin-screw hot-melt extruder. Release of the model drug caffeine was assessed *in vitro* using a custom-built stomach model. Additionally, a three-dimensional cellular automata-based model was applied for the design of *in silico* tablet matrices and for dissolution simulation.

In silico dissolution simulation and scanning electron microscopy suggested a hydrophobization of FCC due to molten paraffin wax at elevated temperatures influencing the arrangement of the formulation components within the tablet matrix. The combination of *in vitro* measurements, statistical analysis, and computer simulations provided a tool to understand the influence of the excipients on the characteristics of multicomponent formulations, taking into an account the effects induced by the unit operation. The simulated thickness of the lipophilic layer ranged from 0.15 up to 3.00 µm resulting in a different degree of FCC hydrophobization; depending on the formulation, the amount of paraffinized FCC was found to range from 5.93 up to 66.31% (w/w).

Keywords

hydrophobic matrix system, floating tablet, melt granulation, twin-screw hot-melt extruder

Abbreviations

API	active pharmaceutical ingredient
FCC	functionalized calcium carbonate
FDDS	floating drug delivery systems
pFCC	paraffinized functionalized calcium carbonate
sFCC	“standard” functionalized calcium carbonate

1. Introduction

Hydrophobic matrix systems are widely used for the preparation of oral controlled-release drug delivery platforms [1]. A hydrophobic matrix system describes a dosage form composed of drug substances being embedded in a water-insoluble, non-swelling matrix material (e.g. fatty acids, fatty alcohols, fatty acid esters, or waxes of natural and synthetic origin) in order to achieve sustained drug release [2]. Several excipients are used as drug release-retarding agents for the preparation of sustained-release, hydrophobic matrix formulations, including materials such as glycerides (e.g. Compritol® 888 ATO (glyceryl behenate) [3], Precirol® ATO5 (glyceryl palmitostearate) [4]), polymeric materials [5] (e.g. ethyl cellulose, methyl cellulose, acrylate copolymers [6]), and waxes (e.g. beeswax [7], carnauba wax [8], candelilla wax [2], microcrystalline wax [2], paraffin wax [9]). The drug release kinetics can be mathematically described by the Higuchi equation; i.e. a direct proportionality between the cumulative amount of drug released and the square root of time is observed [10,11]. The drug release rate-controlling step for this matrix system type is the liquid penetration into the hydrophobic matrix [1]. Upon contact of the delivery device with the dissolution liquid, channels, cracks, and pores appear on the tablet matrix surface due to dissolution of the drug [3]. Depending on the composition of the formulation as well as on the preparation method, the drug release mechanism of hydrophobic matrix tablets is either diffusion-controlled or erosion-by-disintegration-controlled [1,12].

Various processing techniques, including dry blending and direct compression [3], wet granulation [13], melt granulation [14], or extrusion spheronization [15], were applied for the manufacture of hydrophobic matrix systems. Usually, melt granulation and melt pelletization are done using high-shear mixers; thereby, granules and pellets are produced batch-wise [16]. However, in contemporary industrial pharmacy, of special interest are the areas of continuous manufacturing and in technologies and materials enabling a continuous production [17,18]. Despite the fact that the hot-melt extrusion process is normally used to obtain extrudates; its ability to mix components can be used as a continuous granulation technique [19]. The melt granulation process features the advantage that the molten excipient functions as a binding liquid and drug release retardant; thus, an addition of solvents to serve as granulation liquid is not required [20]. In other words, combining the twin-screw granulation at elevated temperatures provide a possibility for processing moisture-sensitive active pharmaceutical excipients (APIs) and enables the use of hydrophobic materials as agents to control drug release [21]. However, the thermal sensitivity of drug substances needs to be taken into consideration. An alternative continuous manufacturing technology for the granulation of hydrophobic matrix formulations is by processing using a roller compactor; hydrophobic excipients may function as plastically deforming binder during roller compaction [22].

Hydrophobic matrix systems are frequently used in order to obtain controlled release of APIs due to the following reasons: high flexibility to generate the desired drug release profiles, easy manufacturability, cost effectiveness, and good drug stability due to the chemical inertness of waxes [3,20]. On the other hand, despite numerous advantages, the type of matrix system has the potential risk of an incomplete drug release due to the immersion of the API crystals in an impermeable hydrophobic layer [23]. Another important point to be considered is the non-homogeneity of the API in the matrix system delivery platform [24]. These shortcomings need to be taken into an account and controlled during the formulation design and development. The co-formulation of soluble ingredients/ channeling agents/release enhancers allows the drug release profiles to be modulated and might help to overcome the drawback of incomplete drug release

[3,20,23].

Several hydrophobic matrix-based sustained release drug delivery platforms have been reported in the literature, in which evidence was provided that, for example floating drug delivery systems (FDDS) may significantly profit from using hydrophobic carrier materials [25–27].

In the present study, we used a twin-screw hot-melt extruder for the granulation of paraffin wax functionalized calcium carbonate (FCC) matrix formulations. The design space for wax-based matrix formulations was examined by applying *in vitro* and *in silico* evaluation methods to the example of hydrophobic tablets using caffeine as a model drug substance. The study was aimed to understand the influence of FCC hydrophobization and formulation component arrangements on the breaking strength and the drug release behavior of tablets. Additionally, it was attempted to propose formulation design guidelines for the preparation of stable paraffin wax FCC matrix systems to overcome the problems of hydrophobic matrix drug delivery platforms, i.e. inhomogeneous distribution of the components within the tablet matrices and incomplete drug release behavior. As a proof-of-concept, the studied principles were applied to design and optimize a floating gastroretentive drug delivery system.

2. Materials and methods

2.1 Materials

FCC (VP-220976 S02, Omya International AG, Oftringen, Switzerland) was used as the porous, flotation-promoting and release-modulating material for the preparation of floating tablets. Paraffin wax (Merck KGaA, Darmstadt, Germany) was selected as meltable binder for granulation and as lipophilic matrix-forming excipient. As gelation-layer forming polymer, water-soluble polyethylene oxide Polyox™ WSR 301 (The Dow Chemical Company, Midland, Michigan, USA) was used. Caffeine (BASF, Ludwigshafen, Germany) served as the model drug substance.

2.2 *In vitro* methods

2.2.1 Preparation of hydrophobic matrix formulations

The design of the hydrophobic matrix formulations was made using the factorial design program Stavex 5.0 (Aicos, Switzerland). An external design, quadratic (D-optimally supplemented), was generated (Table 1). We specified four factors as well as their lower and upper limits, as follows: concentration of caffeine (15-70% (w/w)), concentration of FCC (20-60% (w/w)), concentration of Polyox™ WSR-301 (5-20% (w/w)), and concentration of paraffin wax (5-40% (w/w)). The defined response variables were: tablet breaking strength and coefficient of first order drug release kinetics.

The required amounts of caffeine, FCC, Polyox™ WSR-301, and paraffin wax were weighed and mixed in a tumbling mixer (Turbula type T2C, Willy A. Bachofen, Switzerland) for 10 minutes.

A twin-screw hot-melt extruder (ZE 9, Three- Tec GmbH, Switzerland) was used for melt granulation. The screws had a diameter of 9 mm and an L/D ratio of 40 D. The screw rotation speed was 200 rpm. In order to obtain granules directly, the die-plate of the hot-melt extruder was removed to reduce the degree of densification of the material in the extruder barrel during the granulation process. The temperatures of the eight heating zones were set to 30, 40, 60, 80, 80, 30, 30, and 30 °C.

Table 1 Composition of the tablet formulations.

Formulation	True density (g/cm^3)	Caffeine (%, w/w)		Polyox™ WSR 301 (%, w/w)		FCC (%, w/w)		Paraffin wax (%, w/w)	pFCC[a] (%, w/w)	Paraffin wax layer thickness (µm)
		Experimental	*In silico*	Experimental	*In silico*	Experimental	*In silico*	Experimental	*In silico*	*In silico*
F1	1.8632	15.00	16.54	20.00	21.95	60.00	26.24	5.00	35.27	0.15
F2	1.4225	15.00	15.70	5.00	5.06	40.00	14.13	40.00	65.10	1.10
F3	1.2202	35.00	32.68	5.00	4.67	20.00	2.59	40.00	60.07	1.10
F4	1.2516	15.00	14.57	20.00	18.69	25.00	3.92	40.00	62.82	1.10
F5	1.2546	20.00	18.89	20.00	18.99	20.00	1.37	40.00	60.76	1.10
F6	1.6806	15.00	16.27	5.00	5.45	60.00	53.33	20.00	24.95	3.00
F7	1.8690	35.00	35.02	5.00	5.32	55.00	53.73	5.00	5.93	3.00
F8	1.5328	15.00	15.64	13.00	13.41	46.00	16.30	26.00	54.65	0.70
F9	1.3143	25.00	24.19	5.00	4.93	30.00	4.58	40.00	66.31	1.00
F10	1.2445	28.00	26.18	13.00	12.15	20.00	1.43	40.00	60.24	1.10
F11	1.5149	35.00	33.83	5.00	5.13	38.00	35.52	23.00	25.52	3.00
F12	1.5005	20.00	19.24	20.00	20.05	38.00	12.60	23.00	48.11	0.65
F13	1.8180	23.00	23.77	5.00	5.91	60.00	56.33	13.00	13.99	3.00
F14	1.8777	28.00	28.31	13.00	13.15	55.00	39.50	5.00	19.04	0.30
F15	1.4337	17.00	17.38	5.00	5.34	38.00	11.22	40.00	66.06	1.10

[a] pFCC: FCC particles coated with molten paraffin.

2.2.2 Preparation of floating hydrophobic matrix tablets

A single-punch tablet press simulator (STYL'One, MedelPharm, France) equipped with a Kilian D 11.28 mm round flat-faced tooling was used for the compaction of the low-density hydrophobic matrix tablets. In Table 2, the properties of the experimental tablet formulations are summarized.

Table 2 Characteristics of the experimental prepared floating hydrophobic matrix tablets. The *in silico* tablet matrices designed for the computer simulation had a diameter of 11.36 mm and height of 3.31 mm. The absolute average errors for the *in silico* tablet weight and tablet density were 11.70 mg and 0.0805 g/cm^3, respectively. The discrepancies in tablet weight, diameter, and thickness between the experimental and the simulated parameters were enumerated via the discretization error. It was not possible to simulate *in silico* the mechanical stability of the compacts using the current version of the F-CAD software.

Formulation	Weight (mg)	Diameter (mm)	Thickness (mm)	Tablet density (g/cm^3)	Tensile strength (N/mm^2)	Porosity (%)
F1	300.1±0.7	11.32±0.01	3.37±0.06	0.8846	0.4616±0.0171	52.25±0.68
F2	300.3±0.7	11.30±0.02	3.32±0.03	0.9005	0.5423±0.0040	36.69±0.25
F3	299.9±0.2	11.27±0.01	3.32±0.04	0.9051	0.4306±0.0427	25.86±0.92
F4	300.2±0.2	11.28±0.01	3.34±0.01	0.8991	0.3884±0.0297	28.16±0.13
F5	300.0±0.3	11.29±0.00	3.33±0.02	0.8999	0.3500±0.0262	28.27±0.34
F6	300.0±0.5	11.30±0.01	3.33±0.02	0.8982	0.4680±0.0240	46.55±0.12
F7	300.4±0.3	11.32±0.01	3.34±0.01	0.8929	0.5719±0.0171	52.23±0.03
F8	300.0±0.1	11.30±0.01	3.36±0.03	0.8908	0.4026±0.0179	41.89±0.48
F9	300.3±0.0	11.29±0.00	3.34±0.03	0.8991	0.4955±0.0651	31.60±0.52
F10	300.5±0.4	11.30±0.01	3.31±0.03	0.9049	0.4198±0.0394	27.29±0.78
F11	300.0±0.2	11.31±0.01	3.33±0.02	0.8972	0.3665±0.0201	40.77±0.33
F12	299.6±0.3	11.31±0.00	3.35±0.02	0.8894	0.2798±0.0109	40.73±0.31
F13	300.3±0.4	11.33±0.01	3.36±0.04	0.8862	0.5515±0.0184	51.25±0.63
F14	300.5±0.1	11.33±0.00	3.36±0.03	0.8879	0.4968±0.0295	52.71±0.41
F15	300.1±0.3	11.29±0.00	3.33±0.02	0.9010	0.4746±0.0172	37.15±0.39

2.2.3 Characterization of hydrophobic matrix formulations

The mean tablet weight (n=5, where n is the sampling number of measurements) was determined with an electronic balance (AX204 Delta Range, Mettler Toledo, Switzerland). A slide caliper gauge (CD-15CPX, Mitutoyo, Japan) was used for the determination of the tablet diameter (n=5) and thickness (n = 5). Helium pycnometry (AccuPyc 1330, Micromeritics, USA) was performed in order to measure the true density of the hydrophobic matrix formulations.

Porosity ε of the flat-faced tablets was calculated according to Equation (1):

$$\varepsilon = 1 - (\frac{m}{\rho}) \cdot (\frac{1}{V}) \quad (1)$$

where m is tablet weight (g), ρ is true density of the powder mixture (g/cm^3), and volume is $V\,(mm^3) = \pi \cdot (d/2)^2 \cdot h$, where d is the tablet diameter (mm), and h the tablet height (mm).

Tablet breaking strength (n=3) was determined by a hardness tester (Tablet Tester 8M, Dr. Schleuniger Pharmatron, Switzerland). The tablet tensile strength σ_t (Pa) was calculated according to Equation (2):

$$\sigma_t = \frac{2 \cdot F}{\pi \cdot d \cdot h} \quad (2)$$

where F is the diametrical crushing force (N).

2.2.4 Scanning electron microscopy

Prior to the analysis, the tablet samples were placed on a carbon layer and sputtered with a 40 nm gold layer in a sputter coating device (MED 020, BalTec, Lichtenstein). Scanning electron microscopy (SEM) images of the tablet surface were taken using an ESEM XL30 FEG (Philips, Netherlands).

2.2.5 *In vitro* evaluation of floating behavior and drug release

A custom-built stomach model [28] was used in order to assess *in vitro* the floating behavior and drug release of the hydrophobic matrix tablets (n=2). The measurements were performed in 400 ml 0.1 N HCl as dissolution medium at a temperature of 37 °C. At predetermined time points, the caffeine content in the Erlenmeyer flasks was analyzed online using UV/Vis spectroscopy (Perkin Elmer Lambda 25, Perkin Elmer, Switzerland) at 272 nm. Additionally, floating lag time and floating duration of the tablets were studied by visual observation.

2.3 *In silico* methods

The software package F-CAD v 2.0 (CINCAP GmbH, Switzerland) [29] was applied for the *in silico* preparation and evaluation of the hydrophobic matrix tablet formulations. Table 3 summarizes the F-CAD component types, codes, and constants used for the tablet dissolution simulation.

Table 3 F-CAD component types, codes, and constants used for the *in silico* tablet dissolution.

Component	Apparent true density (g/cm^3)	Type ID	Component code	Dissolution simulation	
				C_1-value	C_2-value
Caffeine	1.4489	1	API	1 300 (1 054[a])	---
FCC	0.7000	81	Porous material	900	15
pFCC	0.7244-0.8743[b]	82	Porous material	50 000	50 000
Polyox™ WSR 301	1.2332	41	Hydrophilic swelling matrix	2 500	4

[a] C_1-value calculated according to Equation 5.

[b] The apparent true density of pFCC was calculated for every formulation depending on the thickness of the paraffin wax layer around the individual FCC particle.

The rate of dissolution dm/dt of a solid in a solvent under sink conditions can be mathematically described by the Noyes-Whitney equation:

$$\frac{dm}{dt} = \frac{A \cdot D}{h'} \cdot C_s \qquad (3)$$

where, m is mass of dissolved material, t is time, A is solid-liquid interface surface area, D is diffusion coefficient, C_s is solubility at equilibrium for the given experimental temperature, and h' is thickness of the diffusion layer [30].

The Noyes-Whitney equation in spatial form has the form of Fick's second law [31] and can be shown in three dimensions, as follows:

$$\frac{\partial \varphi}{\partial t} = D \nabla^2 \varphi \quad \text{with} \qquad \nabla^2 = \left(\frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2} \right) \tag{4}$$

where, φ is concentration and D is the diffusion coefficient.

By applying the finite difference method for computing the numerical solutions of the systems of differential equations, the translation of Equation 4 into cellular automata rules for dissolution simulation is made [29].

The primary constant (C_1-value) can be calculated by Equation 5:

$$C_1 = \frac{m}{dm} \cdot 26 \tag{5}$$

where, the discretized interval dm is from Equation 3 in the case of the equivalent dt=1, mass of the voxel is $m\ (g) = V \cdot \rho$, volume of the voxel is $V\ (cm^3) = l^3$, where l (cm) is the voxel side length, ρ (g/cm^3) is density of the given component, and 26 is the number of surrounding "liquid" voxels in the three-dimensional Moore neighborhood [29].

In the F-CAD dissolution simulation, the digitized time resolution dt is 1 s. According to Equation 3, it follows:

$$dm = \frac{A \cdot D}{h} \cdot C_s \tag{6}$$

where, the diffusion coefficient D (cm²/s) is defined according to the Stokes-Einstein relation $D = \frac{1}{f} \cdot \kappa \cdot (T + 273.15)$ [32], where the frictional coefficient f for a sphere, given by the Stokes' law, is $f = 6\pi \cdot \eta \cdot R$ [33], with the viscosity of water η (Pa·s)= $2.414 \cdot 10^{-5} \cdot 10^{(247.8/((T+273.15)-140))}$ [34], and the voxel surface area is $A\ (cm^2/s) = 6 \cdot h^2$, $\kappa_B = 1.3806488 \cdot 10^{-16}$ cm^2·kg·s^{-2}·K^{-1} is the Boltzmann constant, T (°C) is temperature, and R (Å) is the molecular radius of gyration.

2.3.1 Hydrophobization of functionalized calcium carbonate particles: estimation of paraffin wax layer thickness

It was hypothesized that paraffin wax melted during the granulation process at elevated temperatures and formed a hydrophobic layer around FCC particles. For the computer simulation, the percentage of paraffinized FCC (pFCC), which could be generated, was calculated for each tablet formulation. Based on the composition of the starter powder mixtures, it was tried to predict by simulation the thickness of the hydrophobic coating layer.

FCC particles were reported to have a diameter of about 7 µm [35]. For the determination of the extent of FCC hydrophobization, it was assumed that FCC particles are inscribed by smooth spheres. For simplification of the hypothesis, it was taken into consideration that molten paraffin wax does not penetrate into the porous internal structures of the FCC particles.

The volume of paraffin wax needed in order to create a layer of defined thickness (0.15-3.00 µm) around an individual FCC particle was calculated. It was assumed that the entire amount of paraffin wax contributed to

the coating of the FCC particles. Based on the volume of paraffin wax per tablet formulation, the possible amount of pFCC, which could be created, was determined.

For the *in silico* simulations, pFCC was also classified as porous excipient [28]. In comparison to "standard" FCC (sFCC), the $C_{1,pFCC}$-constant was set to 50 000 in order to generate a material with hydrophobic properties. The $C_{2,pFCC}$-value (i.e. constant responsible for the rate for liquid sorption into porous particle meshwork), was also 50 000 as molten paraffin wax was supposed to form a hydrophobic layer which blocked the pores and channels of the FCC particles and, hence, retarded the penetration of dissolution liquid into the compacts. For all hydrophobic matrix formulations, only one pFCC component type was generated keeping the $C_{1,pFCC}$-constant and the $C_{2,pFCC}$-constant constant; i.e. the composite material pFCC was assigned to have the same F-CAD $C_{1,pFCC}$-value and $C_{2,pFCC}$-value independent of the thickness of the simulated paraffin wax layer.

2.3.2 Simulation of hydrophobic matrices

Flat-faced tablet geometry with a diameter of 11.28 mm and a height of 3.34 mm was designed for the computer simulation. The virtual tablet matrix was transformed into a discrete cubic grid with an individual voxel side length of 75.2 µm. The different components of the hydrophobic matrix formulations were filled in the created grid using the particle arrangement and compaction (PAC) module according to the composition summarized in Table 1. The three-dimensional matrices were simulated assuming 0% interparticle tablet porosity, while the porous sFCC material is considered to account for the experimentally determined tablet porosities, and thus not contributing to tablet bulk permeability.

2.4 Comparison of *in vitro* and *in silico* dissolution profiles

The experimental and simulated dissolution profiles were compared by a model-independent approach using a difference factor and a similarity factor [36].

The difference factor f_1 was calculated according to equation (7), as follows:

$$f_1 = \frac{\sum_{t=1}^{N} |R_t - T_t|}{\sum_{t=1}^{N} R_t} \cdot 100 \qquad (7)$$

where N is number of time points, R_t is the dissolution value of the simulated tablet at time t, and T_t is dissolution value of the experimental tablet at time t. A difference factor f_1 ranging from 0 to 15 indicates equivalence of dissolution profiles.

For the determination of the similarity factor f_2, equation (8) was used:

$$f_2 = 50 \cdot \log\left(\frac{1}{\sqrt{1 + \frac{1}{N} \cdot \sum_{t=1}^{N} (R_t - T_t)^2}} \right) \cdot 100 \qquad (8)$$

where, again, the variables are those defined in Equation 7. A similarity factor f_2 in the range from 50 to 100 implies equivalence of drug release profiles.

Additionally, the degree of linear dependence between the *in vitro* and *in silico* drug release data was assessed by the Pearson correlation coefficient [37].

3. Results

3.1 Characterization of hydrophobic matrix tablets

Fifteen hydrophobic matrix formulations were prepared by factorial design (Table 1) and analyzed. As a representative example, SEM images of formulation F12 are shown in Figure 1 (a, b). The compact surface suggests an inhomogeneous distribution of the components in the tablets. Clusters of needle-like caffeine crystals with a size of about 30 µm surrounded by the tablet matrix were observed (Figure 1b).

The granulation process in the twin-screw hot-melt extruder seemed to generate different degrees of FCC hydrophobization including sFCC which exhibits the characteristic lamellar surface structures. On the other hand, SEM pictures of the tablet surface showed large agglomerates (>60 µm) with a smooth covering. Most likely, these agglomerates were formed out of FCC, Polyox™, and molten paraffin wax during the melt granulation. For all other formulations, the distinction approach was identical.

The virtual compacts of the hydrophobic matrix tablets were constructed based on the structural information gained by SEM. Figure 1(c) displays, as an example, the cross-section of the virtual tablet matrix of F12.

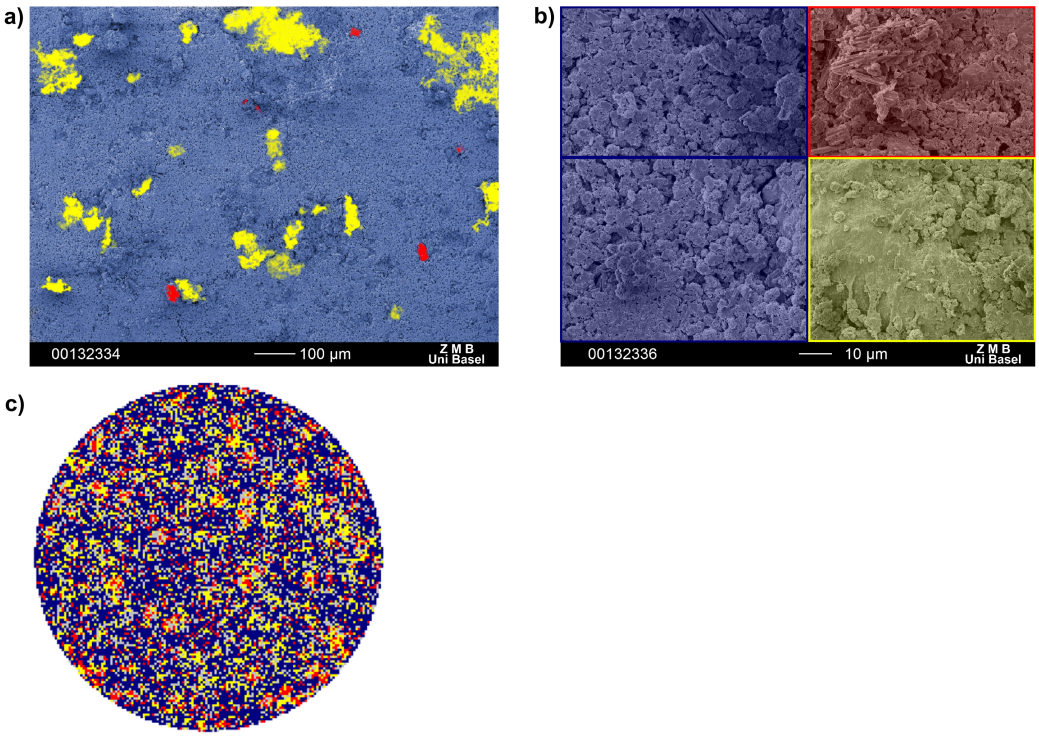

Figure 1 (a) SEM image of the surface of a floating tablet (F12), (b) images magnified further, and (c) cross-section of the F-CAD tablet matrix. Caffeine is displayed in red, sFCC in light gray, pFCC in blue, and the swelling excipient in yellow. A representative example is shown.

3.2 *In vitro* and *in silico* evaluation of tablet dissolution

Figure 2 (a-d) displays the experimental and simulated caffeine release profiles of several selected formulations. In addition, the cross-sections of the simulation matrices are shown. It was observed that for the preparation of the *in silico* tablet matrices, simple virtual mixtures of the formulation components were not sufficient. Taking into account the arrangement of the components within the three-dimensional tablet matrices resulted in a good correlation between *in vitro* and *in silico* dissolution profiles.

A fast caffeine release within 40 to 60 min was obtained for tablet formulations F6 (Figure 2c), F7 (Figure 2d), F11, and F13. The experimental data of these formulations showed high standard deviations; this observation might be explained by erosion by disintegration during *in vitro* dissolution experiments. The simulated tablets of formulation F6 were constructed with variable sizes of pFCC clusters to account for significantly high caffeine release variability.

In the case of formulations F3, F4, F5 (Figure 2b), and F10, an initially fast caffeine release followed by a slowdown in release speed was observed. For F10 the drug release was incomplete; only about 80% of the API was released during the *in vitro* dissolution measurement.

For formulations F1 (Figure 2a), F8, and F14, the tablets eroded completely during the dissolution experiments; in contrast, tablet matrices of formulations F2, F3, F F4, F5, F9, F10, F12, and F15 remained in the Erlenmeyer flasks.

The results of *in vitro* and *in silico* dissolution measurements suggest the dependency of drug release rate on the agglomeration of FCC and paraffin wax.

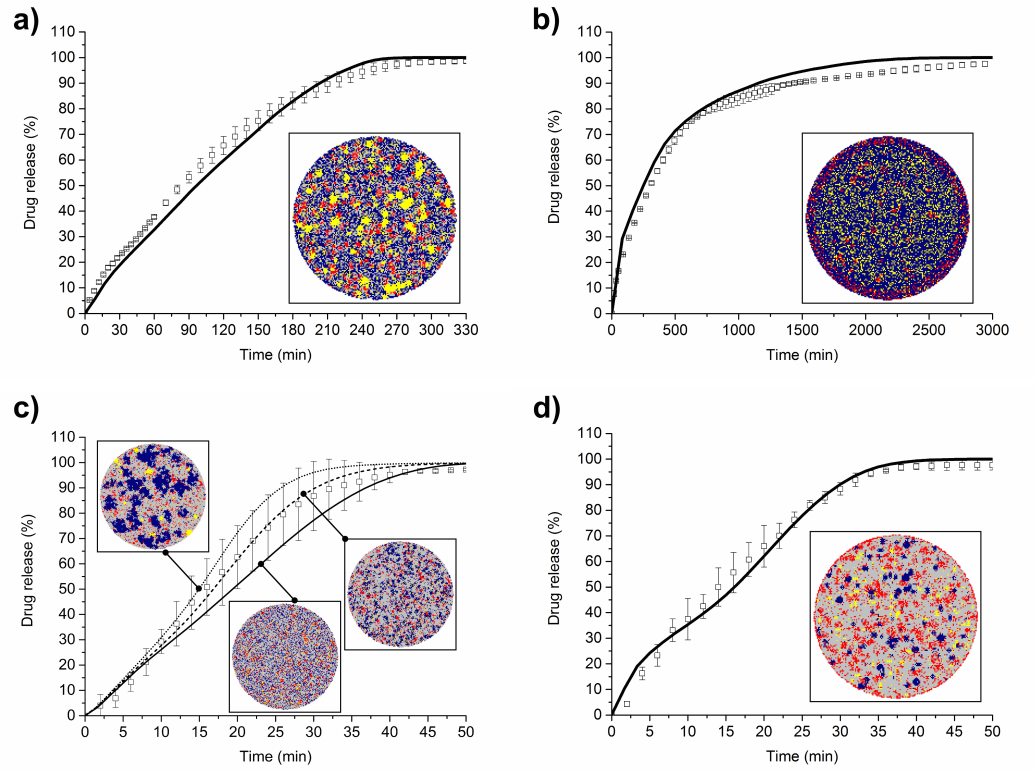

Figure 2 (a) Experimental and simulated caffeine release profile of tablet formulation F1, (b) experimental and simulated caffeine release profiles of F5, (c) experimental and simulated caffeine release profiles of tablet formulation F6. Variations in *in silico* drug release profiles were obtained by different arrangement of the components in the F-CAD tablet matrix to illustrate the effect of formulation-induced deviations. (d) Experimental and simulated caffeine release profiles of tablet formulation F7.

3.2.1 Comparison of *in vitro* and *in silico* dissolution profiles

Good correlation between the experimental and simulated dissolution data was obtained (Table 4). In addition, a model-independent approach by calculating the difference (f_1) and similarity (f_2) factors was used for comparison of the data sets (Table 4). The obtained f_1 values were in the range from 0 up to 15 and the f_2 values greater than 50, ensuring equivalence of the *in vitro* and *in silico* release profiles [36].

Table 4 Comparison of experimental and simulated dissolution profiles of different tablet formulations.

Formulation	Coefficient of first order fitting	R^2	f_1 factor	f_2 factor	Pearson's correlation coefficient, p
F1	0.007	0.9977	10.92	68.72	0.9985
F2	0.007	0.9882	7.33	74.08	0.9969
F3	0.001	0.9728	9.51	62.99	0.9728
F4	0.002	0.9877	5.12	72.88	0.9831
F5	0.002	0.9866	9.72	63.71	0.9987
F6	0.017	0.9795	4.75	78.56	0.9983
F7	0.030	0.9964	6.95	69.42	0.9957
F8	0.005	0.9890	8.93	63.89	0.9942
F9	0.002	0.9403	9.34	58.30	0.9874
F10	0.001	0.9980	5.86	71.91	0.9873
F11	0.070	0.9985	6.48	60.78	0.9921
F12	0.004	0.9863	4.14	82.05	0.9984
F13	0.024	0.9847	7.89	64.65	0.9811
F14	0.009	0.9979	15.55	59.23	0.9965
F15	0.005	0.9754	10.36	64.31	0.9979

3.2.2 Statistical analysis of experimental data: influence of the factors on the response variables

Statistical evaluation revealed that the factors FCC (p=0.0093) and Polyox™ (p=0.0068) had a significant influence on the breaking strength (goodness of fit R^2=0.9553). In contrast, the interaction of FCC and paraffin wax (p=0.0314) influenced negatively the breaking strength; higher concentrations of Polyox™ were also found to reduce the tablet hardness.

For the statistical analysis of the *in vitro* dissolution profiles, the coefficient of first order drug release kinetics was determined (Table 4). The logarithmic transformation of the response variable resulted in a very good fit of the model (R^2=0.9903). The concentrations of the components FCC (p=0.0027), paraffin wax (p=0.0053), and Polyox™ (p=0.0083) were found to influence significantly the speed of drug release from the tablet formulations. The swelling polymeric excipient Polyox™ and the paraffin wax prolonged the drug release; whereas, the highly porous material FCC increased the caffeine release speed. The interaction of the excipients FCC and Polyox™ (p=0.0295) had a significant influence; it decreased the speed of caffeine release from the tablet matrices, indicating a synergistic effect.

Figure 3 displays the ternary contour plot of the response variables tablet breaking strength and the coefficient of first order drug release kinetics of the hydrophobic matrix floating formulations at a caffeine content of 35% (w/w).

For the statistical analysis, F11 was excluded from the data set as the floating tablets disintegrated within approx. 4 min during the *in vitro* dissolution experiments.

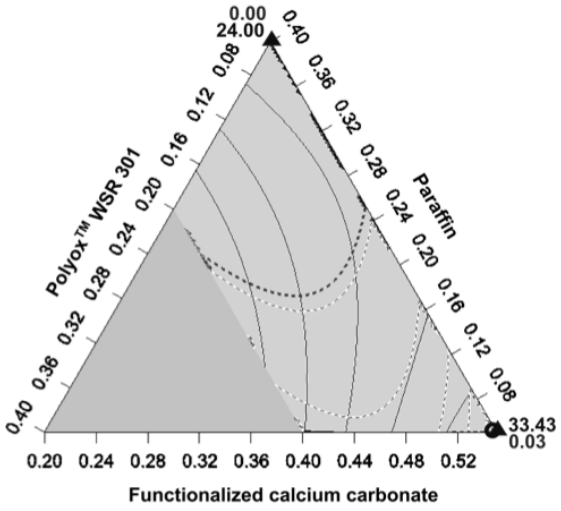

Figure 3 Ternary contour plot of the hydrophobic matrix formulations at a caffeine content of 35% (w/w), where the response variables of tablet breaking strength and coefficient of first order drug release kinetics are displayed in black and light gray, respectively. Dark gray dotted line represents recommended rate of drug release to yield 100% drug release at 12 h time.

4. Discussion

It was hypothesized that the manufacturing process (i.e. melt granulation in a twin-screw extruder) induced a hydrophobization of FCC due to molten paraffin wax. In order to evaluate the extent of hydrophobization, it was assumed for the *in silico* simulations that FCC particles are smooth spheres. The thickness of the simulated paraffin layer around an individual FCC particle was adapted for each formulation to mimic different degrees of hydrophobization. It was hypothesized that up to an equal ratio of paraffin wax to FCC, increasing the amount of paraffin wax in the formulation created a thicker layer around the FCC particles. Further increase of the amount of paraffin wax in the mixtures did not increase the thickness of the simulated paraffin wax layer. Simulated paraffin wax layers around individual FCC particles with a maximum thickness of approx. 1 µm were obtained. The FCC hydrophobization hypothesis was simulated *in silico* and the assumption resulted in a good correlation of *in vitro* and *in silico* tablet dissolution profiles.

A simplified FCC hydrophobization approach was applied for the *in silico* simulations; it did not account for the porous internal structures of the FCC particles and filling of molten paraffin wax into FCC particles was neglected. The simulated paraffin wax layers with a maximum thickness of approx. 1 µm correspond to the thickness of the FCC particle stratum layer [35]. Based on the results of the *in silico* calculations and the *in vitro* data, it was concluded that molten paraffin wax was filled into the pores and channels of the stratum layer of FCC particles during melt granulation; but did not penetrate into the inner pores of the FCC particles. The tablet formulations F6, F7, F11, and F13 showed the fastest caffeine release; despite the fact that they had a simulated paraffin wax layer of about 3 µm around an individual FCC particle. It was hypothesized that the outer porous meshwork of the particles was completely filled with molten paraffin and large agglomerates of FCC, paraffin wax, and Polyox™ were generated during the melt granulation process. These results suggest the dependency of drug release rate on agglomeration of FCC and paraffin wax.

The results of factorial design revealed a significant influence of the excipients FCC, Polyox™ and paraffin wax on tablet breaking strength and caffeine release speed. However, it did not provide any information regarding the impact of the applied continuous melt granulation technique on the formulation components – in particular FCC and paraffin wax – and on their arrangement within the tablet matrices. FCC increased the hardness of the compacts due to its lamellar surface structures that promote a tight interlocking of the FCC particles during compaction; whereas, the interaction of FCC and paraffin wax influenced negatively the breaking strength. This observation provided evidence for the hypothesis of FCC hydrophobization; it can be explained by coating of the FCC particles with a layer of paraffin wax and Polyox™ during melt granulation; hence, rendering ineffective the tight surface-driven interlocking of FCC.

The influence of the factors, identified by factorial design, was well correlated with the experimental data and supports the initial hypothesis. However, the results do not represent sufficiently the complexity of the developed paraffin wax FCC matrix formulations, namely hydrophobization of FCC particles and the influence of pFCC on tablet properties. pFCC was found to feature heterogeneous effects in respect to the formulation release performance.

A combination of *in vitro* measurements, statistical analysis, and a computer simulation approach were applied to gain a deeper understanding of paraffin wax FCC matrix formulations and to explore their design space.

The understanding of the melt granulation process was considered to be of importance due to the formation of agglomerates. The inhomogeneous distribution of the excipients and the API within the hydrophobic matrices may lead to a highly variable drug release behavior (e.g. tablet erosion by disintegration).

In the case of formulations with high paraffin and low FCC contents, an observable change in drug release speed might be due to re-arrangement of the components in the compacts; additionally, softening of paraffin wax might have occurred. Consequently, the permeation of dissolution liquid into the floating compacts would be delayed and the caffeine release would be retarded, or the release of the entire amount of caffeine would be rendered impossible.

The combined factorial design and *in silico* analysis suggest that depending on the composition of the tablet the hydrophobization of the FCC particles has crucial effects on the release and mechanical stability of the compacts. The degree of hydrophobization is a main parameter to keep under control for such formulations; this factor is heavily influenced by a chosen process i.e. melt granulation. In order to achieve a drug release time of about 12 h for FCC-based floating formulations, a degree of hydrophobization of 48 to 55% (w/w) pFCC and a simulated paraffin layer thickness of 0.65 to 0.7 µm are recommended.

5. Conclusions

For the future formulation design and optimization of porous hydrophobic matrix formulations composed of FCC and a lipophilic excipient, not only the formulation composition but also the component arrangement within the tablets which is induced by the manufacturing process, i.e. melt granulation, needs to be taken into consideration.

The combined application of *in vitro* measurements, statistical evaluation of experimental data, and *in silico* simulations has led to a deeper understanding of the interaction of the hydrophobic matrix formulation components and the unit operation, such as granulation in a twin-screw hot-melt extruder.

It was possible to come with recommendations for formulation development strategies in case of porous components such as FCC and hydrophobized material.

Acknowledgements

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3.4 *In vivo* evaluation of floating systems

In vivo evaluation of a gastroretentive drug delivery system based on enteric-coated floating tablets

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In Vivo Evaluation of a Gastroretentive Drug Delivery System Based on Enteric-Coated Floating Tablets

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Abstract

Floating dosage forms are supposed to exhibit an enhanced gastric residence time. Their development is challenging as the prediction of the retention potential in humans based on *in vitro* studies and animal models is difficult.

A strategy to determine the stomach residence time of a floating dosage form with an inherently low density in human without using imaging techniques was explored in a self-experiment.

Floating tablets and non-floating controls were prepared containing caffeine as a model drug. The compacts had a pH-dependent enteric-coating to assess their stomach residence time. Since caffeine is rapidly absorbed in the gastrointestinal tract, the prolonged gastric retention of tablets can be demonstrated by a delayed systemic exposure. Caffeine and paraxanthine were determined in capillary blood by liquid chromatography coupled to tandem mass spectrometry.

An increase in caffeine and paraxanthine blood levels was observed in human volunteers after 90 to 180 min for the non-floating controls. For the floating tablets, no elevated blood concentrations were found in two out of three participants during 8 h of sample collection.

The results demonstrate the technical feasibility of the proposed clinical study protocol. Follow-up clinical trials will be needed to confirm the preliminary data on stomach residence time of our floating dosage form.

Keywords: Gastroretentive dosage form; Floating tablet; *In vivo* gastric residence time; Self-experiment; LC-MS/MS

Abbreviations:

GRDDS - Gastroretentive drug delivery systems; FDDS - Floating drug delivery systems; FCC - Functionalized calcium carbonate; LC-MS/MS - Liquid chromatography coupled to tandem mass spectrometry

Introduction

Gastroretentive drug delivery systems (GRDDS) offer the possibility to prolong and control the residence time of drugs in the stomach and the upper part of the small intestine [1]. The reason and need for a gastroretentive delivery approach is in most cases dictated by physiological necessity [2]. The passage time of conventional oral pharmaceutical dosage forms through the stomach is relatively short; thus, GRDDS provide a technology to overcome this limitation. Several drug substances, e.g. drugs acting locally or being absorbed in the stomach region might benefit from enhanced gastric retention times [3]. Floatation has been proposed as a mechanism to avoid unpredictable and premature gastric emptying of pharmaceutical dosage forms [4]. Due to the low density of the drug delivery systems, they float on stomach contents and are retained while releasing the drug substance.

During the last years, the development of floating drug delivery systems (FDDS) has gained importance. However, there are only few examples of clinical trials or marketed GRDDS. One explanation of this shortcoming is the fact that it is very difficult to extrapolate from *in vitro* studies or from animal experiments to human. Thus, the phenomenon of flotation has to be explored in human to account for the unique anatomical and physiological situation in humans. Nevertheless, even complex clinical trial protocols often fail to show significantly enhanced gastric residence times of FDDS in comparison to non-floating references. A number of shortcomings are associated with the clinical evaluation of floating dosage forms: the gastric retention time is often determined in the fed state; although, high-caloric food is known to delay the gastric emptying rate [5]. Additionally, numerous researchers select non-appropriate non-floating control dosage forms, e.g. immediate release formulations, in order to prove prolonged gastric residence times. In some clinical studies, only pharmacokinetic data are recorded to provide an indirect estimate of the retention time of a dosage form in the stomach.

A FDDS, which is based on the use of the porous carrier functionalized calcium carbonate (FCC), was developed and *in vitro* flotation in a custom-built stomach model was demonstrated. Tablet dissolution and buoyancy behavior were simulated *in silico* and provided insight into drug release and floating mechanism [6]. But, the extrapolation from these model systems to the *in vivo* situation proofed to be a challenge. Therefore, it was decided to evaluate a strategy to test the gastric retention potential in human of FCC-based tablets featuring an inherently low density. The aim of the present project was to design and evaluate a method in human, which can be used to assess and compare the *in vivo* gastric residence time of floating

and non-floating tablets. The compacts contained caffeine as a model drug substance and were coated with a pH-dependent enteric-coating. Upon retention of a tablet in the acidic environment of the stomach, the marker caffeine is thus retained within the tablet. Using minimal amounts of capillary blood, the systemic exposure of caffeine and its metabolite paraxanthine were determined using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS).

Materials and Methods

Materials

Highly porous functionalized calcium carbonate (FCC VP-DP141 S04, Omya, Oftringen, Switzerland) [7] was used as matrix for the preparation of tablets with an inherently low density. Two gelation-layer forming polymers, water-soluble polyethylene oxide (Polyox™ WSR 301, The Dow Chemical Company, Midland, Michigan) and hydroxypropyl methylcellulose (Methocel® K100 Premium LV, Sandoz Pharma AG, Basel, Switzerland) were selected to slow down penetration of liquid into the tablet and retard release of the model drug substance caffeine (Coffeinum WSF, Böhringer-Ingelheim, Ingelheim, Germany). Citric acid (Acid citricummonohydr. pulvis, Hänseler AG, Herisau, Switzerland) was chosen as effervescent excipient. The floating formulation was prepared by wet-granulation with ethanol 96% (SchweizerhallChemie AG, Flawil, Switzerland). The enteric-coating suspension consisted of the following materials: Kollicoat MAE 30 DP (BASF, Germany), propylene glycol (Hänseler AG, Switzerland), talc (Hänseler AG, Switzerland), and titanium dioxide (Hänseler AG, Switzerland).

Methods

Preparation of floating and non-floating tablets: Floating tablet formulation was prepared as described

previously [6]. For *in vivo* investigation of gastric retention times, floating and non-floating tablets using a single punch eccentric press (Styl'One, Medelpharm, France) were manufactured. The convex-shaped tablets had a curvature radius of 12 mm and a tablet radius of 5mm. The cap height was 1.1 mm. The caffeine containing formulation had the same composition for both the floating and the non-floating tablets. Tablet density was adjusted by using different compaction forces. Since non-floating tablets had a reduced tablet height, an additional layer of 130 mg pure FCC was added to obtain identically sized floating and non-floating control tablets. Thus, an impact of tablet size on gastric retention could be excluded. The characteristics of the prepared compacts are summarized in Table 1.

After compaction, the floating and non-floating tablets were coated with an enteric-coating in a drum coater (Lab-Coater GC-300, Glatt, Switzerland).

Evaluation of *in vivo* gastric retention in humans: Prior to the in vivo evaluation, drug release and flotation behavior of the enteric-coated tablets were studied in vitro using a custom-built stomach model [6]. Non-floating tablets were expected to remain in the gastric region for about 2 to 3 h [8]. Within this time, the enteric-coating was supposed to remain intact; thus, no caffeine and paraxanthine should be observable in the blood samples of the volunteers. After being emptied from the stomach, the enteric-coating of the compacts should dissolve due to a pH change in the intestine, and caffeine as well as paraxanthine plasma concentrations increase. In the case of the gastric-coated floating dosage forms, no caffeine and paraxanthine should be present in the blood samples of the volunteers during 8 h of sample collection.

Formulation	Weight (mg)	Diameter (mm)	Height (mm)	Tablet density (g/cm³)
Floating tablet	399.17	10.02	7.06	0.85
Enteric-coated floating atablet	439.77	10.20	7.19	---
Non-floating tablet	530.10	10.03	7.04	1.13
Enteric-coated non-floating tablet	564.80	10.21	7.16	---

Table 1: Properties of the convex-shaped round tablets

Study design: The exploratory experiment in human volunteers (n=3) using the marker caffeine was brought to the attention of the local ethics committee (EKNZ; reference number UBE-15/17) and was considered by the committee to be compliant with Swiss legislation. All participants gave informed consent prior to the study.

The study started with a caffeine washout period of 3 days; the participants were not allowed to consume any caffeine-containing food. In order to evaluate the *in vivo* gastric retention times, tablets were administered at 08:00 a.m. with 300 ml of water after an overnight fasting. Every half hour, 300 ml of liquid was provided. A standardized, low-caloric liquid meal was given 4 h post-administration. Blood samples of 10 µl were collected via capillary puncture of the fingertip at the indicated times. Collected blood samples were diluted with 200 µl methanol containing 50 ng/ml of caffeine-d9 as the internal standard and stored at -20 °C for further analysis.

Determination of caffeine and its metabolite paraxanthine in human plasma: Blood concentrations of caffeine and paraxanthine were determined in collected blood samples using LC-MS/MS. The analytes were extracted by protein precipitation using methanol (see above). Chromatographic separation of sample supernatants was done on a Shimadzu HPLC system consisting of an HTS PAL autosampler (CTC Analytics AG, Switzerland), two Shimadzu LC-20 AD pumps (Shimadzu AG, Switzerland) controlled by a Shimadzu CBM-20A unit, and a Shimadzu CTO-20AD column oven. An Atlantis T3 column (2.1 x 50 mm, Waters AG, Switzerland) was used to separate the analytes. Eluent A (0.1% formic acid in water) and eluent B (0.1% formic acid in methanol) were delivered at a constant flow of 0.8 ml/min. The following gradient was applied: 100% A from 0 to 0.5 min, 50 – 98% B from 0.5 to 2 min, 98% B from 2 to 2.5 min, 100% A from 2.5 to 2.8 min. Total run time was 2.8 min. A thermo stated column oven was set to 60 °C. The injection volume was 10 µl. The flow was directed to waste for the first and last 0.6 min, to minimize contamination of the MS source. Mass spectrometric detection was performed using a triple quadrupole mass spectrometer (API4000, Applied Biosystems, Switzerland) operating in electrospray-ionization positive-ion mode. Samples were quantified using peak area ratios and caffeine-d9 as the internal standard. The assays were linear in the concentration ranges of 25 – 1000 ng/ml for caffeine and paraxanthine.

Statistical analysis: A one-sided Grubb's test for outliers with a 90% confidence interval was used in order to detect outliers in the *in vivo* caffeine plasma concentration profiles of floating tablets [9].

Results and Discussion

Figures 1a-1c displays the caffeine and paraxanthine blood concentrations measured in human volunteers (n=3) after administration of the prepared non-floating enteric-coated tablets. Participants 1, 2, and 3 showed no elevated caffeine and paraxanthine plasma concentrations up to 90, 126, and 175 min, respectively. Thus, the enteric-coating of the compacts remained intact within this time period and no caffeine was released from the tablets. We assume that the control tablets were located in the stomach of the participants during this time.Afterwards,a caffeine

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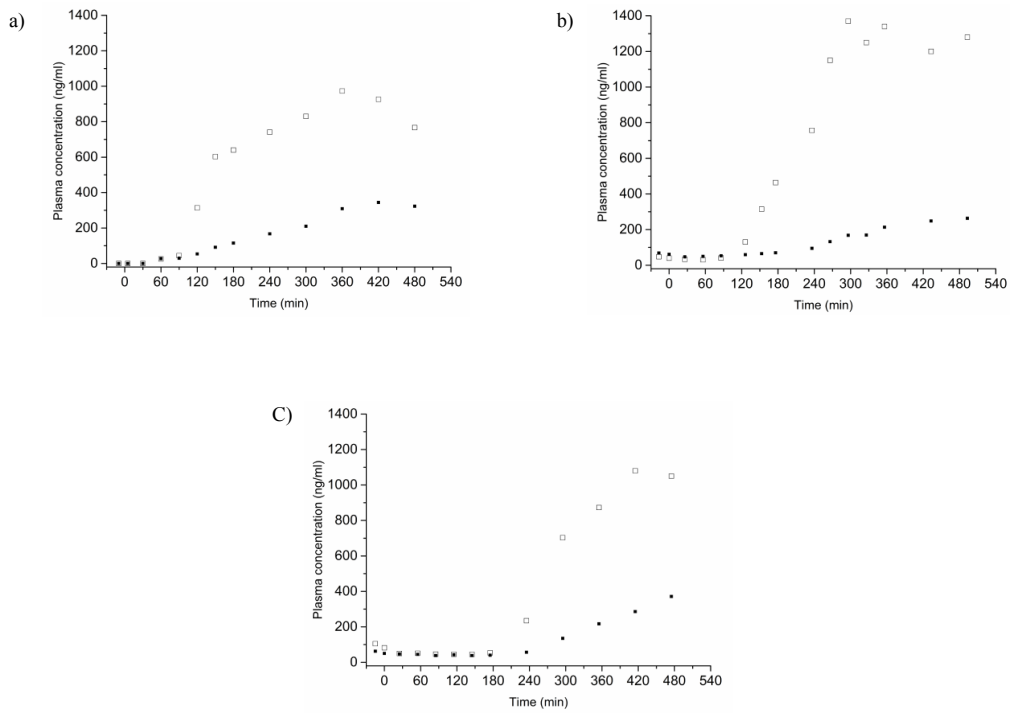

Figures 1: *In vivo* caffeine (□) and paraxanthine (■) concentrations in the plasma of three human volunteers after administration of the non-floating enteric-coated control tablet. Each data point represents one blood sample.

release from the tablets was observed, resulting in an increase in caffeine and paraxanthine levels. It can be concluded that the tablets passed through the pylorus into the small intestine. Due to a change in pH in the intestinal environment, the enteric-coating started dissolving and caffeine was released. Consequently, blood concentrations of caffeine and its metabolite paraxanthine increased. For the non-floating tablets, the time points at which caffeine and paraxanthine blood concentrations increased after administration were comparable for all three study participants. The results were in good agreement with another study performed by Podczeck et al., where the mean gastric residence time was determined to be 91 min for 10 mm tablets administered with a dextrose drink. The gastric emptying of food and its influence on the gastric emptying of tablets of different dimensions was measured by γ-scintigraphy and electrical impedance tomography [10].

In contrast, in two out of three participants no increase in caffeine and paraxanthine concentrations was measured during 8 h blood sample collection for the floating tablets (Figures 2a and 2b). Elevated caffeine plasma concentrations were observed at isolated time points. However, high caffeine levels were not accompanied by high paraxanthine levels. No systemic exposure of caffeine and its metabolite paraxanthine could be detected; hence, indicating that the floating dosage forms remained in the human stomach.

In the case of one study participant, plasma profiles after administration of the floating enteric-coated tablet were similar to the ones of the non-floating tablet; an increase in caffeine and paraxanthine concentrations was seen after approximately 90 min. In this situation, it was not possible to determine the reason for failure of the experiment. It might be that either the enteric coating of the tablet was defective or that the tablet was emptied prematurely from the stomach.

The pilot experiment did reveal shortcomings of the chosen study design. Blood sample collection during 8 h was found to be not sufficient in order to detect the increase in caffeine and paraxanthine plasma concentrations caused by gastric emptying of the FDDS. First, blood sampling time should be extended to at least 24 h to cover longer than expected gastric retention times of the tablets. Second, increased caffeine levels at isolated time points were obtained in two volunteers. They were identified as outliers based on statistical analysis and the absence of a concomitant occurrence of the caffeine metabolite paraxanthine. We concluded that these outliers were due to a contamination of samples by caffeine. In addition, analytical methods have to be used which cover both caffeine and its metabolite paraxanthine to exclude blood sample contaminations. It might be advisable to validate in a second step the position of the tablets in the stomach by e.g. γ-scintigraphy and not to rely exclusively on pharmacokinetic analysis of plasma profiles of a marker substance.

The volunteers in this study were provided with low-caloric and liquid food in order to exclude the effects of high-caloric meals, which delay the gastric emptying process and thus influence the gastric retention of pharmaceutical dosage forms. The amount of liquid and food consumed during the experiment should therefore be strictly controlled. The

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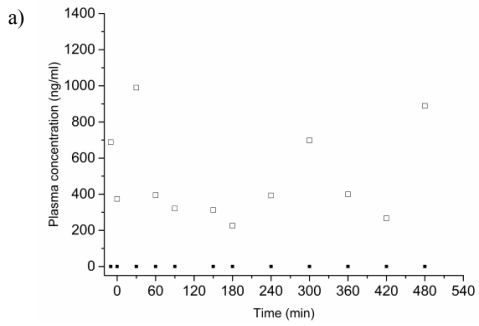

Figures 2: *In vivo* caffeine (□) and paraxanthine (■) concentrations in the plasma of two human volunteers after administration of the floating enteric-coated tablet. Each data point represents one blood sample. Caffeine outliers identified by a one-sided Grubb's test for outliers with a 90% confidence interval are not shown on the graph.

volunteers had to maintain an upright position during the duration of the experiment; however, they were allowed to move and to do light exercise. Our preliminary results seem to suggest that body motion was not a critical factor.

Conclusions

Coating of tablets with a pH-dependent enteric-coating seems to be an interesting strategy to compare the retention times in the human stomach of floating tablets with non-floating reference systems. Non-floating controls can be designed to differ only by their density from the test tablets. They are superior to immediate-release formulations, which are often used as controls. The use of the marker component caffeine seems to be an alternative to more expensive imaging techniques.

It was the aim of the present pilot study to demonstrate the technical feasibility of a clinical study protocol. Obtained preliminary results demonstrate that *in vivo* characterization in human of a floating dosage form is possible. Floating and non-floating control tablets can be compared without applying complex imaging technologies.

The performed exploratory study is encouraging and will therefore serve as a basis for the preparation of clinical phase I studies to evaluate the properties of FCC-based floating dosage forms. In addition, the pilot experiment will help to define study conditions and parameters. The experience gained from this exploratory study might convince other researchers that *in vivo* performance of FDDS can potentially be explored using a relatively simple clinical study design. We hope that our preliminary findings might therefore promote the use of this innovative drug delivery strategy. Follow-up clinical trials using larger cohorts of volunteers will be needed to obtain statistically significant data on stomach residence time of our floating dosage form.

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4

Discussion

In the following chapter, the suitability of FCC for the manufacture of instantly floating drug delivery platforms is discussed on the example of FCC-based floating tablets and mini-tablets. In addition, the advantages of the proposed formulation strategy for the efficient and successful development of FDDS are illustrated.

4.1 Applicability of functionalized calcium carbonate

In the introduction, various mechanisms to achieve flotation of dosage forms are summarized (1.3.1.6 Floating systems). Some of the described approaches feature the disadvantages of being expensive and complex from the manufacturing point of view. The development of FDDS, which float in the stomach due to an inherently low density, is favored; because, the floating mechanism does not need to be activated first. But, immediately floating tablets have to combine two, often self-excluding, properties. They must feature an inherent density less than unity and a sufficient hardness to be further processable and to withstand the destruction by gastric peristalsis. Up to now, there is no pharmaceutical excipient available on the market which seems to render possible the compaction of tablets that fulfill both requirements.

FCC was identified as a material that is suitable for the manufacture of tablets featuring the above-mentioned characteristics. It exhibits unique properties: a high porosity of approx. 70% (v/v) and a high specific surface area of 40-60 m^2/g due to the lamellar structure of the particles (Figure 4.1). During the compaction process, an interlocking of the FCC paddle-like surface structures occurs. Even at low compression pressures, tablets with a high tensile strength are obtained and a high tablet porosity is retained [215]. The key element of

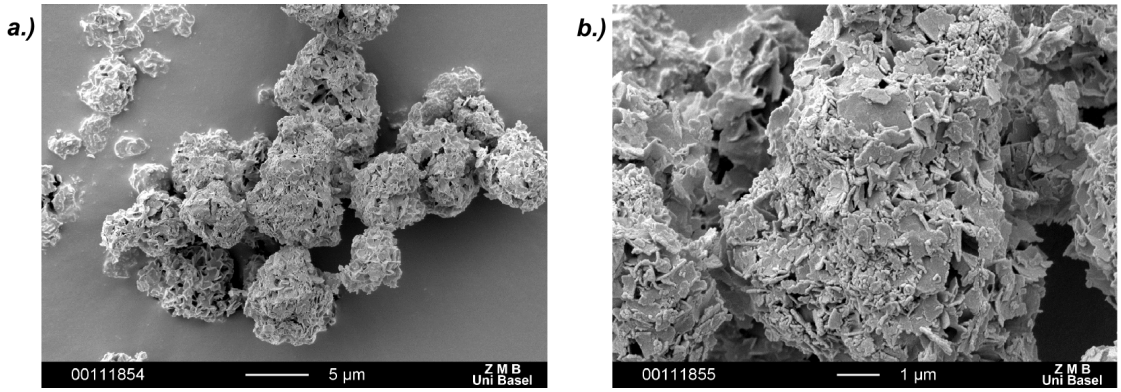

FIGURE 4.1. Scanning electron microscopy images of FCC. *(a.)* magnification: x3'000. *(b.)* magnification: x10'000 [216]. FCC particle sizes range from 5-15 µm [215].

FCC - its lamellar structural organization - makes FCC a promising material for the manufacture of floating tablets featuring no floating lag time.

The intermixing of API and FCC exclusively was not sufficient for the preparation of floating tablets with targeted flotation behavior and drug release profiles. Due to the porous structural organization of FCC particles, the liquid sorption into the compact was triggered. As a result, the tablet density increased quickly and, finally, the floating device sank down. Additionally, it had to be taken into account that a reaction-based erosion of FCC took place under acidic conditions. For the successful development of FCC-based floating drug delivery platforms, the porous component FCC had to be combined with appropriate excipients.

4.1.1 Hydrophilic floating systems

For the hydrophilic floating systems, FCC was co-formulated with gelation-layer-generating components (e.g. Methocel®, Polyox™). The formulation was prepared by wet granulation. It had to be kept in mind that during the granulation process, in particular at high shear forces, the lamellar organization of the FCC particles might be partially destroyed or completely covered with a layer of granulation binder. The lamellae of the particle's stratum layer [215] provided a large contact area which allowed a tight interlocking of the FCC particles during compaction. This was essential for the manufacture of tablets featuring a sufficiently high tensile strength. Thus, the paddle-like structures of FCC needed to be preserved during the granulation step.

Upon contact of the delivery device with the gastric fluids, hydration and swelling of the polymeric excipients occurred at the surface of the tablet. The swollen polymer layer around the compact played an essential role regarding the flotation mechanism of the hydrophilic systems. On the one hand, it retarded the penetration of gastric fluids into the porous FCC-based tablet matrix. The liquid sorption would result in an increase of the tablet density higher than unity and, consequently, would force the compact to sink down. On the other hand, the surface

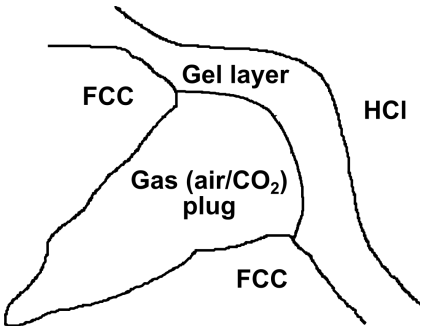

FIGURE 4.2. Schematic representation of "gas plug" formation.

gelation layer can entrapp air and carbon dioxide, that was formed by the reaction of FCC with the acidic dissolution medium, within the internal porous structures of the FCC-based matrix (FIGURE 4.2). As the gas bubbles needed to diffuse through the gel layer, they were enclosed in the matrix and buoyancy of the dosage form was maintained for a prolonged period of time. This mechanism was referred to as "gas plug" formation.

The analysis of the hydrophilic formulations by displaying the floating force of the tablets as a function of drug release revealed that the flotation performance belonged to the type *I* model behavior of our classification system. While the API was released, the floating capability of the compacts decreased linearly and a floating force value of zero was obtained after almost entire caffeine release. This observation was explainable by the reaction-based erosion process of the flotation-promoting FCC in HCl.

4.1.2 Lipophilic floating systems

For preparation of the lipophilic floating formulation type, FCC was combined with a lipophilic component (e.g. Lubritab®, paraffin wax). Though, the co-formulation of FCC and lipophilic material by intermixing did not result in the targeted drug release and flotation times. The FCC pores were not blocked and, consequently, the immediate wetting of the porous matrix was not prevented. The hydrophobization of FCC due to melting of the lipophilic excipient was of relevance for this formulation type; different degrees of FCC hydrophobization (i.e. thickness of the lipophilic layer) were assumed.

A critical role played the selection of the pharmaceutical manufacturing process, as the lipophilic component had to be melted and distributed homogeneously within the porous FCC matrix. Despite the twin-screw hot-melt extruder, which was used in the context of this thesis, the melt granulation process may be performed in a high-shear mixer or fluidized melt granulation is applicable.

The lipophilic coating layer of FCC particles (FIGURE 4.3) delayed or prevented the erosion of FCC under acidic conditions. In addition, it slowed down the penetration of dissolution liquid into the tablet. Consequently, air and/or carbon dioxide can be entrapped within the

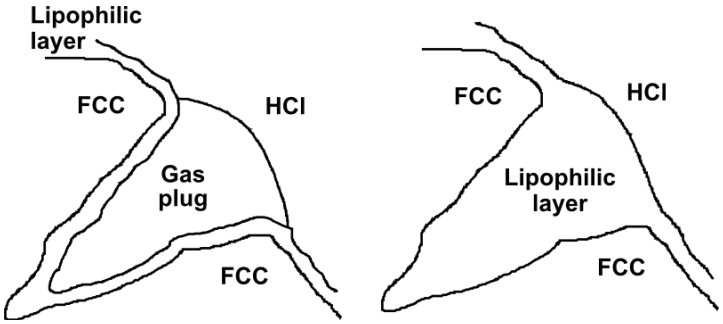

FIGURE 4.3. Hydrophobization of FCC: the particles are covered with a lipophilic layer and/or the lipophilic excipient is filled into the stratum voids of the particles.

porous matrix system in form of a "gas plug".

A floating system consisting of an inert, lipophilic drug-releasing matrix is supposed to show a type *III* floating behavior: the floating force of the FDDS increases as the API is released and is replaced by the dissolution medium. For the lipophilic FCC-based mini-tablets, two types of floating kinetics - type I and type V - were identified depending on the formulation composition. We hypothesized that in the case of the mini-tablet formulations with a type I floating behavior, the amount of lipophilic excipient was not sufficient to ensure complete hydrophobization of the FCC matrix. Therefore, an erosion reaction of non-hydrophobized FCC under acidic conditions occurred. The floating force increase, induced by drug release from the floating tablet, was compensated and predominated by the floating force decline due to mini-tablet erosion. As a result, the floating potential of the FDDS decreased linearly. In the case of the lipophilic mini-tablet formulations featuring a type V floating behavior, a mass exchange between dissolved API and dissolution liquid took place. The resulting increase of floating capacity was compensated by erosion of the tablet matrix. In consequence, the mini-tablets maintained their resultant floating force while the drug substance was released. The erosion of the lipophilic tablet matrix was possible due to the dissolution of caffeine and non-hydrophobized FCC which resulted in the detachment of buoyancy-promoting, hydrophobized FCC particles from the tablet core. After almost complete release of the API, the flotation capability of the mini-tablets decreased; it implied that the erosion by disintegration process exceeded.

Floating systems with an inherently low density due to the incorporation of porous excipients, such as FCC, have the advantage that higher drug loads are feasible. In particular in the case of effervescent FDDS, the drug load of the delivery platforms is limited by the need of co-formulated effervescent excipients. Our FCC-based approach describes industrially-manufacturable floating devices with drug loads of up to 35% (w/w).

4.2 *In vitro* evaluation of flotation and drug release

As mentioned in the introduction, several parameters exist to characterize FDDS (1.3.3 Methods for the evaluation of floating systems). However, there are no generally-accepted considerations which of the factors are fundamental. The relevance of the individual parameters is discussed in the following section.

First, the density of the dosage form, before its immersion into liquid, is an important property of FDDS. An inherent density below unity implies immediate flotation of the device in the dissolution medium. However, we consider the exclusive assessment of the density before immersion of the dosage form into liquid as insufficient for the appropriate characterization of FDDS. The parameter, initial density, does not provide any information about the floating behavior of the device over time while the drug substance is released.

Further relevant factors for the *in vitro* investigation of FDDS are floating performance and drug release behavior. For the design of floating formulations, most researchers characterize FDDS based on visually-assessed floating behavior (i.e. floating lag time and total floating time) and do not take into account floating kinetics.

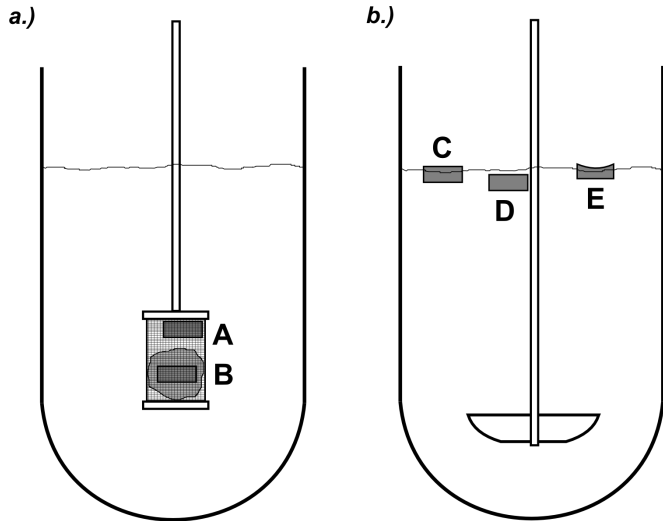

Figure 4.4. Limitations of the United States Pharmacopeia methods. *(a.)* USP I dissolution apparatus: the dosage form is forced to stay immersed in the medium (**A**); the floating system sticks to the basket or the swelling of the device is inhibited (**B**). *(b.)* USP II dissolution apparatus: the floating system is not completely submerged into the liquid (**C**); the device sticks to the paddle shaft (**D**); the floating tablet surface dries, a crater is formed, and the floating time is artificially prolonged (**E**).

A reason may be the fact that there is currently no evaluation system available to investigate simultaneously *in vitro* drug release and *in vitro* floating force. From our point of view, the visual observation of floating characteristics seems not sufficient for the successful development, comparison, and optimization of floating formulations. The approach does not quantify the

floating capability of FDDS; i.e. it does not allow to determine the resultant floating force of dosage forms.

Additionally, there does not exist a generally-accepted method for the *in vitro* evaluation of drug release behavior of FDDS and different approaches are described in literature. The conventional USP I and II dissolution methods show limitations regarding the analysis of FDDS which are highlighted in FIGURE 4.4. In order to overcome these shortcomings, we proposed a custom-built stomach model. The features of the custom-built stomach model were evaluated in comparison to the available models for simulation of the human GI tract (3.1 PREPARATION AND IN VITRO EVALUATION OF FLOATING GASTRORETENTIVE DRUG DELIVERY SYSTEMS). Our method allowed for a combined analysis of drug release by UV/Vis spectroscopy and floating behavior by visual observation. But, it was not possible to perform the combined *in vitro* assessment of drug release and resultant floating force. In order to compensate this drawback, the *in vitro* evaluation method was combined with *in silico* computer simulations.

To sum up, the determination of the density, the *in vitro* evaluation of floating behavior, the *in vitro* and *in silico* analysis of drug release, and the *in silico* assessment of floating kinetics were found to be essential for the successful development of FDDS.

4.3 *In silico* simulation of tablet dissolution

In general, computer simulations offer the possibility to assess parameters which cannot be experimentally determined or which require a complex experimental setup. The F-CAD software (CINCAP GmbH, Switzerland) is an approach to drug release simulation based on the mathematical concept of cellular automata [177]. Cellular automata present an idealization of a physical system in which time and space (i.e. equal-sized voxels arranged in a regular grid) are discrete, and physical quantities take a finite set of values (i.e. each voxel owns a finite number of states). After every time step/iteration step, the state of each individual voxel in a new generation of voxels is defined by its previous state and by the state of the voxels in its neighborhood [34, 177].

The Noyes-Whitney equation mathematically expresses the rate of dissolution dm/dt of a solid in a solvent, as follows:

$$\frac{dm}{dt} = \frac{A \cdot D}{h} \cdot (C_\mathrm{s} - C_\mathrm{t}) \qquad [155] \tag{4.1}$$

where, m is mass of dissolved material, t is time, A is solid-liquid interface surface area, D is diffusion coefficient, C_s is solubility on the equilibrium at experimental temperature, C_t is concentration of the solid in the bulk of the dissolution medium at time t, and h is thickness of the diffusion layer.

By maintaining sink conditions during the dissolution, the resulting equation is:

$$\frac{dm}{dt} = \frac{A \cdot D}{h} \cdot C_{\mathrm{s}} \quad \text{for } C_t \to 0 \qquad [180] \tag{4.2}$$

The Noyes-Whitney equation in spatial differential form has a form of the Fick's second law and can be shown in three dimensions, as follows:

$$\frac{\partial \phi}{\partial t} = D\nabla^2\phi \quad \text{with } \nabla^2 = (\frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2}) \qquad [66] \tag{4.3}$$

where, ϕ is concentration, t is time, and D is diffusion coefficient.

By applying the finite difference method for computing the numerical solutions of the systems of differential equations, the translation of Eq. 4.3 into cellular automata rules for dissolution simulation is done. The voxels are classified in different types and a finite number of rules are applied on every voxel type. For the dissolution simulation, every cellular automaton has a primary constant (C_1) and a secondary constant (C_2).

The C_1-value indicates the number of iterations which are needed to change the state of a voxel from "solid" to "liquid" [177]; it can be calculated as shown below:

$$C_1 = \frac{m}{dm} \cdot 26 \tag{4.4}$$

where, dm is from Eq. 4.2 in case of $dt = 1$, mass of the voxel m (g) is $m = \mathrm{V} \cdot \rho$, volume of the voxel V (cm^3) is $V = h^3$, h (cm) is voxel side length, ρ ($\mathrm{g/cm}^3$) is density of the component, and 26 is number of surrounding "liquid" voxels in the three-dimensional Moore neighborhood [177].

In the F-CAD dissolution simulation, the time resolution is 1 sec; according to Eq. 4.2, it follows:

$$dm = \frac{A \cdot D}{h} \cdot C_{\mathrm{s}} \quad \text{for } dt = 1 \tag{4.5}$$

$$\text{with the Stokes-Einstein relation:} \quad D = \frac{1}{f} \cdot \kappa_{\mathrm{B}} \cdot (T + 273.15) \qquad [116] \tag{4.6}$$

$$\text{with } f \text{ for a sphere given by the Stokes' law:} \quad f = 6\pi \cdot \eta \cdot R \qquad [92] \tag{4.7}$$

$$\text{with viscosity of water:} \quad \eta = 2.414 \cdot 10^{-5} \cdot 10^{(247.8/((\mathrm{T} + 273.15)-140))} \qquad [2] \tag{4.8}$$

where, voxel surface area A (cm^2) is $A = 6 \cdot h^2$, D (cm^2/s) is diffusion coefficient, f is frictional coefficient, $\kappa_{\mathrm{B}} = 1.3806488 \cdot 10^{-16}$ $\mathrm{cm}^2 \cdot \mathrm{kg} \cdot \mathrm{s}^{-2} \cdot \mathrm{K}^{-1}$ is Boltzmann constant, T (°C) is temperature, 6π is dimensional factor [58], η (Pa·s) is viscosity of the dissolution medium at given

temperature, and R (Å) is molecular radius of gyration.

TABLE 4.1 provides an overview about the primary constants used for the *in silico* tablet dissolution simulations and the constants calculated according to EQ. 4.4.

TABLE 4.1. Comparison of the constants used for the F-CAD simulations and the calculated values. For the polymeric excipients (e.g. Polyox®, Methocel®) the calculation of the C_1-values according to EQ. 4.4 was not possible.

Component	**C_1-constant**	**Calculated C_1-constant**
Lipophilic mini-tablet formulation:		
Caffeine	700	765; (230 [1])
FCC	500	2
Hydrophobized FCC	100 000	$\rightarrow \infty$
Lubritab®	7 000 000 [2]	$\rightarrow \infty$
Hydrophilic tablet formulation:		
Caffeine	800	998
Citric acid	10	20
FCC (in water)	4 000	3 368 569
FCC (in 0.1 N HCl)	1 800	11

[1] C_1-value calculated according to EQ. 4.4.

[2] Minimum C_1-value required to prevent reduction of the number of voxels during dissolution simulation.

In the case of the hydrophilic tablet formulation, the primary constant of caffeine, which was applied for the F-CAD simulation, was in accordance with the calculated value. On the contrary, a three-times higher $C_{1,\,\text{caffeine}}$-value than the estimated one was used for the *in silico* simulation of the lipophilic mini-tablet matrices. We hypothesized that melting of the co-formulated lipophilic excipient during the granulation process resulted in a hydrophobization of caffeine, i.e. immersion of the caffeine crystals (or with regard to the F-CAD simulation of the caffeine voxels) in a lipophilic matrix. This led to a significant difference in diffusion behavior of the component between unrestricted and porous medium due to elongated flow pathways. The change in diffusion behavior of the material was included in the C_1-value calculation by adapting the voxel surface area, resulting in an estimated C_1-constant of 765 for caffeine.

In a saturated porous medium, the effective diffusion coefficient D_{eff} can be represented by the following equation [191]:

$$D_{\text{eff}} = \frac{D \cdot \delta \cdot \phi}{\tau} \tag{4.9}$$

where, D is diffusion coefficient, δ is constrictivity factor taking into an account the constricted transport paths in a porous medium, ϕ is effective transport-through porosity, and τ is tortuosity factor to account for the reduction in diffusive flux due to the tortuous path lengths compared to straight paths in an unrestricted medium.

We introduced an F-CAD component type for porous material (type ID 80) to be capable of assessing the performance of FCC during *in silico* tablet dissolution. In the case of component type 80, the secondary constant (C_2) defines the rate of liquid sorption into the porous material. The penetration of dissolution medium into FCC is an important parameter for the evaluation of the flotation performance as the wetting of the porous material results in a density increase [57]. In order to simulate the behavior of FCC in dissolution media with different pH-values, the C_1-constant was accordingly adapted. In terms of the Noyes-Whitney equation (Eq. 4.2), the C_1-value can be described as a reciprocal of the constant term.

Under acidic conditions, a reaction-based erosion of FCC (calcium carbonate) occurs:

(4.10) $$CaCO_{3(s)} + 2HCl_{(aq)} \rightarrow CaCl_{2(aq)} + H_2CO_{3(aq)}$$

(4.11) $$H_2CO_{3(aq)} \rightarrow H_2O_{(l)} + CO_{2(g)}$$

(4.12) $$CaCO_3 + 2H^+ \rightarrow Ca^{2+} + H_2O + CO_2$$

FCC dissociates in solution by:

(4.13) $$CaCO_3 \rightleftharpoons Ca^{2+} + CO_3^{2-} \qquad K_{sp} = [Ca^{2+}][CO_3^{2-}] = 4.8 \cdot 10^{-9} \qquad [167]$$

(4.14) $$H_2O + H_2CO_3 \rightleftharpoons H_3O^+ + HCO_3^- \qquad K_{a1} = \frac{[H_3O^+][HCO_3^-]}{[H_2CO_3]} = 2.5 \cdot 10^{-4} \qquad [96]$$

(4.15) $$H_2O + HCO_3^- \rightleftharpoons H_3O^+ + CO_3^{2-} \qquad K_{a2} = \frac{[H_3O^+][CO_3^{2-}]}{[HCO_3^-]} = 4.69 \cdot 10^{-11} \qquad [238]$$

The molar solubility of FCC at pH 1.2 can be calculated, as follows:

(4.16) $$\frac{dm}{dt} = \frac{A \cdot D}{h} \cdot C_s^{pH=1.2} \quad \text{with } C_s^{pH=1.2} = \sqrt{\frac{K_{sp}}{\alpha_2}}$$

where, fraction of dissociation α is $\alpha_2 = \frac{[CO_3^{2-}]}{F_A} = \frac{K_{a1} \cdot K_{a2}}{[H_3O^+]^2 + K_{a1} \cdot [H_3O^+] + K_{a1} \cdot K_{a2}}$ and F_A is formal concentration.

The calculated $C_{1,\,FCC}$-values for the hydrophilic and lipophilic formulations (Table 4.1) indicate immediate dissolution of FCC in an acidic medium. But, the $C_{1,\,FCC}$-values obtained

according to Eq. 4.4 represent the number of iterations which are needed to dissolve an FCC component voxel being surrounded by 26 "liquid" voxels respecting the three-dimensional Moore neighborhood. For the F-CAD simulation, the impact of co-formulated excipients on the dissolution behavior was included in the $C_{1,\,FCC}$-values. They account for the average length of the diffusion pathway which dissolved FCC needs to travel in order to reach the bulk solution. Due to the slower dissolving tablet matrix, the diffusion pathway of FCC was assumed to be obstructed and prolonged.

As calcium carbonate is practically insoluble in water, it results for the C_1-constant of FCC:

$$\frac{dm}{dt} = \frac{A \cdot D}{h} \cdot {C_s}^{pH \geq 7} \quad \text{with } {C_s}^{pH \geq 7} \to 0 \tag{4.17}$$

$$C_1 = \frac{m}{dm} \Rightarrow C_1 = \frac{m}{\frac{A \cdot D}{h} \cdot C_s \cdot dt} \quad \text{with } dt = 1 \tag{4.18}$$

$$C_{1,\,FCC} = \lim_{C_s \to 0} \frac{m}{\frac{A \cdot D}{h} \cdot C_s} = \infty \tag{4.19}$$

For FCC in water, a high C_1-constant of approx. 3 000 000 was calculated by applying Eq. 4.4. The value was in accordance with the conclusion drawn from Eq. 4.19 which implies that in dissolution media with neutral pH the primary constant of FCC goes to infinity due to its low solubility ($CaCO_3$ solubility in water at 25 °C: 0.013 g/L [227]). The C_1-value used for the dissolution simulations of the hydrophilic tablet formulation in water was about 840-fold smaller than the calculated value. It has to be taken into account that the hydrophilic formulation contained citric acid which promoted the erosion of FCC and reduced its primary constant. For FCC in water, as well as for hydrophobized FCC, it has to be kept in mind that not only dissolution of FCC occurred, but also erosion processes took place *in vitro*. However, the detachment of FCC particles from the tablet matrix - without dissolving FCC voxels - cannot be simulated *in silico*. It can only be mimicked and controlled by the primary constant of the component voxels, i.e. the reduction of the $C_{1,\,FCC}$-value to simulate a faster state change of the cellular automaton from to solid to "liquid".

For the computer simulation of the lipophilic FCC-based tablet formulations, an additional type of FCC - hydrophobized FCC - was introduced. We assumed that hydrophobized FCC had a solubility equal to the lipophilic component Lubritab® which formed a hydrophobization layer around the FCC particles.

Lubritab® is practically insoluble in water; accordingly, it follows for the primary constant of Lubritab® and hydrophobized FCC:

$$\frac{dm}{dt} = \frac{A \cdot D}{h} \cdot C_s \quad \text{with } C_s \to 0 \tag{4.20}$$

According to Eq. 4.18, it results:

$$(4.21)\quad C_{1,\ \text{Lubritab}^{®}} = \lim_{C_\text{s}\to 0} \frac{m}{\frac{A\cdot D}{h}\cdot C_\text{s}} = \infty \quad ; \quad C_{1,\ \text{Hydrophobized FCC}} = \lim_{C_\text{s}\to 0} \frac{m}{\frac{A\cdot D}{h}\cdot C_\text{s}} = \infty$$

It was hypothesized that a re-arrangement of the lipophilic material took place during the *in vitro* drug release measurement. In consequence, pre-hydrophobized FCC became accessible for the acidic dissolution medium. This assumption may provide an explanation for the variation between applied and calculated primary constant of hydrophobized FCC. As mentioned above, the primary constant of hydrophobized FCC did not only reflect the reciprocal solubility per unit of time. The value also took into consideration the detachment of hydrophobized FCC particles from the tablet matrices during dissolution.

4.4 Quality by Design

The Food and Drug Administration (FDA) issued a guidance for industry "Q8R2 Pharmaceutical Development" describing the principles of Quality by Design (QbD). It has been stated that quality should be built-in or should be by design and cannot be tested into the product. In pharmaceutical formulation design and process development, the starting point of the QbD approach is to define the quality target product profile (QTTP) dealing with quality, safety, and efficacy (i.e. route of administration, characteristics of the dosage form, bioavailability, strength, stability). Furthermore, the potential critical quality attributes (CQA) of the drug product, of the drug substance, and of the excipients, which may have an influence on the final product quality, need to be identified and understood. The QbD approach includes the selection of appropriate pharmaceutical manufacturing processes. To design, monitor, and control the production processes by in-line or on-line measurements of critical process parameters (CPP), which may effect the CQA, process analytical technology (PAT) is applied [69]. The *in silico* dissolution simulation model is considered to be a valuable additional element for the pharmaceutical QbD approach: it allows to gain an enhanced knowledge of raw material characteristics and product quality attributes as well as an improved understanding of process parameters; thus, it facilitates to establish an appropriate control strategy.

4.5 Characterization of floating behavior

To facilitate the analysis and comparison of floating kinetics of FDDS, we proposed to display the floating force of dosage forms as a function of drug release. Based on the literature data of resultant-weight measurements and on our results of the floating performance analysis of

FCC-based tablets, a classification system was introduced. It describes five floating model behavior which are commonly observed among FDDS.

So far, there exists no proposal for a floating behavior which is considered to be "optimal" for floating GRDDS. In general, a short or no floating lag time is targeted to reduce the risk of premature, uncontrolled stomach emptying of the delivery device. The development of FDDS is, in most cases, aimed to achieve the longest possible buoyancy time.

From our point view, the unidirectional design and optimization of floating formulations to achieve the longest flotation time seemed not appropriate. In the context of the classification system for FDDS, we defined an "ideal" floating behavior which took into account the drug release behavior (3.2 In vitro and in silico evaluation of floating gastroretentive drug delivery systems). The "ideal" floating behavior was characterized as follows: the dosage form features no floating lag time, maintains its floating force until complete drug release, and finally, exhibits a floating force decrease to zero.

4.6 Gastric retention potential of floating systems in human

The *in vitro* and *in silico* analytical methods for FDDS allowed a detailed characterization of the drug release and the floating behavior of dosage forms. But, they were not capable of replacing the *in vivo* evaluation of the GI transit behavior and they could not predict the gastric retention potential of the FDDS in humans. Thus, it implied that an excellent *in vitro* floating performance in the experimental setup did not necessarily result in a prolonged *in vivo* GRT. Additionally, it has to be kept in mind that the *in vivo* evaluation in animals does not allow to draw a conclusion about the gastric retention potential of a FDDS in humans. The reasons are significant species differences regarding GI tract anatomy and physiology between humans and commonly-used laboratory animals. A clinical evaluation in humans is obligatory to assess the gastric retention potential of floating dosage forms.

Instead of using imaging techniques to track the GI transit of the dosage forms, we applied an enteric-coating concept for determination of the stomach residence time of our floating tablet formulation. The enteric-coating was only for analytical purpose and was not of relevance for the flotation mechanism of the dosage form. In comparison to the marker-based imaging methods, our approach featured the advantage that a modification of the floating system due to the co-formulation of marker substances was not required. The addition of a labeling substance in sufficiently large amounts to the "original" floating formulation effects the characteristics of the dosage form (e.g. density, floating kinetics). Consequently, it may influence the *in vivo* gastric retention capability of the FDDS.

The *in vivo* behavior of the enteric-coated tablets could be depicted in the floating behavior classification graph by two points. The enteric-coated FCC-based floating tablet featured an

inherently low density. Therefore, it was supposed to float immediately on the stomach contents after oral administration. This property complied with our requirements for "ideal" floating properties. Under acidic conditions in the human stomach, the pH-dependent tablet coating remained intact. Thus, the reaction-based erosion of the tablet and the release of the marker substance caffeine were prevented. At zero percent drug release, the enteric-coated floating compact exhibited a positive resultant force. We hypothesized that the enteric-coated dosage form maintained its floating capability while being retained in the stomach. Following stomach emptying, the pH-dependent enteric coating dissolved due to the elevated pH in the intestinal environment. As a consequence, the markers substance caffeine was released from the dosage form. We assumed that the FCC-based tablets had a resultant force close to zero or below zero at 100% drug released. The shown performance was close to the defined "ideal" floating characteristics.

5

Conclusion and outlook

Despite the research performed in the field of gastroretentive drug delivery during the past decades, the development, the manufacture, the analysis, and the optimization of floating drug delivery platforms remain a challenging task. In the context of this thesis, the novel pharmaceutical excipient FCC, an innovative *in vitro* evaluation method, a computer-based simulation model, and an *in vivo* clinical study design were combined in a tool box in order to facilitate the formulation development of FDDS and to design robust floating formulations "right-first-time".

5.1 Functionalized calcium carbonate - a pharmaceutical excipient with an inherently high porosity

FCC is a microporous to mesoporous material with characteristic lamellar structures that form a porous meshwork. The lamellae provide a large contact area allowing to tightly interlock the particles. Due to its unique properties, the excipient is applicable and advantageous for the compaction of tablets featuring an inherently low density less than unity accompanied by a sufficiently high tensile strength. The design of floating tablets and mini-tablets revealed that FCC is an enabling excipient for the manufacture, also on larger scale, of innovative instantly floating drug delivery platforms [77].

At present, it is worked on the registration of FCC as pharmaceutical excipient. The market launch of FCC as a new generation of mineral excipient is planned to take place in the year 2015. The commercially available pharmaceutical excipient will be registered and sold under the brand name "Omyapharm" [160]. The encouraging results of our research group provide a first

evidence for the successful applicability of FCC in pharmaceutical industry [57, 175, 215, 216].

5.2 Floating drug delivery platforms based on functionalized calcium carbonate

In the context of this thesis, two types of FCC-based floating tablet formulations were designed and investigated. The production of the hydrophilic and lipophilic formulations was done by batch-wise wet granulation and continuous melt granulation, respectively.

Caffeine was selected as a model drug substance in order to characterize the drug release mechanism of the delivery platforms. For further optimization of the FCC-based floating tablets, it is recommended to replace the model drug substance by an API which benefits from a gastroretentive delivery approach.

The hydrophilic FCC-based FDDS presented a surface-eroding drug delivery platform with a linear decrease in floating capability while releasing the API in an erosion-controlled manner. The degradation process at the tablet surface was faster than the diffusion of the simulated gastric fluids into the porous tablet matrix. The pH-dependent flotation mechanism can be described as a gas-generating erosion mechanism with polymers as imbibition-inhibiting and gas-entrapping components. Concerning the administration to humans, we concluded that the hydrophilic formulation type does not have the risk of retention in the human stomach beyond the targeted GRT; hence, the accumulation of delivery devices in the GI tract following multiple administrations is rendered almost impossible.

On the basis of FCC as matrix-forming material combined with a lipophilic meltable ingredient, we designed floating tablets and multiple-unit floating mini-tablets. The degree of FCC hydrophobization and the arrangement of the components within the tablet matrices were critical attributes for the design of robust lipophilic-excipient-FCC matrix formulations. They influenced tablet properties such as breaking strength, dissolution behavior, and flotation performance. There seems to be a negligible risk for the dosage units to accumulate in the gastric region as the *in silico* simulations of the mini-tablet matrices suggested a resultant floating force close to zero at 100% drug released. FCC, due to its porous structural organization, may function as release-controlling excipient for hydrophobic matrix systems. It enables to overcome the shortcoming of incomplete API release which is often observed in the case of hydrophobic matrix delivery platforms.

To sum up, the formulation of porous material - such as FCC - with diverse types of excipients renders possible the manufacture of instantly floating systems with different flotation and drug release characteristics.

5.3 Techniques for the analysis of floating systems

The applied approach of combining *in vitro* and *in silico* methods offered the possibility to compare and to characterize in detail the floating systems. This point was considered to be of fundamental importance for the efficient preparation of innovative FDDS with targeted drug release profiles and floating performance as well as for the understanding of the underlying mechanisms.

In order to overcome the shortcomings associated with the conventional dissolution methods, we proposed and applied a custom-built stomach model which was based on a horizontally-moving water bath shaker. The horizontal movement was beneficial as it kept the FDDS moistened during the *in vitro* drug release measurement and mimicked the GI tract motility. Additionally, our experimental setup enabled the simultaneous investigation of drug release and flotation behavior (i.e. visual assessment of floating lag time and total floating time).

The necessity of using *in silico* simulations resulted from the fact that the available *in vitro* techniques do not allow for a simultaneous assessment of drug release and quantification of the resultant force. For the future formulation development in the field of FDDS, the construction of a test setup to perform this combined evaluation would be a great benefit.

In the context of the thesis, the three-dimensional cellular-automata-based computer model was successfully applied to quantify the floating potential of tablets. Furthermore, the computer simulations will advance the further optimization of the invented FCC-based hydrophilic and lipophilic floating drug delivery platforms. They render possible to vary the amount of drug substance and to substitute the used model drug caffeine by other APIs with an unmet medical need for a gastroretentive delivery approach. The impact of formulation changes on tablet dissolution and resultant floating force can be first studied *in silico* without the need of carrying out all respective experiments *in vitro* in the laboratory.

5.4 Evaluation of floating systems in human

Our approach (i.e. pH-dependent enteric coating and caffeine as marker substance) presents a simple method to study in human the stomach residence time of non-effervescent floating tablets with an inherent density less than unity. The results of the pilot experiment, performed in three human volunteers, provided an indication for the *in vivo* gastric retention potential of floating tablets based on FCC and for the applicability of the flotation concept, in general, to achieve an extended stomach residence time.

The primary objective of the self-experiment was to investigate, on the example of enteric-coated FCC-based tablets, whether a mechanism of flotation results in a prolonged GRT of dosage forms in comparison to non-floating devices. However, the setup of the *in vivo* study

did not provide any information regarding the GI performance and drug release behavior of uncoated FCC-based floating tablets.

The encouraging findings of the pilot study seem to justify a follow-up with clinical trials in humans. Thus, for follow-up clinical evaluations the enteric tablet coating will be omitted in order to analyze drug concentrations at predetermined time points in endoscopically-collected gastric juice samples. It is suggested to replace the model/marker drug substance by an API which features an unmet medical need for a gastroretentive delivery approach. The preferred dosage forms to be evaluated in follow-up clinical trials regarding their gastroretentive potential are multiple-unit FDDS. They have a reduced risk of "all-or-nothing" gastric emptying and, hence, a lower intra-individual and inter-individual variability in drug bioavailability. In the context of a clinical study, factors that may influence the gastric retention potential of FDDS (e.g. liquid intake, composition of food, body position, physiological conditions) need to be investigated.

5.5 Classification system for floating systems

Our classification system was found to be a valuable element of the established FDDS formulation design tool box. It links two important response variables of floating systems - namely drug release and resultant force - which are often considered independent from each other. However, it has to be kept in mind that the classification system is for illustrative purpose and displays model floating behavior; more complex floating behavior may be experimentally observed. The classification system is not limited to the distinguished five types of flotation and a larger number of categories is possible.

We defined "ideal" floating kinetics, taking into consideration the anatomical and physiological conditions and organization of the human stomach, as follows:

- The floating system exhibits immediate flotation to reduce the risk of an uncontrolled and premature gastric emptying from the stomach.
- While the API is released, the floating system maintains its resultant floating force.
- After complete drug release, the floating system shows a "switch-off" effect regarding flotation capability to trigger the stomach emptying of the device.

Nevertheless, the classification system is not only a theoretical concept. The practical relevance of our considerations was demonstrated by applying the classification system for the formulation development and optimization of FCC-based mini-tablets. Mini-tablet formulations which exhibited a floating behavior close to the described "ideal" floating characteristics were identified in the experimental setup. In addition, our definition of "ideal" floating kinetics was

supported by the results of the *in vivo* pilot experiment.

The approaches proposed and applied in the context of the thesis were summarized in a FDDS formulation design tool box to promote the formulation development of floating systems. As elaborated in the introduction, there are several APIs which may profit from a prolonged GRT. The FDDS formulation design tool box, which includes floating drug delivery platforms based on FCC, provides the opportunity to reconsider and extend the existing therapies and to design innovative and feasible treatments using the concept of floating gastroretentive drug delivery.

A

Appendix

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