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Research Article

Theme: Advancements in Dissolution Testing of Oral and Non-Oral Formulations
Guest Editor: Sandra Klein

Influence of Postprandial Intragastric Pressures on Drug Release from Gastroretentive Dosage Forms

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Abstract. Despite extensive research in the field of gastroretentive dosage forms, this "holy grail" of oral drug delivery yet remained an unmet goal. Especially under fasting conditions, the reproducible retention of dosage forms in the stomach seems to be an impossible task. This is why such systems are often advised to be taken together with food. But also the postprandial motility can contribute significantly to the failure of gastroretentive dosage forms. To investigate the influence of postprandial pressure conditions on drug release from such systems, we used a novel *in vitro* dissolution tool, the dissolution stress test device. With the aid of this device, we simulated three different intragastric pressure profiles that may occur after postprandial intake. These transit scenarios were based on recently obtained, postprandial SmartPill® data. The tested systems, Glumetza® 1000 and Madopar® HBS 125, are marketed dosage forms that are based on different approaches to achieve proper gastric retention. All three transit scenarios revealed a highly pressure-sensitive drug release behavior, for both drugs. For Madopar® HBS 125, nearly complete drug release was observed even after early occurring pressures. Glumetza® 1000 seemed to be more resistant to these, most likely due to incomplete wetting of the system. On the contrary to these findings, data from standard dissolution tests using the paddle apparatus displayed controlled drug release for both systems for about 6 h. Based on these results, it can be doubted that established gastroretentive systems stay intact over a longer period of time, even under postprandial conditions.

KEY WORDS: SmartPill; gastric pressure; dissolution stress test device; *in vitro* model; gastroretentive dosage forms.

INTRODUCTION

Despite decades of extensive research in the field of gastroretentive dosage forms, very few concepts were at best partly satisfactory *in vivo*. Although some dosage forms on the market are termed gastroretentive, the goal of a clearly prolonged gastric residence time under different prandial conditions has not been demonstrated yet. But still, gastroretention of solid oral dosage forms remains highly desired for certain drug substances in order to reduce stability issues, to improve bioavailability and to reduce dosing intervals (1,2).

In general, the three main approaches to achieve prolonged gastric residence time include (I) mucoadhesion to the stomach wall, (II) floating on top of gastric contents, and (III) swelling/expansion at best beyond the size of the pyloric resting diameter (2,3). However, the outcome of *in vivo* studies, in which these concepts were tested, and the increased understanding of gastrointestinal physiology revealed that there are still considerable hurdles to overcome. Mucoadhesive systems mainly suffer from the high, stimulated gastric secretion rate, which can amount to values of about 10 mL/min (4–6). The basic requirement for floating systems is the presence of gastric contents. Contrary to this, the residual gastric volume in fasted state is only about 50 mL and the 240 mL water that is usually co-ingested together with the dosage form was shown to be emptied within about 30 min (7–9). Not only for expandable systems but for all approaches, the gastric motility is the major challenge, especially during the fasted state. In phase III of the

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interdigestive migrating motor complex (MMC), strong propulsive contraction waves, able to empty even large objects, clean the stomach from indigestible material (10). However, this fasted-state motility can be interrupted by the intake of food or caloric liquids, which results in a change of the motility pattern (11,12). Large and expandable objects have been demonstrated to be retained in the stomach during postprandial motility and also floating systems could exhibit prolonged residence time under fed conditions (13). However, these systems offer only limited therapeutic advantages over conventional extended release dosage forms (1,13). A putative proof of functionality of gastric retention principles may also arise from the choice of improper animal models. For example, ruminant animals like cattle, sheep, and goats will not empty larger particles from their stomach. But also pigs show very long gastric retention times for large objects (14).

Apart from the physiological factors mentioned above, no or little attention has been paid to intragastric forces acting on gastroretentive dosage forms. High gastric pressures have been shown to increase drug release rate of specific dosage forms and are considered to be highest during phase III of the MMC (10,15). Moreover, postprandial intake may lead to similar stresses on dosage forms (16,17). With the dissolution stress test device, Garbacz and colleagues could demonstrate *in vitro* that especially hydrogel matrix tablets are sensitive towards intragastric pressures (15,18). As a result of such stresses, the drug release rate is significantly increased which explains dose dumping or irregular plasma profiles of such dosage forms *in vivo* (15,18). Based on those findings, it is likely that the *in vivo* performance of sustained releasing gastroretentive systems is also affected by intragastric pressure events and hence, a thorough understanding of gastric motility is mandatory to comprehend their *in vivo* drug release behavior. In recent years, data from freely movable telemetric capsules that are able to measure luminal pressures (SmartPill®) expanded our knowledge of the gastrointestinal conditions that large non-disintegrating dosage forms experience (10,17,19). Besides providing deeper insights into gastric motility in health and disease, the pressure data can be used to improve novel *in vitro* dissolution tools, such as the dissolution stress test device (20). Owing to the lack of predictive and explanatory power of the current *in vitro* tools with respect to the *in vivo* performance of gastroretentive dosage forms, there is an increased need for the implementation of these physiological data (1). It seems obvious that usual tests for parameters such as floating time or swelling ratio along with standard dissolution test methods are not able to fully characterize novel gastroretentive dosage forms with respect to their drug release behavior *in vivo*.

The aim of the present study was to investigate the influence of *in vivo* occurring intragastric pressure events on the drug release behavior of two products that are marketed as gastroretentive systems (Glumetza® 1000, Madopar® HBS 125). For this purpose, intragastric pressure data, obtained by using the SmartPill® in healthy volunteers (17), were considered during *in vitro* dissolution testing. First, we defined test scenarios as basis for *in vitro* simulation of realistic gastric conditions experienced by gastroretentive dosage forms. In a next step, we used the dissolution stress test device that was developed by Garbacz and colleagues (15) and applied these scenarios during *in vitro* dissolution testing of the mentioned products. Madopar® HBS and Glumetza® 1000 represent the most promising and most marketed gastroretentive concepts (*i.e.*, floating and large in size). Thereby, the broad applicability of the dissolution stress test device regarding the *in vitro* testing of gastroretentive systems should be demonstrated.

MATERIALS AND METHODS

Materials

Hydrochloric acid (Merck, Darmstadt, Germany) and sodium chloride (Carl Roth, Karlsruhe, Germany) were used for preparation of the dissolution medium (Simulated Gastric Fluid *sine pepsin*). For the preparation of standards, metformin hydrochloride and levodopa were purchased in form of powder from Alfa Aesar (Karlsruhe, Germany). Investigated products were Glumetza® 1000 (Valeant, Laval, Canada) and Madopar® HBS 125 (F. Hoffmann-La Roche, Basel, Switzerland). Glumetza® 1000 is a large, oval-shaped tablet (12 mm [w] × 20 mm [l] × 10 mm [h]) containing metformin hydrochloride, a BCS class III compound which occurs in its highly soluble cationic form (pKa 11.5) in GI fluids (21). The sustained release is achieved *via* diffusion controlling coating (22,23). Among others, the tablet contains polyvinyl alcohol, hypromellose, polyethylene glycol, polyacrylate dispersion, and crospovidone. Madopar® HBS consists of a hard gelatin capsule containing levodopa (BCS class III) and benserazide hydrochloride (24). Among others, it contains povidone, hypromellose, and hydrogenated vegetable oil. The contents are considered to form a sustained releasing, mucous body that floats on top of the gastric contents by exhibiting a density below 1 g/cm^3 (25).

SmartPill® GI Monitoring System

The SmartPill® GI monitoring system (Medtronic plc, Dublin, Ireland) consists of a telemetric capsule (13 mm × 26 mm), a data receiver, and the MotiliGI® software. The receiver is equipped with an event button that allows registering any events relevant for data analysis and interpretation. The telemetric capsule is able to measure pressure, pH, and temperature. In the present study, the baseline-corrected pressure data were used for data analysis (cfr. reference 20). The data were analyzed by OriginPro 8.5.1.G (OriginLab Corporation, Northampton, MA, USA).

Dissolution Stress Test Device

The dissolution stress test device was used to simulate physiologically relevant pressure profiles during *in vitro* testing of the two drug products. The device allowed us to exert pressure events of different magnitudes on the dosage forms and to simulate dosage form movement as occurring *in vivo*. A detailed description of the device is given elsewhere (15). In brief, the central part of the device is a pipe-like bar with probe chambers attached. The spherical probe chambers consist of steel netting wire and hold the dosage form during dissolution testing. Balloons inside the

probe chambers can be inflated *via* compressed air supply which results in an exerted pressure event. Moreover, a stepping motor can rotate the bar with subsequent movement of the dosage forms within the probe chambers. The probe chambers are submerged in standard vessels containing dissolution medium, which is adequately stirred by an impeller.

Simulation of Gastric Pressure Profiles

For the simulation of realistic pressure profiles, we used data from a previously published study in which the SmartPill® was administered to 19 healthy human subjects under postprandial conditions according to the FDA guidance on food-effect bioavailability and fed bioequivalence studies. Detailed information is given elsewhere (17).

We analyzed all 19 pressure profiles with focus on characteristic intragastric pressure events. If possible, we checked a connection of these events with information recorded by the subjects *via* event button. Interestingly, in some cases, food intake and drinking seemed to favor the occurrence of pressure events. In most of the subjects, the administered standard breakfast, water and lunch led to few and only slight pressure events. However, in five subjects, the intake of a standardized lunch caused pressure events of more than 200 mbar at high frequency. In between the meals, only smaller pressure events were observed. In three subjects, a small dinner resulted in an increased pressure activity with amplitudes of more than 100 mbar. In most cases, the highest pressures (up to 500 mbar) were recorded during gastric emptying of the SmartPill®.

Based on the *in vivo* data for the different subjects, we defined three exemplary transit profiles for each case that was mentioned above, *i.e.*, pressure events after lunch, after dinner, and upon gastric emptying. Based on the amplitude, the pressure events from the *in vivo* study were classified into five ranges (50–100, 100–200, 200–300, 300–400, 400–500 mbar). Together with the corresponding time points, these classes formed the basis for the *in vitro* simulation of the pressure profiles in the dissolution stress test device. In order to simplify the test programs, the following pressures were used to represent the five classes: 50, 150, 250, 350, and 450 mbar. To assure comparability between the *in vitro* pressures with the ones determined *in vivo*, an activated SmartPill® was placed inside a probe chamber on a silicone inlay and used to calibrate the dissolution stress test device.

Based on the pressure profiles observed *in vivo*, we defined three realistic transit profiles that should simulate the borderline conditions and the "average" profile (Fig. 1). Thereby, program 1 (P1) was the low stress program with no pressure events occurring during gastric transit except for gastric emptying. Program 2 (P2) was regarded as the average profile. Program 3 (P3) displayed the high stress program, with the maximum number of pressure events. In particular, early occurring pressures were considered. For all test programs, we assumed a considerable prolongation of gastric residence time for the investigated gastroretentive dosage forms and thus, the time point of simulated gastric emptying in all test programs was set to 24 h.

Test Conditions

Other important parameters (*e.g.*, pH, temperature) were kept constant throughout the experiments in order to correctly interpret the dissolution data regarding the possible influence of intragastric pressures on drug release. Therefore, the dissolution stress test investigations were performed at a rotational speed of the impeller of 75 rpm. Simulated gastric fluid *sine pepsin* (SGF sp) pH 1.2 at 37 °C was used as a dissolution medium. The media volume was 1100 mL. All tests were performed in triplicate. For the correct exertion of pressure, the spherical probe chambers contained silicone inlays on which the dosage forms were placed during dissolution testing. Slight intragastric movement of the dosage form was simulated by the rotation of the central bar at 10 rpm every 5 min during each program.

Analytics

Measurements were performed with fiber optics at least every 5 min for a period of 24 h. During phases of high-frequency pressure events, the measurement intervals were decreased to every 3 min. Sample analysis was done with an UV-Vis spectrophotometer (Varian Cary® 50 Bio UV-Vis Spectrophotometer, Agilent Technologies, USA). For this purpose, levodopa and metformin hydrochloride were measured at 279 nm (5 mm probe tips) and 235 nm (1 mm probe tips), respectively. Data acquisition was performed with Cary WinUV software. Volume loss over time due to evaporation was assumed linear and calculated based on the initial volume and the volume at the end of each test.

Standard Dissolution Testing

Compendial dissolution tests were carried out in USP apparatus 2 (paddle apparatus, PT-DT70, Pharma Test Apparatebau AG, Hainburg, Germany) at a rotational speed of 75 rpm. Simulated gastric fluid *sine pepsin* pH 1.2 at 37 °C was used as a dissolution medium. The media volume was 1000 mL. Due to the floating of Madopar® HBS 125, the capsules were placed in a sinker during dissolution testing. All tests were carried out in triplicate. Drug release was measured with the aid of fiber optics every 5 min for 24 h. Sample analysis was done with a UV-Vis spectrophotometer (Varian Cary® 50 Tablet UV-Vis Spectrophotometer, Agilent Technologies, USA). The measurement parameters are consistent with the ones described above (see the "Test Conditions" section). Data acquisition was performed with Cary WinUV software. Volume loss was considered as described above.

RESULTS

Dissolution Experiments with Madopar® HBS 125

The dissolution data of Madopar® HBS 125 revealed a decreased levodopa release rate for the dissolution stress test device running program 1 (P1) compared to compendial dissolution testing. Around 80% of the drug was released after about 5 h in the paddle apparatus (Fig. 2). The results obtained with programs P1 and P2 showed that Madopar®

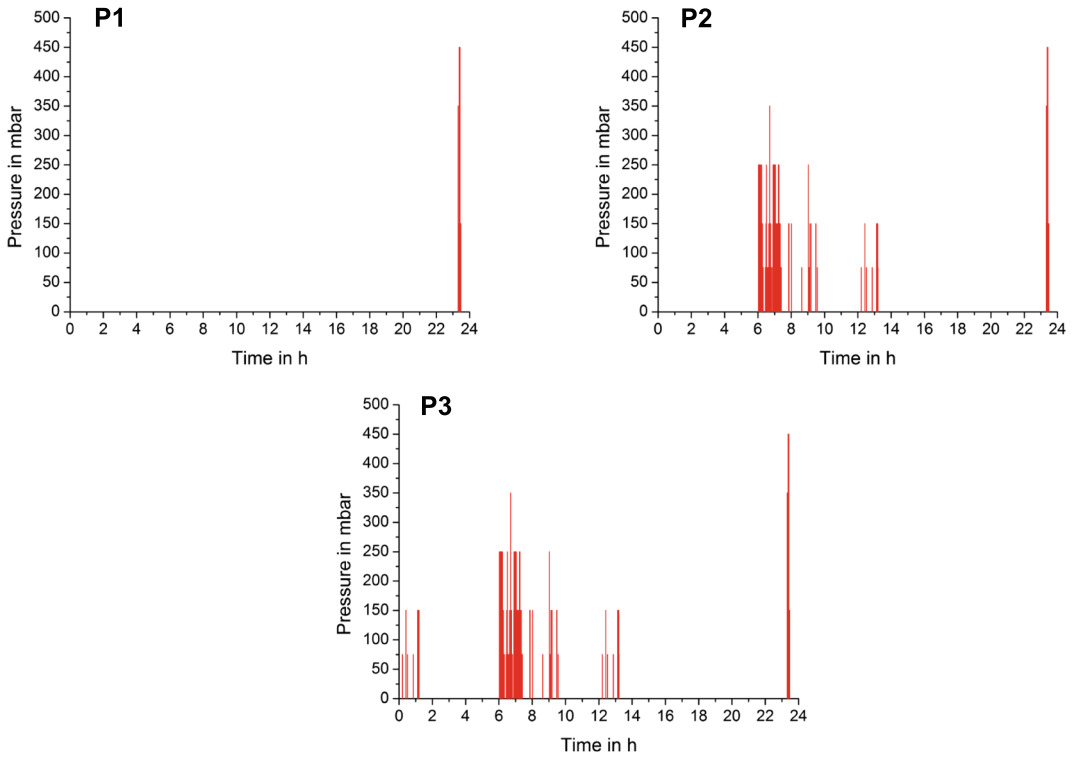

Fig. 1. Pressure programs performed using the dissolution stress test device. Program 1 (P1), program 2 (P2) and program 3 (P3)

HBS 125 is highly pressure sensitive. In P2, the pressure sequence after 6 h resulted in a complete release of the drug after around 8 h. In case of P3, drug release was even faster and complete drug release was reached after around 6 h. Even the low-amplitude pressure events during the first 90 min led to 80% drug release after about 3 h. In this case, sampling was stopped after about 14 h due to complete drug release.

Dissolution Experiments with Glumetza® 1000

In comparison to Madopar® HBS 125, the drug release from Glumetza® 1000 was slightly slower. In the paddle apparatus, 80% of the drug was released after about 6.5 h (Fig. 3).

Regarding the different programs in the dissolution stress test device, the slowest drug release was again observed in P1. This can be attributed to the lack of pressure events except for simulated gastric emptying at the end of the test. Under these conditions, 80% of the drug was released after about 18 h. In contrast to what was seen for Madopar® HBS 125, the last pressure sequence after 23.5 h increased drug release by about 20% within a short period of time.

With respect to P2 and P3, it can be seen that during phases of highly frequent pressure events, a rapid increase of metformin release rate occurred. In both programs, complete drug release was reached already at the beginning of the pressure sequence at 6 h. Thus, the sequence of smaller pressure events at about 12 h had no further effect. During the first 6 h of P3, in which smaller pressure events were included at the beginning of the tests, the metformin release rate was comparable to the data from the paddle apparatus. Sampling was stopped in P3 after 19 h due to completed drug release. The results clearly indicated the pressure sensitivity of the dosage form in terms of its drug release behavior.

DISCUSSION

Gastroretentive dosage forms remain a “holy grail” of oral drug delivery due to the various potential benefits for oral pharmacotherapy, but also due to the fact that none of the dosage forms developed in the last decades sufficiently demonstrated gastroretention especially in fasted state. Thus, the total number of marketed dosage forms termed gastroretentive remains limited so far (26).

At the moment, the most descriptive way to test potentially gastroretentive dosage forms is *via* extensive *in vivo* investigations. In this connection, data from animal models such as the pig or the dog have to be interpreted carefully, since anatomy and physiology of the human gastrointestinal tract is significantly different. Even between animal species, great differences are present (26,27). Consequently, time- and cost-intensive human *in vivo* studies remain the gold standard for the evaluation of gastroretentive dosage forms. But here, several aspects have to be considered. In particular, the study design and the nutritional regime are critical. It was shown in recent studies that the intake of caloric food and liquids significantly prolongs the gastric residence time of large non-digestible objects (10,19,28). For instance, Ewe and co-workers could prolong the gastric residence time of non-disintegrating tablets for up to 10 h by administering several meals and snacks (28). With respect to gastroretentive dosage forms, this may lead to biased results in favor of the tested system (3,13). For

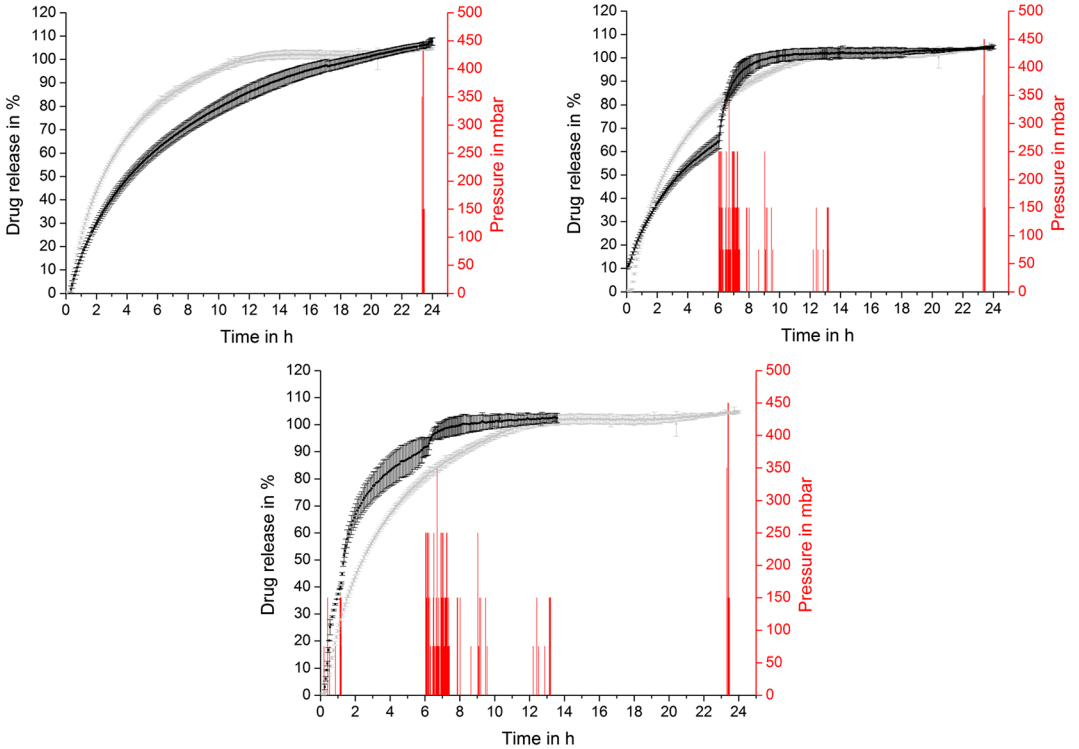

Fig. 2. Levodopa release from Madopar® HBS 125 under different test conditions: P1 (top left, black), P2 (top right, black), P3 (bottom, black) and in paddle apparatus (gray). Pressure events are indicated by red lines. Mean ± SD, $n = 3$

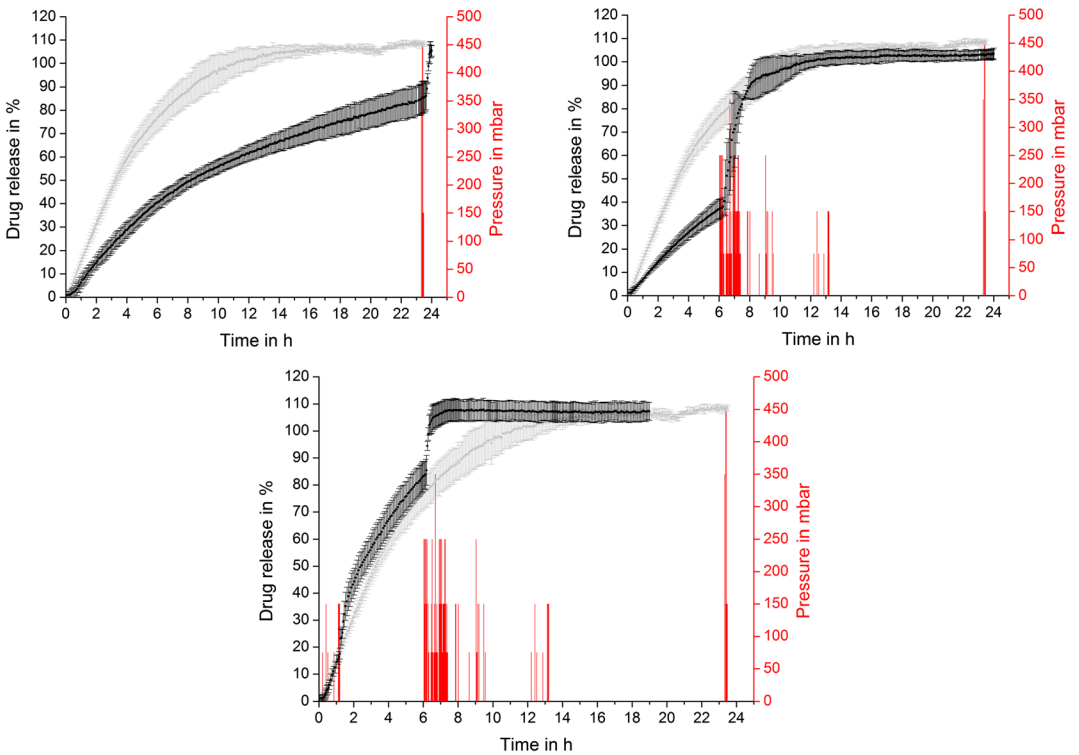

Fig. 3. Metformin release from Glumetza® 1000 under different test conditions: P1 (top left, black), P2 (top right, black), P3 (bottom, black), and paddle apparatus (gray). Pressure events are indicated by red lines. Mean ± SD, $n = 3$

example, the gastroretention of Glumetza® 500 was nicely demonstrated under fed conditions, *i.e.*, drug administration after a heavy meal of approximately 1000 kcal, with 50% of the calories coming from fat. In contrast, after fasted state intake, the gastroretention of Glumetza® 500 remained limited (29,30). Berner and Cowles have further shown that a reduction of the fat content of the co-administered meal from 50 to 30% already results in a decrease of mean gastric residence time of 5 h (30).

In order to improve the success rate of the development of gastroretentive dosage forms, powerful *in vitro* tools are needed that allow an early and descriptive evaluation. Owing to the expected long gastric residence time of gastroretentive dosage forms, the biorelevant simulation of physiological stresses arising during gastric transit seems to be highly important for the *in vitro* testing of such systems. This was already noticed by Nakagawa and colleagues, who developed a novel floating system and applied the paddle-beads method proposed by Aoki *et al.* for drug release testing (31). In this setup, polystyrene beads within the vessel of a standard paddle apparatus should lead to increased stress on the dosage form (32,33). However, occurring collisions and additional stress due to the beads are evenly distributed over the whole test duration, whereas this is clearly not the case *in vivo* (33–35).

A recent SmartPill® study showed that significant, single gastric pressure sequences can occur after concomitant intake of the high-caloric, high-fat FDA standard meal and during the following gastric transit (17). Comparable pressure events were already shown to affect drug release from hydrogel matrix tablets *in vitro*, and also, hard gelatin capsules are influenced by simulated intragastric pressures (18,36).

In order to detect possible drug release problems associated with such pressure events, we developed an *in vitro* test setup that mimicked realistic gastric pressure profiles. The results of the present study showed that both products, Glumetza® 1000 and Madopar® HBS, do not stay intact under simulated gastric conditions for a longer period of time. Both investigated dosage forms showed a drug release behavior that was sensitive to pressure events as they occur in the human stomach under postprandial conditions. According to our results, this may even lead to intragastric dose dumping. However, this does not necessarily translate into a sharp plasma peak. Drug that is released in the stomach is likely mixed with gastric contents due to postprandial peristalsis. Since gastric emptying under postprandial conditions is significantly prolonged compared to fasted state, gastric emptying and not the drug delivery system itself will then control the onset of drug concentration in plasma (37).

Our data for Madopar® HBS indicated a high sensitivity towards pressures that are realistic for the human stomach. The simulation of early pressure events of low amplitude already caused a significant increase of drug release. Moreover, the experiments in the dissolution stress test device revealed that the capsule contents were easily dispersed during the pressure sequences (Fig. 4). An *in vivo* study by Grahnen and colleagues with Madopar® HBS suggests that the gastroretentive properties of the drug are likely negligible. Comparable pharmacokinetic profiles after postprandial intake can also be achieved by administering a conventional, non-floating sustained release tablet (38). Furthermore, based on the results from the present study, the prolonged drug release from the intact system is also unlikely under fasted conditions. Even if the dosage form is able to float in the fasted stomach, it will most likely be destroyed by the intense peristalsis occurring during MMC phase III ("housekeeper waves").

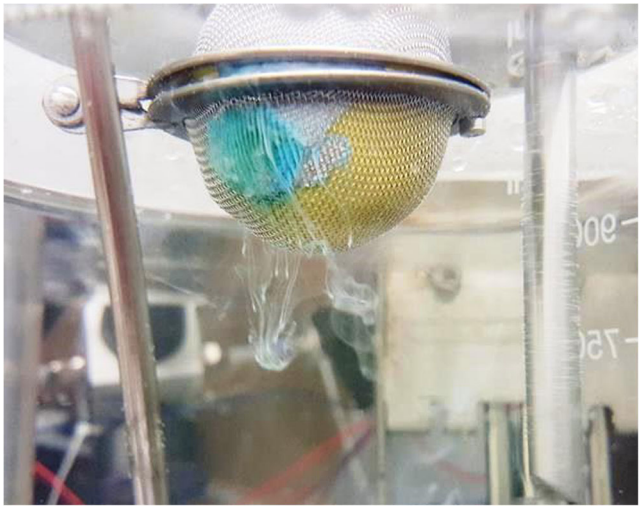

Fig. 4. Photograph of Madopar® HBS after a pressure sequence

In case of Glumetza® 1000, metformin release is controlled by a coating. Increased gastric residence time is mainly enabled by the size but, as already mentioned, the success of this principle is most likely restricted to postprandial conditions. In comparison to Madopar® HBS, the dosage form was less affected by early pressure events of low amplitude. In contrast, events of higher pressure at later time points resulted in complete drug release within short periods of time, which indicates that the tablet was highly sensitive towards pressures in the swollen stage. Figure 5 shows a photograph of one tablet during dissolution testing in the dissolution stress test device. The disrupted coating (white) can be optically delimited from the yellow balloon.

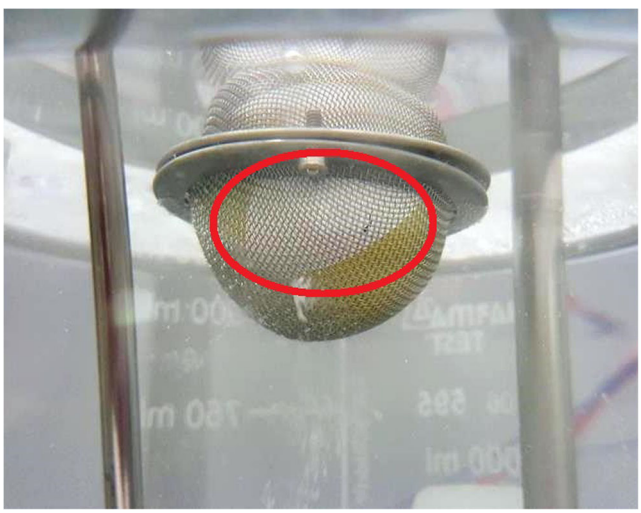

Fig. 5. Photograph of Glumetza® 1000 after a pressure sequence. The red circle highlights the disrupted coating (white)

The demonstrated *in vitro* drug release behavior suggests that the oral bioavailability may be decreased significantly when gastric emptying happens early, *e.g.*, after fasted state intake of the drug. Since early pressure events during gastric emptying will have only minor effects on drug release and intestinal pressure events were shown to be clearly lower, the drug may stay intact during the whole gastrointestinal transit. A rapid gastric emptying under fasting conditions could then lead to fecal excretion of a large portion of the drug. For Glumetza® 500, Schwartz and colleagues could indeed show that the relative oral bioavailability drops to about 58% when administered under fasting instead of postprandial conditions (29,30).

In the present study, physiological *in vivo* data on pressure events were implemented into the biorelevant dissolution stress test device. By considering a broad range of possible transit scenarios, we were able to simulate the extremes in terms of gastric stresses. However, some limitations have to be mentioned. Assuming actual gastroretentive properties for the two tested dosage forms, we defined a test duration of 24 h, which was based on maximum transit times determined in the previous SmartPill® study. In that study, gastric residence times were highly variable and ranged from 4.3 to 20.2 h, mainly depending on the individual eating habits of the subjects (17). Since the SmartPill® transit times are considered to be comparable to the expected transit times of large monolithic dosage forms, it is likely that the gastroretentive properties of the tested systems were overestimated. Furthermore, it is also unclear whether the intragastric localization, and thus the pressure profile of the SmartPill®, is applicable to floating dosage forms. However, by applying three different pressure profiles, the extremes of gastric transit were considered and pressure sensitivity for both systems could be verified. These data further indicate high variability of drug release *in vivo*.

Our study demonstrated the value of simulating realistic gastrointestinal pressure events during drug dissolution testing of gastroretentive dosage forms. Besides established methods for the characterization of such dosage forms, a test investigating the sensitivity towards physiologically relevant pressures can significantly improve the drug development process.

CONCLUSION

In the present study, we could show the value of considering realistic, intragastric transit data during *in vitro* dissolution testing of gastroretentive dosage forms. By defining edge profiles of gastric pressure events, the resulting data suggest high variability of plasma concentration *in vivo*. The simulation of relevant gastric pressures was crucial for the drug release profiles of the two tested dosage forms, which are marketed as gastroretentive systems. Besides the well-known physiologic hurdles for gastroretentive systems to overcome, we could demonstrate that intragastric pressure events are an additional factor that should be taken into account during *in vitro* testing. Our results showed that appropriate *in vitro* tests to foresee the mentioned problems could be highly valuable and may aid the drug development process of novel gastroretentive systems.

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