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Prolongation of the gastric residence time of caffeine after administration in fed state: Comparison of effervescent granules with an extended release tablet

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ABSTRACT

The aim of the present study was to investigate the gastroretentive capacity of different formulation principles. This was indirectly determined by the absorption behavior of caffeine from the dosage forms. A slow and continuous appearance of caffeine in the saliva of healthy volunteers was used as a parameter for a prolonged gastric retention time. For this purpose, a four-way study was conducted with twelve healthy volunteers using the following test procedures: (1) Effervescent granules with 240 mL of still water administered in fed state, (2) effervescent granules with 20 mL of still water in fed state, (3) extended release (ER) tablet with 240 mL of still water in fed state, and (4) effervescent granules with 240 mL of still water in fasted state. The initial rise of the caffeine concentrations was more pronounced after the intake of the effervescent granules in the fed state compared to that of the ER tablets. However, t_{max} tended to be shorter in the fed study arms following administration of the ER tablet compared to the granules. Overall, the application of active pharmaceutical ingredients formulated as effervescent granules seems to be a promising approach to increase their gastric residence time after intake in fed state.

1. Introduction

There are several reasons to increase the gastric residence time of drugs [1]. Often the primary goal is to improve the bioavailability of drug candidates, that either suffer from low solubility (e.g. cinnarizine [2]), instability at different pH values (e.g. verapamil [3]) or the candidates are only absorbed in certain regions of the intestine (e.g. pregabaline [4]). A common approach for this concept are gastroretentive drug delivery systems (GRDDS) [1]. For example, major efforts have been made to develop gastroretentive formulations of antibiotics for the local treatment of *Helicobacter pylori infections* to increase the chance of the therapeutic success and also to reduce side effects [4–9]. Reducing the dosing interval and thus improving patient compliance is another possible advantage of this strategy researcher regularly aiming for [10].

Different aspects have to be considered, when local treatment of the stomach and due to that prolonged gastric residence time of a dosage form shall be achieved. The retention time in the stomach is mainly determined by the physiology of the stomach. In humans, gastric emptying of indigestible solids in the fasting state is controlled by the interdigestive migrating motor complex (IMMC) [11,12]. This physiological phenomenon is characterized by phases of very different contractile activity in terms of frequency, duration and intensity. Especially in the third phase of the IMMC, pronounced antral contractions, also known as housekeeping waves, promote the emptying of even larger objects, such as non-disintegrating tablets, from the stomach. Accordingly, large monolithic dosage forms are also emptied from the human stomach under fasting conditions [13,14]. Ingestion of food disrupts the course of the IMMC. In fed state, gastric emptying behavior changes and only small particles with a diameter below approximately 2 mm can pass the pylorus [15]. Large objects, such as monolithic non-disintegrating tablets, are usually retained in the postprandial stomach until the reoccurrence of the fasted state motility cycle [15,16]. However, the

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physiological behavior of the human stomach represents a major challenge in terms of achieving therapeutic drug concentrations for local treatment. Established dosage forms may face challenges in ensuring effective concentration and transport to the site of the stomach due to the dynamic conditions inside the stomach and their influence on the dosage form, such as shear forces on a monolithic dosage form through food or placement of the dosage form in a full stomach [17]. Additionally, there are several other important factors to consider achieving an effective local therapy, e.g. the distribution of the meal components or the viscosity of the ingested food [18].

Another important factor to consider is the emptying of water from the stomach. Under postprandial conditions, administered water, together with dissolved or dispersed API, rapidly passes through the stomach by a mechanism called stomach road or "*Magenstraße*". Due to that, the intake of medications after a meal in the hope of prolonged gastric residence time, may result in surprisingly fast emptying kinetics followed by rapid drug absorption. In clinical studies solid dosage forms are applied together with 240 mL of water and this volume is being emptied from the stomach within 15 to 45 min in fasted as well as fed state [18–20]. But not only the emptying rate of the co-administered water but also the amount of water is important, especially looking at real life dosing conditions. Several studies have shown that most patients take their mediactions with less than 240 mL water [18,21]. Overall, the emptying of water can be an additional challenge achieving gastric retention.

As mentioned above, major efforts are being made to extend the gastric residence time of APIs. Regarding the first line therapy of *Helicobacter pylori* for example, prolonging the gastric residence time of antibiotics could result in a better eradication and an increased therapeutic success [22–24]. Especially the eradication with amoxicillin is time dependent [25]. Nowadays, the first line treatment recommends the triple-therapy for 7 days or the non-bismuth quadruple therapy for 10–14 days [24,26]. The standard therapy always includes a proton-pump-inhibitor (PPI) and at least one antibiotic [24,25]. *Helicobacter pylori* is a gram-negative bacteria with 4.4 billion individuals infected worldwide [25]. Therefore, *Helicobacter pylori* is one of the main factors causing gastric ulcers in addition to the widespread of use of non-steroidal anti-inflammatory drugs (NSAIDs) [27,28]. These ulcers are small open wounds in the mucosa of the stomach that are larger than 5 mm. The standard therapy of these ulcers is usually based on PPIs, but these are associated with several side effects, including renal disorders, cardiovascular risks and micronutrient deficiencies [29,30]. Local therapy could reduce these side effects, but has to deal with several challenges [31]. On the one hand, the drug has to be transported to the target site and more important, the drug must remain over a longer period of time at this site. This requires a homogenously mixing of the drug in the chymus in fed state. A constant and effective concentration has to be reached for a local treatment of the stomach walls. Due to the physiological behavior of the stomach, it is only possible to increase the gastric residence time of drugs in the fed state so far [17,31]. For example, hydroxypropylmethylcellulose (HPMC)-based ER tablet represented a well established way to achieve a prolonged release of drugs inside the stomach after administration in fed state [32,33]. This can dramatically increase the period of time in the stomach and thus the period of time at the target site of gastric diseases like gastric ulcers. Today's established gastroretentive drug delivery systems have difficulties in meeting these mentioned requirements. For example, the transport to the target site or generating a homogeneous mixture as prerequisite for locally high concentrations, to ensure a local therapy is very challenging and can be difficult to achieve.

Increasing the gastric residence time of active pharmaceutical ingredients (API) can have other important benefits besides a local therapy especially for diseases that would benefit from a constant and steady drug emptying from the stomach, and thus a constant absorption in the small intestine, corresponding to constant plasma concentrations [31,34]. For example, the pancreatic enzyme replacement therapy (PERT) requires a slow and constant emptying in the small intestine to ensure effective digestion and absorption [35]. These PERT enzymes are often administered in microgranules or minimicrospheres with a pH sensitive coating due to the possible inactivation by the gastric acid [36]. Due to the established dosage forms, inconsistent concentrations in the small intestine could occur after gastric emptying, as the mentioned microgranules or minimicrospheres are not homogenously contributed in the food content [37]. In this case, possibly a homogenous mixing in the co-administered food could result in a more constant drug emptying out of the stomach.

Another therapy that would benefit from a constant and slow drug emptying from the stomach is the treatment of bowel diseases such as Crohn's disease or Ulcerative Colitis [37]. Actually, oral administration of drugs is preferred, and the characteristics of Crohn's disease, especially the discontinuous inflammatory regions of the bowel, would make a continuous and steady concentration of effective anti-inflammatory agents desirable. The constant and slow emptying of homogeneous food content could provide a constant drug concentration in the following parts of the gastrointestinal tract (GIT). This would potentially increase the therapeutic success and reduce the risk of adverse effects.

In the present study, we investigated the potential of different formulations to achieve higher concentrations in stomach for a longer period of time. By generating and releasing the incorporated carbon dioxide, these granules should be mixed into the gastric content. The incorporated model drug caffeine should be distributed homogenously within the chyme. Moreover, we studied the impact of different amount of co-administered water on the magnitude of this mixing effect. Due to the emptying behavior in the fed state, the concentration of caffeine in the stomach should be increased over an extended period of time. Additionally, we compared the potential to increase the gastric residence time of these effervescent granules with that of a hydrogel forming extended release tablet based on HPMC. The extended release tablet represents a common approach of a large monolithic dosage form to continuously release drug into the stomach. Furthermore, the effervescent granules were also administered under fasted state conditions to investigate the absorption profile of the incorporated caffeine when intragastric chyme is not present prior to intake.

2. Material

Caffeine, citric acid (anhydrous), glycerol anhydrous, black iron oxide (E172) and blue food coloring (E131) were obtained from Caesar & Loretz GmbH (Hilden, Germany). Macrogol 4000, magnesium stearate and silicon dioxide have been purchased from Fagron GmbH & Co. KG (Barsbüttel, Germany). Mannitol (Mannogem EZ) as well as sodium hydrogencarbonate (EfferSoda 12) were obtained from SPI Pharma (Wilmington, USA) Microcrystalline Cellulose (VIVAPUR 101) was purchased from JRS PHARMA GmbH & Co. KG (Rosenberg, Germany). Kollidon 90F and Kollicoat IR were ordered from BASF SE (Ludwigshafen, Germany). Hypromellose (Methocel K4M) was obtained from Dow Pharma & Food Solutions (Bomlitz, Germany). Polyvinyl alcohol (PVA) 4–88 Parteck MXP was supplied by Merck KGaA (Darmstadt, Germany). Lactose-monohydrate was purchased from DFE Pharma (Goch, Germany).

The components of the meal consisting of bacon (Tulip bacon, Tulip Food Company, Hamburg, Germany), butter (Meggle Alpenbutter, MEGGLE GmbH & Co. KG, Wasserburg, Germany), white toast (Sammy's Super Sandwich, Harry-Brot GmbH, Schenefeld, Germany), eggs (Freilandeier Größe L, Poseritzer EierHOF, Poseritz, Germany), hash browns (Gut&Günstig Rösti-Ecken, Gut&Günstig brand of the EDEKA group, Hamburg, Germany), whole milk (Gut&Günstig H Vollmilch 3.5 % Fett, Gut&Günstig brand of the EDEKA group, Hamburg, Germany) were purchased at a local supermarket.

Hydrochloric acid for the preparation of dissolution media was purchased from Walter-CMP GmbH & Co. KG (Kiel, Germany). Sodium hydroxide has been ordered from Honeywell Fluka (Seelze, Germany).

Sodium chloride was obtained from Sigma-Aldrich (Steinheim, Germany). Potassium dihydrogen phosphate was purchased from neoLab Migge GmbH (Heidelberg, Germany).

All solvents used for LC-MS analysis, *i.e.* water, methanol, formic acid and acetonitrile were purchased in LC-MS grade from VWR international (Fontenay-sous-Bois, France). Ammonium acetate was obtained from Merck KGaA (Darmstadt, Germany).

3. Methods

3.1. Preparation of effervescent granules

In Table 1, the composition of the effervescent granules is presented. The manufacturing process was identical with the manufacturing in a previous study [38].

All ingredients were pulverized, dried and sieved. The compounds were mixed and the granules were formed by hot melt extrusion using a twin-screw extruder (Three-Tec ZE12, Three-Tec GmbH, Seon, Switzerland). Here, screws with a diameter of 12 mm and a length/diameter ratio of approximately 20:1, four heatingheated zones, and a water-cooled feeding zone was used. The dried powder mixture was fed using a Flat-Tray Fedder (ZD 9 FB, Three-Tec GmbH, Seon, Switzerland) and the extrusion was performed without a nozzle plate at a rotation speed of 100 rpm. The filling rate of the extruder by the Flat-Tray Feeder was set to 15% and the filling segment was cooled to 20 °C and all four heated zones of the extruder were tempered to 70 °C. The extruded granules were collected on a glass container and after a cooling period the size distribution of the manufactured granules were determined by the use of a sieve tower (Retsch AS 200 basic Retsch GmbH, Haan, Germany). The granules were assigned in three fractions and the 0.5 – 1.7 mm fraction was used to fill the granule carrier [38].

3.2. Preparation of granule carrier

The produced granules were covered by a thin polymer layer to avoid oral caffeine contamination after ingestion. In Table 2, the composition of the granule carriers is shown.

The detailed description of the manufacturing process can be also found in our previous publication [38]. Briefly, a test tube was dip coated into the polymer solution. After drying, this procedure was repeated twice, to create a round and stable film and a reproducible form. The round carrier was filled with 1.5 g of the granule (corresponding to 100 mg caffeine) and sealed with a small amount of polymer solution.

Table 1
Composition of the effervescent granules [38].

Compound	Quantity (%)	Manufacturer
Caffeine	6.67	Caesar & Loretz GmbH (Hilden, Germany)
Sodium hydrogen carbonate - EfferSoda 12®	26.07	SPI Pharma (Wilmington, USA)
Citric acid, anhydrous	9.93	Caesar & Loretz GmbH (Hilden, Germany)
Microcrystalline cellulose (MCC) VIVAPUR 101®	20.00	JRS PHARMA GmbH & Co. KG (Rosenberg, Germany)
Polyvinylpyrolidone (PVP) Kollidon 90F®	2.00	BASF SE(Ludwigshafen, Germany)
Mannitol – Mannogem EZ	8.67	SPI Pharma (Wilmington, USA)
Macrogol 4000	20.00	Fagron GmbH & Co. KG (Barsbüttel, Germany)
Lactose monohydrate	6.67	Caesar & Loretz GmbH (Hilden, Germany)

Table 2
Composition of the effervescent granule carriers.

Compound	Quantity (%)	Manufacturer
Polyvinylalcohol (PVA) 4–88 Parteck MXP®	10	Merck KGaA (Darmstadt, Germany)
Polyvinyl alcohol-polyethylene glycol copolymer (Kollicoat® IR)	20	BASF SE (Ludwigshafen, Germany)
Glycerol (anhydrous)	5	Caesar & Loretz GmbH (Hilden, Germany)
Deionized water	64	
Blue food colorant (E131)	1	Caesar & Loretz GmbH (Hilden, Germany)

3.3. Preparation of the ER tablet

The composition of the tablet is summarized in Table 3.

Caffeine, HPMC, lactose monohydrate, MCC and PVP were mixed in a 3D shaking mixer (TURBULA Typ T2F, Willy A. Bachofen AG, Muttenz, Switzerland) at a speed of 49 rpm for 10 min. Water was added to create granules with a size of 1 mm. These granules were dried in a drying cabinet (FDL 115–230 V, Fa. BINDER GmbH, Tuttlingen, Germany) for 2 h at 50 °C. The dried granule was mixed with silicon dioxide for 3 min. After the addition of magnesium stearate, the mixing process was continued for another 2 min. Subsequently this mixture was pressed into biconvex oval (capsule shaped) tablets by the use of a rotary tablet press (PICCOLA – CLASSIC B-D 4 + 4, RIVA EUROPE, Hampshire, UK) with a targeted breaking strength of 100 N.

Black iron oxide (E172) was added to enable the detection of the tablet for MRI measurements. Each 20 x 9 mm oval tablet should weigh 800 mg and contain 100 mg caffeine as well as 10 mg iron oxide.

The mass of the tablets was determined using an analytical balance (Sartorius MSW2.8-S-0CE, Sartorius AG, Göttingen, Germany). The resistance to crushing of the tablets was tested with the tablet hardness tester TBH 210 (ERWEKA GmbH, Heusenstamm, Germany).

3.4. In vitro testing of the dosage forms

The dissolution behavior of the ER tablet was investigated in a compendial paddle apparatus (PT-DT70, PharmaTest Apparatebau AG, Hainburg, Germany) in 900 mL 50 mM phosphate buffer pH 6.8 at 37 °C at a rotational speed of 75 rpm. The dissolution behavior of the effervescent granules in compendial (USP 2) and biorelevant (GastroDuo) test setups have been reported in a previous publication [38].

The quantification of caffeine was performed by a UV/VIS-spectrophotometer (Cary 60 UV–VIS, Agilent, Santa Clara, CA, USA) that was equipped with a fiber optic system. The detection wavelength was 272 nm. A second measurement was performed at 500 nm for

Table 3
Composition of the ER tablet.

Compound	Quantity (%)	Manufacturer
Caffeine	12.35	Caesar & Loretz GmbH (Hilden, Germany)
Hydroxypropylmethylcellulose (HPMC)	14.81	Dow Pharma & Food Solutions (Midland, USA)
Lactose monohydrate	45.93	DFE Pharma (Goch, Germany)
Microcrystalline cellulose (MCC)	21.73	JRS PHARMA GmbH & Co. KG (Rosenberg, Germany)
Polyvinylpyrrolidon (PVP)	1.98	BASF SE (Ludwigshafen, Germany)
Silicon dioxide	0.99	Fagron GmbH & Co. KG (Barsbüttel, Germany)
Magnesium stearate	0.99	Fagron GmbH & Co. KG (Barsbüttel, Germany)
Black iron oxide (E172)	1.23	Caesar & Loretz GmbH (Hilden, Germany)

baseline correction.

3.5. In vivo study

Twelve healthy volunteers (six female and six male) aged between 20 and 27 years (BMI 18—30 kg/m^2) were included. Written informed consent was obtained from each participant. Inclusion and exclusion criteria were adapted to EMA and FDA guidance for bioequivalence studies [39,40]. Known problems in swallowing larger monolithic dosage forms as well as metallic implants led to exclusion of candidates due to the large granule carriers and MRI investigation.

The study was performed in a cross-over-design with four study arms in fixed sequence. All volunteers followed the same sequence of study arms (1 → 2 → 3 → 4) on different days with a wash-out phase of at least 72 h. The volunteers had to start with study arm 1 to avoid dropouts, due to possible problems in swallowing the relatively large granule carriers. These procedures were in accordance with the Declaration of Helsinki (2013, Fortaleza, Brazil) and the Professional Code for physicians in Germany (amended 2015 in Frankfurt, Germany). The ethics committee of the University of Greifswald approved the study protocol and all related documents. (Registration number BB 203/18b). The study is registered in the German Clinical Trials Register (DRKS00031999).

Seventy-two hours before intake of the dosage form, the volunteers had to abstain from caffeine containing products. The consumption of food and beverages prior to and during the study day was restricted. The volunteers had to abstain from food for 10 h The major procedures of the study days are shown in Table 4.

The volunteers had to ingest the high fat meal within 15 min in the first three study arms. The composition of the meal was in accordance with the recommendation for a high caloric meal of the FDA guidance for assessing the effect of food on orally administered drugs [39].

The total energy content of the meal amounted to 1000 kcal. More specifically, it consisted of two slices of bacon, two slices of white toast with butter, two fried eggs in butter, 113 g of hash brown potatoes and a glass (240 mL) of whole milk.

30 min after the beginning of the meal, the dosage forms were administered, either with 20 mL (study arm 1) or 240 mL of still water (study arm 2 and 3). Five minutes prior to the intake of the dosage form, the participants had to provide a blank saliva sample. Over the following 6 h, the participants had to collect saliva samples at 2.5, 5, 15, 15, 20, 25, 30, 45, 60 min, and onwards after every 15 min. Ingestion of food and drinks was prohibited during this period. Thus, 4 h after the intake of the dosage form, the participants received 240 mL of still water. In addition, the participants were asked, to refrain from strenuous physical exercise

The study protocol for the fourth arm differed slightly, as the granule bags had to be taken in the fasted state. In all study arms, the volunteers had to fast for at least 10 Again, 5 min prior to the intake of the granule carrier, a blank saliva sample had to be taken by the volunteers. After the intake of the granule carrier together with 240 mL of still water, saliva sampling continued for 12 h with the same sampling schedule as on the other study days. After 4 h, the volunteers received a standardized meal (Spaghetti Bolognese, apetito AG, Theine, Germany) together with 240 mL of still water. After completion of the first 6 h, saliva samples were taken every hour.

3.6. Determination of salivary caffeine concentrations

Caffeine is an established marker for gastric emptying [41]. It is highly soluble at gastrointestinal pH values and highly permeable (BCS class 1) [42]. The rate limiting step in caffeine absorption is the emptying of the drug from the stomach. As salivary caffeine kinetics correlate with plasma concentration profiles, the absorption of caffeine can be studied by determining its salivary concentrations [43,44]. Therefore, in this study, the salivary pharmacokinetics of caffeine could be applied to evaluate the gastric residence time of caffeine indirectly. A slow and continuous increase of salivary caffeine concentration would indicate a slow emptying of the drug from the stomach into the small intestine.

Saliva samples of the volunteers were collected by spitting into SafeSeal 2 mL microtubes (Sarstedt, Nümbrecht, Germany). Stimulating the saliva flow by chewing on parafilm, using citric acid or other commonly used techniques was not allowed. Saliva samples were stored at −80 °C until further preparation and analysis. Saliva samples were analyzed with a validated LC-MS/MS method. The bioanalytical method has been validated and the parameters can be found in a recent work [45]. The samples were thawed at room temperature, vortexed and centrifuged at 18,000 rpm for 15 min (SIGMA 3 – 30 KH, Sigma Zentrifugen GmbH, Deutschland). 100 µL of the supernatant was transferred into 1.5 mL microtubes (Sarsted, Nürnbrecht, Germany) and mixed with 200 µL of acetonitril and 6 % formic acid, to precipitated the proteins of the saliva sample. The mixtures were vortexed again for 1 min and again centrifuged at 13,000 rpm for 15 min. 150 µL of the supernatant was transferred in a 300 µL microtube and mixed again with 150 µL of water (containing 4 % formic acid). The prepared samples were analyzed by a use of an Agilent 1100 series HPLC system (Agilent Technologies, Waldbronn, Germany) coupled to a triple quadrupole mass spectrometer API4000 QTRAP (AB Sciex, Darmstadt, Germany) via the electrospray ionization source Turbo V^{TM} [41].

3.7. Magnetic resonance imaging

In the third arm of the study, the localization and condition of the ER tablet in the gastrointestinal tract was assessed by MRI 4 h after the administration of the dosage form. These examinations were performed using a Siemens MAGNETOM Aera MR–Scanner (Siemens Healthcare, Erlangen, Germany) with a field strength of 1.5 T. The volunteers were in supine position and were asked to hold their breath to reduce motion artefacts in the images. Two true fast imaging with steady precession (TRUFI) sequences (transversal and coronal) were acquired. The sequences had a repetition time of 3.55 s, an echo time of 1.48 s, a flip angle of 61 – 64° and a slice thickness of 5 mm. The voxel size was 0.98 x 0.98 x 5 mm^3 for the coronal and 0.88 x 0.88 x 5 mm^3 for the transversal scans, respectively. TRUFI sequences were chosen because of their sensitivity to artefacts caused be the iron oxide that was included in the tablets. Images were evaluated by use of Horos v2.2.0 freeware (The Horos Project).

3.8. Statistics

Due to caffeine contamination of the blank saliva sample by

Table 4
Overview of the study procedures.

		Day 1	Day 2	Day 3	Day 4
Administered dosage form		Effervescent granules	Effervescent granules	ER tablet	Effervescent granules
Amount of administered still water		20 mL	240 mL	240 mL	240 mL
Meal intake	Prior application of the dosage form	High caloric meal (1000 kcal)	High caloric meal (1000 kcal)	High caloric meal (1000 kcal)	Fasted
	During study day	–	–	–	Lunch after 240 min
Magnetic resonance imaging		No	No	Yes	No
Saliva sampling time (h)		6	6	6	12

volunteers not complying with the restrictions, the caffeine of the blank saliva sample was subtracted from all subsequent salivary caffeine concentrations for statistical analysis. In the case of oral contamination with caffeine from a dosage form, apparent by an initial peak at the first sampling point with subsequent decline of concentration, all following salivary caffeine concentrations were excluded from determining C_{max} and calculating the mean caffeine concentration profile and the AUC until the next minimal concentration value was reached. The AUC was calculated by applying the linear trapezoidal rule using Microsoft Excel 2019 (Microsoft Corporation, Redmont, WA, USA).

The parameters C_{max}, $t_{max,}$ $AUC_{0\text{-}120}$ and $AUC_{0\text{-}360}$ were statistically compared for all study arms. It was checked, if the datasets were normal distributed. For this purpose, Kolmogorov-Smirnov test and D'Agostino and Pearson omnibus normality test were applied. If one dataset did not comply with normal distribution, all datasets were compared non-parametrically. If this was the case, non-parametric Friedman test with Dunn's post-hoc test was used. For normal distributed datasets, a one-way ANOVA with Tukey post-hoc test was applied. All statistical evaluations were performed with GraphPad Prism 5 (GraphPad Software, Inc., San Diego, CA, USA).

3.9. Wagner-Nelson deconvolution

The Wagner-Nelson method was used to estimate the percentage of caffeine absorbed [45]. This equation (1) uses deconvolution to calculate the fraction in a single compartment model. Due to the rapid and complete absorption of caffeine in the small intestine, the calculated fraction of absorbed caffeine A represents the amount of caffeine emptied out of the stomach.

$$A = V_D{*}C_p + k_{10}{*}\int_0^t C_p{*}dt \quad (1)$$

The fraction absorbed A was calculated with $k_{10} = 0.0027\ min^{-1}$ as determined from the mean plasma concentrations profiles obtained in the fasted study arm and the volume of the inner central compartment (V_D) = 90 L.

All parameters used to calculation are presented in Table 5.

4. Results

The carrier that is filled with granules is shown in Fig. 1. The carrier had a cylindrical shape with a length of about 22 mm and a diameter of about approximately 16 mm. As mentioned above, the granule bag was filled with 1.5 g of granules corresponding with 100 mg caffeine.

4.1. In vitro results

As described above, the results of the *in vitro* tests of the granule filled carrier can be found in our recent publication [38]. Overall, the effervescent granules showed a fast and complete release of the contained caffeine. As can be seen in Fig. 2, the polymer carrier did not substantially delay the release of the model drug. More than 90 % of the incorporated caffeine was released after 2 min.

Table 5
Used parameters of the Wagner-Nelson equation to deconvolution of fraction absorbed.

Variable of Wagner-Nelson equation	
t	time/min
C_p	Mean concentration units at timepoint t/ng/mL
V_D	90 L
k_{10}	0.0027 min^{-1}
dose	100 mg

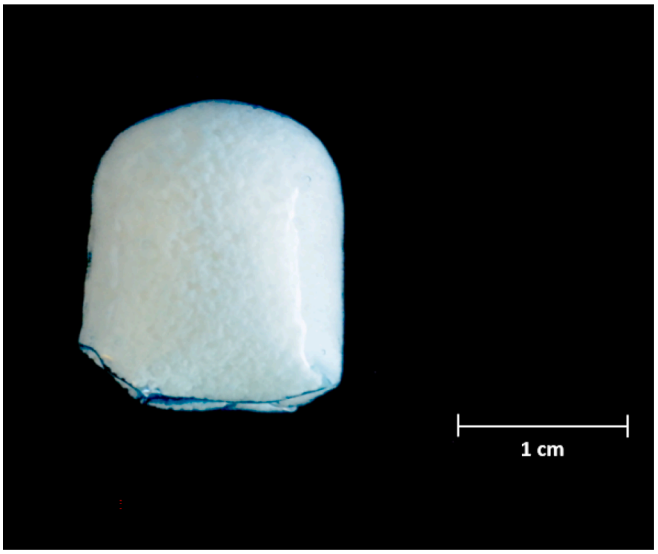

Fig. 1. Polymer granule carrier filled with 1.5 g of the granule (corresponding to 100 mg caffeine) for administering in the *in vivo* study.

The extended release tablet showed a sustained release in the compendial paddle apparatus. Only after 9 h, more than 85% of the caffeine dose was released. As can be seen in Fig. 2 after 60 min, there was a decrease of the amount of released caffeine and an increase in variability. This was probably related to large amounts of iron oxide, that sedimented on the mirror of the fiber optics. However, by tapping the fiber optics, the sedimented particles could be removed.

4.2. In vivo study

The individual salivary concentration profiles are shown in Fig. 3. In some cases, low concentrations of caffeine were measured in the blank samples of some volunteers. These blank caffeine concentrations were subtracted from all measured values. In the case of oral contamination with caffeine from a dosage form, apparent by an initial peak at the first sampling point with subsequent decline of concentration, all following salivary caffeine concentrations points were excluded until the next minimal concentration value was reached.

The mean salivary caffeine profiles after intake of the dosage forms are shown in Fig. 4.

Overall, the intake of the effervescent granules with 240 mL water in fasted state led to the shortest t_{max}. As shown in Fig. 5, the $AUC_{0\text{-}120}$ was significantly higher compared to the fed state study arms. In contrast, $AUC_{0\text{–}360}$ was similar for all four study arms, showing that the total exposure was identical.

After administration of the ER tablet, salivary caffeine concentrations increased slowly in the initial phase. However, the $AUC_{0\text{-}120}$ was not statistically different compared to the postprandial administration of the effervescent granules with 20 or 240 mL still water. In addition, C_{max} was reached earlier in most cases after the postprandial intake of the ER tablet compared to the granules, although no statistically significant difference of t_{max} between the fed state study arms was observed (Fig. 5).

The salivary concentration profiles resulting for the application of the granules with 20 or 240 mL water were well comparable. Overall, a slow and continuous increase of salivary caffeine concentrations was observed. C_{max} was reached significantly later compared to the administration in the fasted state as can be seen in Fig. 5.

After 4 h, the integrity of the ER tablets was investigated by MRI. In 10 out of 12 subjects, disintegration of the ER tablets was observed. An exemplary image, which shows dispersed fragments of the tablet, can be seen in Fig. 6. The intact tablets were located in the stomach in both subjects. In five subjects, the fragments of the tablet were located

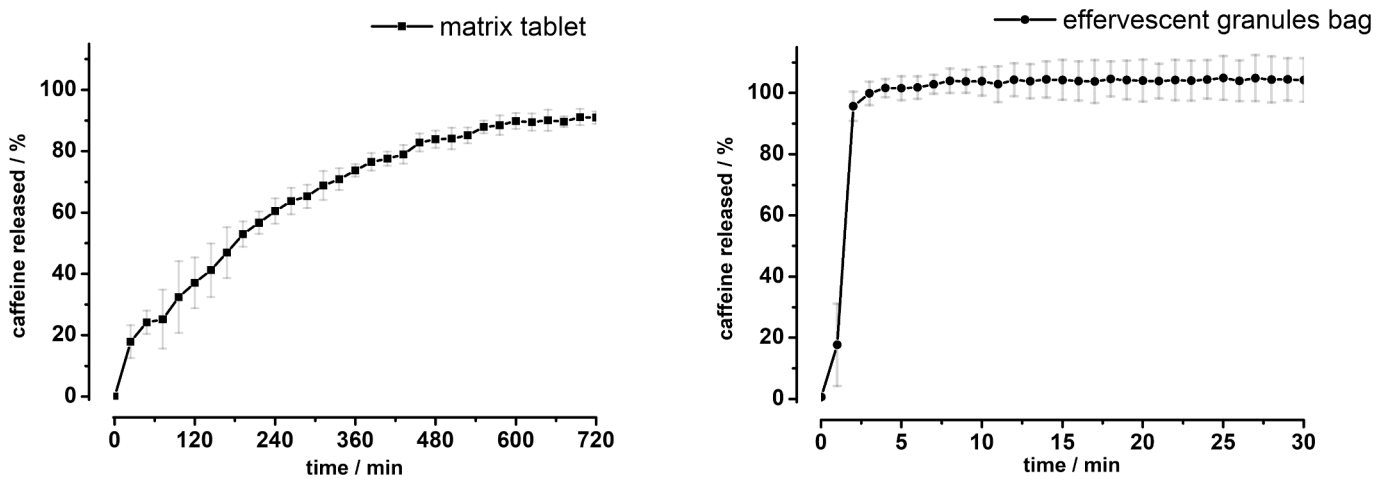

Fig. 2. Dissolution profile of the ER tablet (left) in the paddle apparatus with a stirring speed of 75 rpm, at 37 °C, in 900 mL 50 mM phosphate buffer pH 6.8. Dissolution profile of the effervescent granules bag (right) in the paddle apparatus with a stirring speed of 75 rpm, at 37 °C, in 900 mL 50 mM phosphate buffer pH 6.8 (All values are shown as n = 5 ± SD).

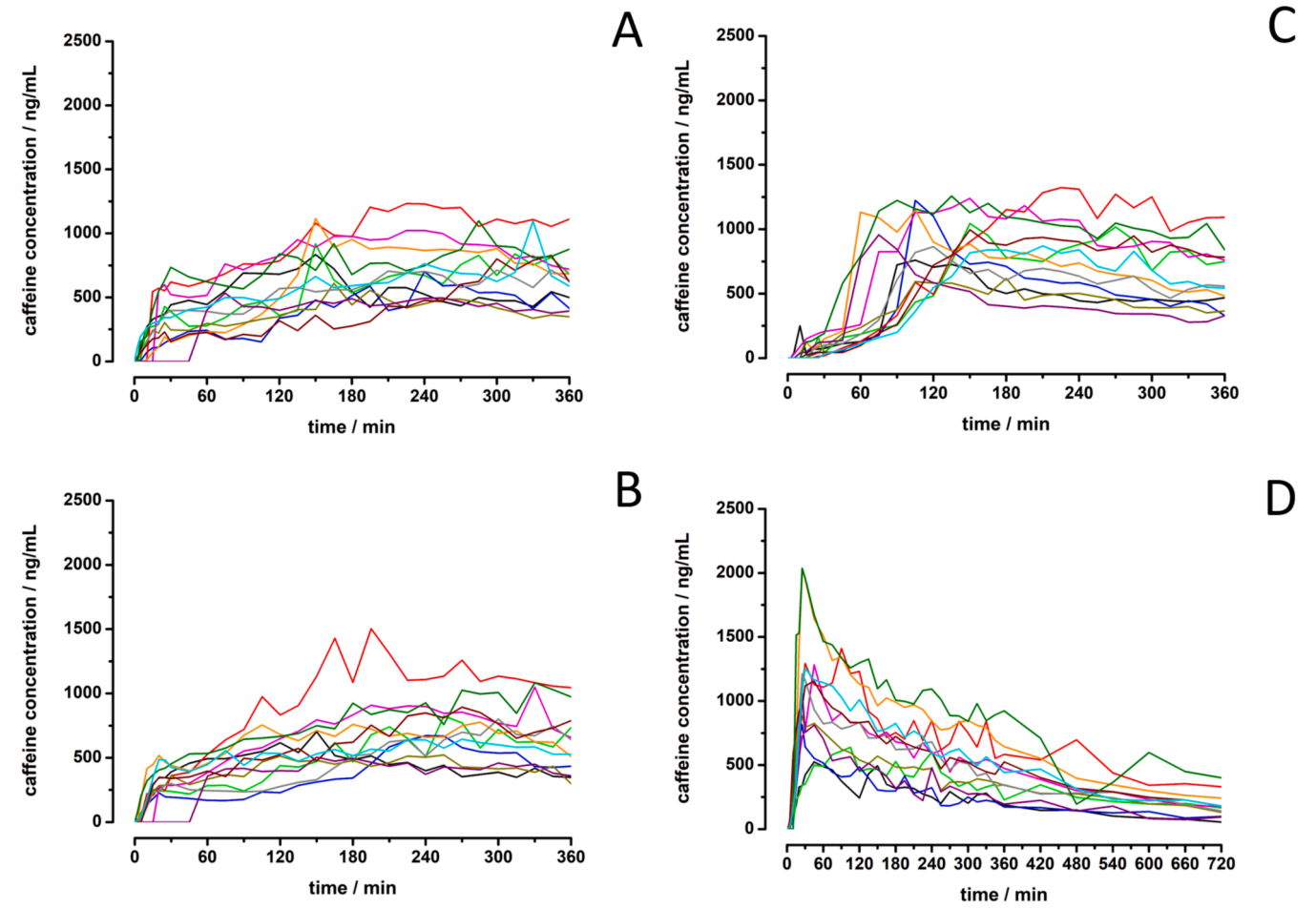

Fig. 3. Individual salivary caffeine concentration profiles (spaghetti plots) (A) Effervescent granules taken with 20 mL water in fed state. (B) Effervescent granules taken with 240 mL water in fed state. (C) ER tablet taken with 240 mL water in fed state. (D) Effervescent granules taken with 240 mL water in fasted state. Subjects are colored the same in all graphs.

exclusively in the stomach. In the other five subjects, the fragments of the tablet were distributed in the stomach and the small intestine.

The results of the deconvolution are presented in Fig. 7, where the fraction absorbed is presented as inverted fraction remaining in the stomach.

Overall, the intake of the effervescent granules with 240 mL in the fasted state led to the smallest fraction of dose remaining in the stomach after 30 min. The calculated dose remaining in the stomach increased after 45 min due to variability of the used mean for calculation. The fraction of caffeine remaining decreased very similar after intake of the

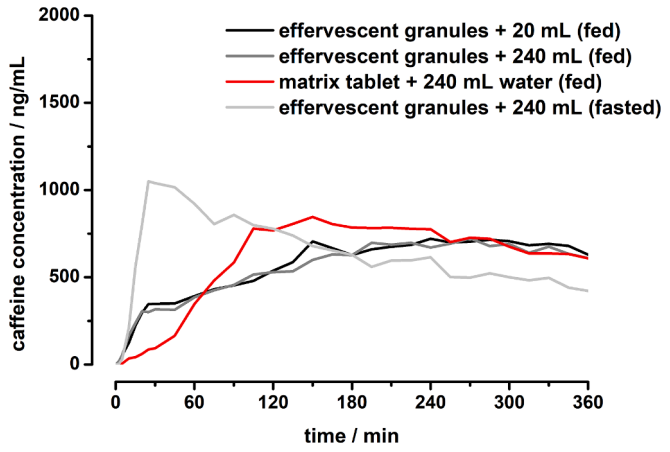

Fig. 4. Mean salivary caffeine concentration profiles after the intake of the effervescent granules together with 20 mL water (black) and 240 mL water (dark gray) in fed state, the ER tablet together with 240 mL water in fed state (red) and after intake of the granules together with 240 mL water in fasted state (light gray). (n = 12).

effervescent granules with 20 or 240 mL of water.

5. Discussion

The objective of this study was to develop a dosage form that prolongs gastric residence time while achieving homogeneous distribution in the stomach filled with chyme, thus enabling a local therapy. Two different dosage forms, an effervescent granule formulation and an extended-release tablet, were tested. Both formulations contained caffeine as the model drug. The effervescent granules were designed to disintegrate rapidly and mix their contents into the chyme by the release of carbon dioxide. The granule carrier contained 1.5 g of the effervescent granule. This is equal to 391 mg sodium hydrogen carbonate, which would be converted to 205 mg carbon dioxide [38]. Onwards a slow emptying of the incorporated model drug caffeine together with the chyme into the small intestine was expected. In a previous study, the effervescent granules administered with 240 mL still water led to a significantly prolonged gastric residence time of the active substance compared to the administration a non-effervescent granule formulation with 240 mL still water, or administration of non-effervescent granules with 240 mL sparkling water [38].

The gastric residence time of the model drug caffeine was indirectly evaluated by its salivary pharmacokinetics. This non-invasive technique is an established method for determining gastric emptying since caffeine is immediately absorbed and distributed after emptying from the stomach [41]. Thus, by determining salivary caffeine kinetics, it is possible to estimate the amount of drug, which was still remaining in the stomach.

After application of the effervescent granules in fasted state, a fast and pronounced increase of salivary caffeine concentrations could be observed. This resulted in a significantly shorter t_{max} and a significantly increased $AUC_{0\text{-}120}$ compared to all fed state study arms (Table 6). This was related to the rapid emptying of the co–administered water into the duodenum, together with the dispersed caffeine. The gastric water emptying in the fasted state normally follows a first-order like kinetic with 240 mL of water getting emptied from the stomach within 15 to 45 min [18,19]. Obviously, the granules disintegrated and released the incorporated caffeine very fast. Due to that, the obtained salivary caffeine concentration profiles after the intake of the granules in the fasted state were similar to previous results described in the literature [38].

Here, effervescent granules were compared with ER tablets in the fed state. Due to the food digestion related gastric retention of large particles

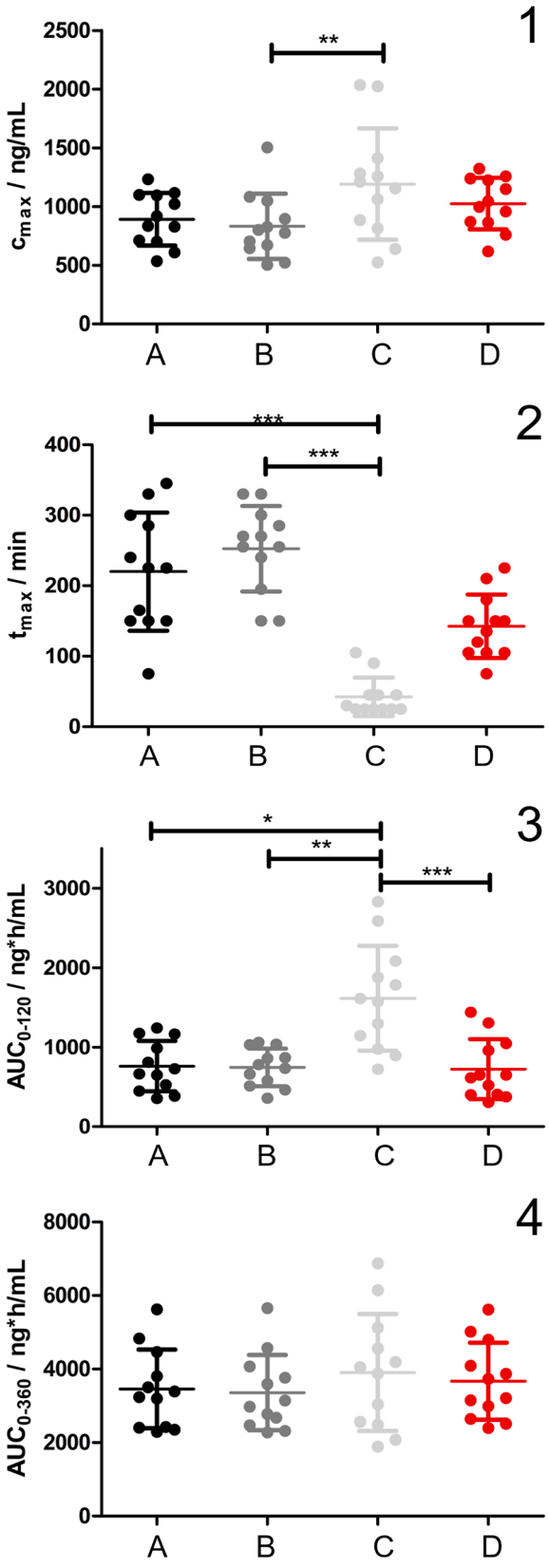

Fig. 5. (1) Salivary $C_{max,}$ (2) t_{max}, (3) $AUC_{0\text{-}120}$ and (4) $AUC_{0\text{-}360}$ of caffeine after the administration of the effervescent granules with 20 mL water in (A) and 240 mL water (B) in the fed state, effervescent granules taken with 240 mL water in fasted state (C) and ER tablet taken with 240 mL still water in the fed state (D) (n = 12, mean ± SD, points represent individual values). Significant difference of t_{max} and C_{max} and checked by Friedmann's test with Dunn's post-hoc test. *($p < 0.05$), **($p < 0.01$), ***($p < 0.001$).

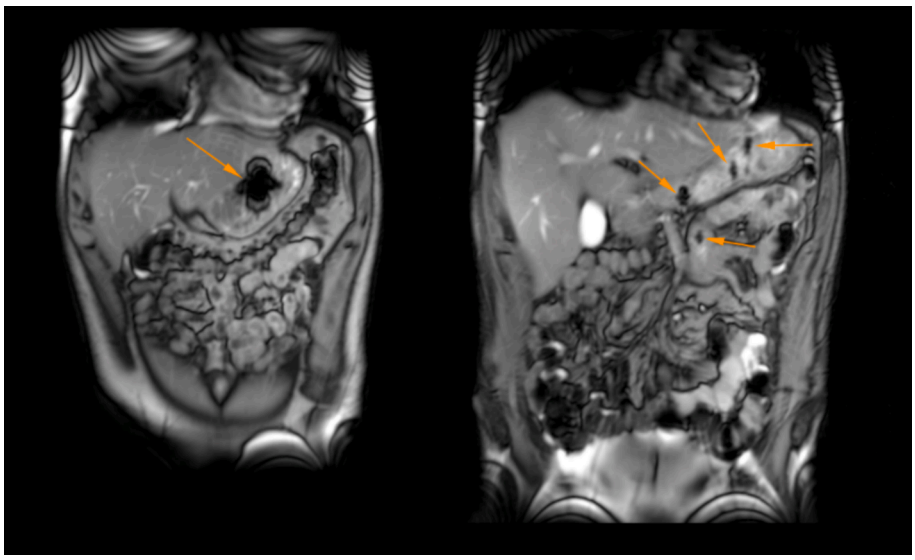

Fig. 6. Exemplary coronal T2 weighted MRI images taken 4 h after food intake. Objects are indicated by arrows. In the left image an intact tablet is located in the stomach (subject 9). In the right image, dispersed fragments of a tablet are located in the stomach and in the small intestine (subject 1).

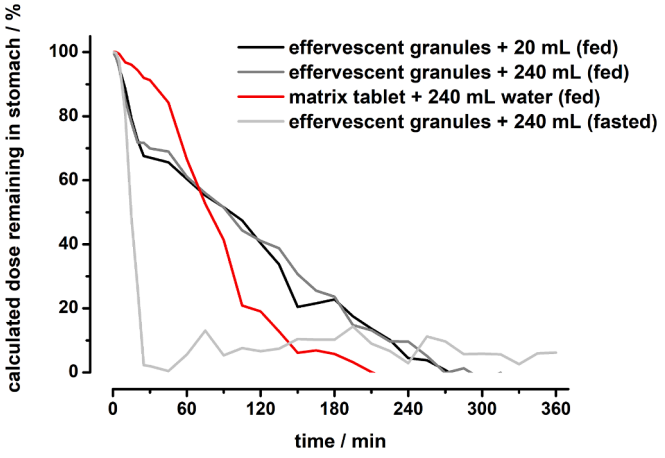

Fig. 7. Fraction of caffeine remaining in the stomach after intake of the effervescent granules together with 20 mL water (black) and 240 mL water (dark gray) in fed state, the ER tablet together with 240 mL water in fed state (red) and after intake of the granules together with 240 mL water in fasted state (light gray). (n = 12).

Table 6
Pharmacokinetic parameters divided by treatment (n = 12; mean ± SD). Effervescent granules taken with 20 mL water in fed state (A). Effervescent granules taken with 240 mL water in fed state (B). ER tablet taken with 240 mL water in fed state (C). Effervescent granules taken with 240 mL water in fasted state (D).

PK parameter	A	B	C	D
c_{max}/ng/mL	891.5 ± 223.7	831.6 ± 278.1	1025 ± 220.6	1192 ± 474.2
t_{max}/min	220.0 ± 83.96	252.5 ± 60.62	142.5 ± 45.00	42.50 ± 27.26
$AUC_{0\text{-}120}$/ng*h/mL	760.6 ± 316.4	744.9 ± 236.0	722.6 ± 378.5	1615 ± 660.3
$AUC_{0\text{-}360}$/ng*h/mL	3459 ± 1070	3358 ± 1023	3668 ± 1048	3906 ± 1590

as the tested ER tablet, it is unlikely that the dosage form is able to pass through the pylorus and enter into the small intestine during the first hours after administration of the dosage form. In this study, this assumption was supported by the fact that no intact tablet could be found in the small intestine on any of the MRI images taken after 4 h. In fact, tablet fragments were found only in the stomach and very few in the small intestine.

After ingestion of the ER tablet together with food and 240 mL still water only low salivary concentrations were observed within the first 30 min. Slowly increasing caffeine concentrations in all subjects in the initial phase indicated a prolonged release of caffeine into the gastric content due to the fact that caffeine would get rapidly absorbed after emptying in the small intestine [44]. Obviously, the ER tablet swelled and the model drug was released slowly, such as *in vitro* dissolution profiles would have suggested. This indicated that the gastric residence time of the incorporated caffeine was controlled by the erosion rate of the ER tablet as well as the emptying rate of the administered food out of the stomach. However, compared to the administration of the effervescent granules under postprandial conditions together with still water, t_{max} tended to be shorter after administration of the ER tablet. This could be related, as already described previously in the literature, to insufficient mechanical robustness of the dosage form in combination with the high and continuous pressure and shear forces, which are present in the distal postprandial stomach [46–49]. These mechanical stresses might have led to a kind of dose dumping from the ER dosage form as indicated by the rapid caffeine emptying from the stomach. This assumption is supported by the MRI images taken after 4 h. However, these physiological factors could have accelerated the drug release vastly and have possibly also adversely affected the robustness of the ER tablet [50–52]. Some tablet fragments had even been emptied from the stomach, because of a size which allows emptying from the stomach even under fed state conditions. Moreover, they also could have presented a higher dissolution rate due to an increased effective surface area for drug release. It should be mentioned, that mechanical sensitivity and other characteristics are often dependent on the type and amount of HPMC [53]. This increases the tablets susceptibility to pressure and shear forces. These forces are highly dependent on the position of the tablet in the stomach and therefore often contribute to a high variability of plasma profiles [15,16].

The stability, the release rate and therefore the gastric residence time of the extended release tablet and the contained drug could possibly be improved by adjusting the amount of HPMC, as well as by adjusting pressure forces during the manufacturing process. Jain *et al.* showed that the erosion rate of ER tablets decreased with increasing amounts of HPMC [53]. The use of higher pressing forces (>100 N) during the manufacturing process could also result in a better resistance to the high

intragastric mechanical forces. Furthermore, the disintegration and dissolution processes from monolithic ER dosage forms also depends on the position of the dosage form in the postprandial stomach [32,33].

After administration of the effervescent granules with 20 and 240 mL still water under postprandial conditions, comparable caffeine profiles were obtained. These were also similar to the profiles obtained with the same effervescent granule formulation in a previous study [38]. In the fed state, a rapid initial rise of salivary caffeine concentrations could be observed, even besides oral contamination in some subjects. As can be seen in our recently published study, the granule carrier showed a rapid *in vitro* disintegration after contact with the co-administered water. This suggests that the carrier rapidly disintegrated within the stomach and releases the granules with the embedded caffeine. Thus, this has no influence on the emptying and absorption process. This indicates, that in fed state, the rate of absorption in the small intestine is controlled only by the gastric emptying of the chyme. Accordingly, the fast initial rise of salivary concentrations could be explained by the emptying of a part of the caffeine already together with the administered water by the mechanism of the stomach road. As can be seen in Fig. 7, after application of the effervescent granules, approximately 30% of the administered dose were immediately emptied with the co-administered water within the first 30 min. This is because, the predominant amount of postprandially administered water usually does not mix with the chyme, but is rapidly emptied into the small intestine [18,20]. It remains unclear to which extent an intermixing due to local effervescent affects the stomach road happened, but in general it still seems to be present. Likewise, small particles such as granules or drug particles that are dissolved or dispersed in the water can be rapidly emptied from the stomach. This might be an explanation for the difference of the emptied amount of caffeine within the first 30 min between the effervescent granules and the monolithic ER tablet, which showed a depletion of 8% of the contained caffeine within the first 30 min.

However, after the fast initial rise, salivary caffeine concentrations only increased at a low rate, indicating a slow and continuous emptying of the drug from the stomach into the intestine, as can be seen in Fig. 4. The respective mean C_{max} was measured beyond 200 min after the intake of the dosage form in the effervescent granules study arms. In fact, a concentration of over 600 ng/mL was maintained by the effervescent granules in the fed state from 165 min to the end of the measurements after 360 min. In contrast, in the fasted state arm with the effervescent granules overall C_{max} was determined 43 $\pm$ 27 min after meal ingestion and thus much earlier than in the fed state trials. Both granule arms showed the similar profile of remaining dose in the stomach too. All granule profiles suggested, that the carbon dioxide released by the granules led probably to a prolonged gastric residence time due to an intense mixing of caffeine into the gastric contents. This seemed to be regardless of the amount of the co-administered water. This was in line with the results of the previous study and confirmed again, that the incorporated carbon dioxide led to a significantly slower onset of caffeine after administration of the effervescent granules with water [38]. However, the results of both granule arms suggested, that the mixing process is possibly independent to the different gastrointestinal conditions. This is because, as mentioned before, the caffeine profiles after application of the effervescent granules in fed state were very consistent. It should also be noted, that the profiles are very similar regardless of the amount of co-ingested water.

After the intense mixing with the high-caloric food, caffeine was emptied together with the chyme into the small intestine. The gastric emptying rate usually follows a calorie-controlled zero order kinetic with described emptying rates of 2 – 4 kcal/min [20]. Due to the total energy content of 1000 kcal of the high-fat meal, the gastric residence time of the mixed caffeine was improved vastly. Koziolek *et al.* showed that the intragastric volume after the ingestion of the same high-fat meal, as in the presented study, does not reach fasted state values even within 6 h after meal ingestion [20]. In the best-case scenario, the model drug would have been mixed homogenously into the chyme. Then it would be emptied over several hours from stomach and rapidly absorbed in the small intestine, resulting in prolonged onset of salivary caffeine concentrations. The fraction of caffeine remaining in the stomach incorporated by effervescent granules decreased similar between both granule arms. The calculated emptying rates for the caffeine and therefore for the caffeine containing chyme of both granules arms were 0.248 %/min for the study arm with 20 mL administered water and 0.242 %/min for the granules administered with 240 mL water. It has to be considered, that the calculated rates were based on the measured values from 30 min to 360 min, in order to not include the amount of emptied caffeine by the co-administered water within the first 30 min. However, compared to the gastric content volume by *Koziolek et al.*, the emptying behavior was slightly faster, indicating almost complete mixing with the chyme [20]. The calculated emptying rate of the chyme in this study was 0.235 %/min over the same time. Otherwise, compared to the gastric emptying of caffeine released by the ER tablet, a prolonged emptying from the stomach was observed. Nevertheless, the ER tablet also showed the desired extended concentration profile in the first 60 min. As mentioned above, due to different *in vivo* factors, the profile of calculated dose remaining in the stomach decreased rapidly.

In fact, the homogeneously intermixing of a drug compound with chyme due to effervescent effect would be advantageous for a local gastric treatment. This is because a homogeneously mixed chyme always implies that a certain amount of the mixed drug has contact with the stomach wall or the desired local site. Therefore, this requires a rapid and complete distribution into the chyme, e.g. in case of antibiotics for *Helicobacter pylori* treatment. Distributing the entire drug and thus achieving a uniform concentration within the chyme would be in a strong contrast to a monolithic dosage form, that typically causes a small area with a higher drug concentration [54]. Thus, by achieving this homogeneous concentration, an important requirement for realizing a local therapy strategy could be met. Indeed, the overall observed t_{max} values after application of the effervescent granules with the different volumes of water in the fed state were approximately 4 h. In addition, the concentration of caffeine remaining in the stomach incorporated by the effervescent granules was higher over a longer period of time, compared to the ER tablet. The constant emptying of the caffeine suggests, that the effervescent granules were mixed homogeneously into the chyme. Different positions of the granule carrier and the released granules would have led to different influence of gastrointestinal conditions, like different motility patters, contact time with the administered water and in general different amount of volumes. Additionally, the gastric motility patterns are different in the various regions of the stomach [16]. By homogeneous mixing of the granules or the released drug compound into the chyme, the variability of these factors was probably reduced and resulted in relatively uniform emptying of the chyme in all subjects. A homogeneous mixing can be assumed due to the small standard deviations of C_{max} and $AUC_{0–120}$. However, the postprandial application of effervescent granules achieved high and constant intragastric drug concentrations for a longer time period. This better and more consistent distribution of caffeine in chyme could imply that local therapies of gastric diseases, such as *helicobacter pylori* infections can be addressed using this approach. The required drug concentrations over a long period of time inside the stomach, could be ensured using these effervescent granules. Such a constant emptying from the stomach also ensures a continuous absorption from the small intestine comparable to gastroretentive systems. This might be beneficial in the therapy of diseases where long lasting drug absorption cannot be achieved due to absorption windows. For example, in the case of furosemide and acyclovir or in case when constant plasma profiles are highly beneficial such as in the treatment of Parkinson's disease with Levodopa [55–57]. Various formulation strategies have been developed to address the major challenge of maintaining Levodopa plasma concentrations, and these effervescent granules represent a new approach [57–59]. However, it must be noted that the utilization of this retardation mechanism is highly dependent on the amount of calories consumed prior to

application of the dosage form. Anyway, in terms of necessary post-prandial application, food effects need to be considered.

Interestingly, the amount of the co-administered water did not have any relevant effect on the initial salivary caffeine concentration profiles after the ingestion of the effervescent granules in the fed state. Due to the more pronounced stomach road effect, which also could take place for a longer time period, a faster increase of the salivary caffeine concentration when administered together with the higher amount of water would have been expected. Subsequently, a higher amount of water and dissolved caffeine would have been emptied into the small intestine. However, this effect was negligible, because in both granule arms only approximately 30% of administered dose were emptied in the first 30 min. As described above, most likely a sufficient mixing of the model drug was achieved by the released carbon dioxide, irrespective of the amount of water applied.

As already mentioned above, a better and more homogeneous mixing into the chyme could be also advantageous for a local gastric treatment such as therapy of *Helicobacter pylori infection*. This local gastric treatment could have the advantage of fewer systemic side effects, compared to the currently established treatment [25,60]. Especially the quadruple therapy is linked with heavy side effects, due to the fact the applied antibiotics have a significant impact on the gastrointestinal microbiota [22,24,61]. Another disadvantage of the present therapies of *Helicobacter pylori infection* is the lack of compliance due to the mentioned side effects and the high frequency of medication intake to achieve effective therapeutic concentrations [25,26,61,62]. Due to that the administration of locally acting antibiotics in the form of effervescent granules in the fed state might be an interesting alternative to the common therapies. As mentioned above, local therapy by amoxicillin eradication is time dependent. Due to that, a prolonged gastric residence time and thus a prolonged contact time to the stomach wall would be a big advantage. Another advantage could be the increased patient compliance, due to the smaller dose regime by administrating the granules in the fed state [24,25]. Overall, the application of effervescent granules in the fed state could be a promising alternative to ensure high concentrations in case of local gastric treatments or to ensure constant concentrations in the small intestine for treatments requiring slow and constant concentration profiles.

6. Conclusion

In the present study, the potential to increase the gastric residence time of a drug by use of effervescent granules was compared with that of ER tablets after ingestion of a high-fat, high-caloric standard meal. After application of the granules with different volumes of water the salivary caffeine concentrations increased slowly and continuously in both fed state study arms. This showed that the released carbon dioxide led to a mixing of caffeine into the gastric content and this effect worked reliably and independent form the amount of co-administered water. The ER tablets used in this study, which represented an established way of enhancing gastric residence time, did not prove to be a comparably reliable approach.

Accordingly, effervescent granules administered after a meal represent a promising alternative for enhancing the gastric residence time of drugs. Effervescent granules can also be used to achieve high local concentrations in the stomach.

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Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki (2013, Fortaleza, Brazil) and the Professional Code for physicians in Germany (amended 2015 in Frankfurt, Germany). The ethics committee of the University of Greifswald approved the study protocol and all related documents. (Registration number BB 203/18b) The study is registered in the German clinical trials register (DRKS00031999).

Informed consent statement

Informed consent was obtained for experimentation with human subjects from all included subjects.

CRediT authorship contribution statement

Constantin Foja: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation. **Stefan Senekowitsch:** Writing – original draft, Methodology, Data curation. **Fabian Winter:** Methodology, Formal analysis. **Michael Grimm:** Data curation. **Christoph Rosenbaum:** Methodology. **Mirko Koziolek:** Supervision, Project administration, Data curation, Conceptualization. **Maximilian Feldmüller:** Validation, Methodology, Conceptualization. **Marie-Luise Kromrey:** Investigation. **Eberhard Scheuch:** Validation. **Mladen V. Tzvetkov:** Writing – review & editing. **Werner Weitschies:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Philipp Schick:** Writing – review & editing, Supervision, Project administration, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Maximilian Feldmüller was an employee of the University of Greifswald during his contribution to this work and is now an employee of Bayer. Mirko Koziolek was an employee of the University of Greifswald during his contribution to this work and is now an employee of Abbvie.

Data availability

The authors are unable or have chosen not to specify which data has been used.

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