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In vitro simulation of realistic gastric pressure profiles

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ABSTRACT

Novel in vitro dissolution tools can aid the development of orally administered drugs by explaining dosage form related in vivo phenomena that are not explainable with standard test apparatuses. Such novel tools are able to mimic various parameters in accordance with gastrointestinal conditions. Hereby, in vivo occurring pressure events were shown to be of major importance since they largely affect dosage form disintegration, drug dissolution and subsequently resulting drug plasma concentration profiles. The aim of the present study was to investigate the feasibility of producing biorelevant pressure events with standard test apparatuses and with the dynamic open flow through test apparatus. For this purpose, we used the SmartPill®, a swallowable capsule that houses a pressure sensor and that was already applied to gather human in vivo data. Among the standard apparatuses, highest pressures were measured in the reciprocating cylinder apparatus and the disintegration tester. No relevant pressure peaks could be detected in the paddle apparatus and the mini paddle apparatus. In contrast, the dynamic open flow through test apparatus enabled the simulation of complete gastric pressure profiles as they occur in vivo. The present work underlines the potential of novel in vitro dissolution models as useful tools during the drug development process as well as for explanatory purposes.

1. Introduction

During gastrointestinal transit, solid oral dosage forms are exposed to a number of different parameters that can affect drug release and absorption. Among these, luminal forces are of major importance for disintegration and dissolution of oral drug products. For instance, hydrogel matrix tablets were shown to be highly sensitive to compressive forces (Garbacz et al., 2008, 2009, 2014a). It is generally assumed that within the human gastrointestinal tract, the shear forces (acting parallel to the surface) are rather low, but the compressive forces (acting perpendicular to the surface) can be high at certain critical points such as the distal stomach and the pylorus. In a recent SmartPill® study that was conducted with fasted healthy volunteers, we could show that high stresses mainly occur in the stomach and thus, gastric residence plays a major role in exerting forces on dosage forms (Schneider et al., 2016). These forces typically facilitate the process of disintegration of immediate release (IR) products and hence, contribute to a fast onset of drug plasma concentrations (Vardakou et al., 2011a). On the other hand, in case of modified-release (MR) dosage forms, these forces can also be a threat to safe pharmacotherapy. It was already shown for various MR products that high compressive forces may be the root for undesired drug release phenomena such as dose dumping (Garbacz et al., 2008, 2009, 2014a; Koziolek et al., 2014).

Information on luminal forces in the human stomach can be assessed in vivo by applying different techniques. Non-invasive imaging techniques such as scintigraphy or magnetic resonance imaging (MRI) can be used to study the gastric distribution of a marker and thus, allow generating information on shear conditions in the stomach. The determination of compression is mainly done by either catheter manometry or capsule manometry. Catheter manometry allows to measure compression along a certain distance of the human gastrointestinal tract, whereas capsule manometry is based on the measurement at a single, often unknown location. However, freely moving capsule manometry systems such as SmartPill® can generate a pressure profile that is representative for the stresses solid oral dosage forms experience in the gastrointestinal tract. After swallowing the SmartPill®, it also generates a pH profile during its transit that can be used to estimate residence times in the different parts of the gastrointestinal tract (Koziolek et al., 2015; Schneider et al., 2016).

In order to study drug release from solid oral dosage forms, numerous compendial as well as novel in vitro test apparatuses were developed. As the stresses in the stomach are mainly important for disintegration and dissolution behavior of oral dosage forms, several biorelevant systems at least partly focus on gastric motility. These devices include highly complex systems such as the TIM-1 system and the Dynamic Gastric Model (DGM), but also simpler systems such as the

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dissolution stress test device (Garbacz et al., 2008, 2009; Minekus et al., 1995; Vardakou et al., 2011b; Vatier et al., 1994). These models were already successfully applied to explain the in vivo performance of different orally administered dosage forms (Blanquet et al., 2004; Garbacz et al., 2014a; Vardakou et al., 2011a). Using these models it could be shown that physiologically correct in vitro simulation of gastric forces can be of great value for the evaluation of novel formulations before testing them in clinical trials. This allows to specifically design dosage forms that release the drug nearly irrespective of the physiological conditions. In case of MR dosage forms, undesired dose dumping can be foreseen.

On the other hand, the majority of compendial dissolution methods are still based on more or less static test conditions. This does by no means reflect the human gastrointestinal physiology as already been demonstrated by several in vivo studies. Even for the investigation of drug release in fasted state, highly variable conditions can be expected influencing the in vivo performance of orally administered dosage forms (Kalantzi et al., 2006; Mudie et al., 2014; Schneider et al., 2016). After fasted state administration, the gastric residence time of non-disintegrating solids can be highly variable in the range from few minutes up to 3 h (Schneider et al., 2016). Moreover, the intraluminal pH value as well as the temperature further depend on the amount and temperature of the co-ingested water. These parameters were shown to affect the disintegration behavior and drug dissolution of IR dosage forms (Garbacz et al., 2014b; Van Den Abeele et al., 2015). To adequately simulate the mentioned parameters with respect to the low volumes in fasted state, Garbacz et al. developed the dynamic open flow through test apparatus (Garbacz et al., 2014b). This model is designed to simulate pressure, pH and temperature changes as they also occur in vivo. Furthermore, the media flow and the simulated gastric residence time can also be adapted to the conditions described for the fasted state intake of a dosage form. However, the simulation of gastric pressure events with this and comparable novel models is based on artificial test programs that shall cover a broad range of possible cases. Our knowledge from a recent SmartPill® study could significantly increase the correctness of simulation by adapting the test programs to in vivo observed pressure profiles.

Therefore, the aim of this study was to assess the stresses occurring in various compendial dissolution test apparatuses under different conditions with the aid of the SmartPill® system. Furthermore, the opportunities of the dynamic open flow through test apparatus in terms of the physiologically relevant simulation of gastric pressure events should be evaluated. For this purpose, the SmartPill® was chosen to serve as a reference system since it was already used to gather in vivo data for fasted state conditions (Schneider et al., 2016).

2. Materials & methods

2.1. SmartPill® GI monitoring system

The SmartPill® GI monitoring system (Given Imaging Ltd., Yoqneam, Israel) consists of an ingestible capsule (13 mm × 26 mm), a data receiver to store the data transmitted by the capsule and the MotiliGI® software for transmission and analysis of the data stored on the receiver via a personal computer. The receiver is equipped with a display and an event button. Hereby, the dataset can be marked at special time points whereby different test conditions get assignable during data analysis. The telemetric capsule is able to measure pH, temperature and pressure in the ranges of pH 0.5 to pH 9.0, 25 °C to 49 °C and 0 mbar to 467 mbar, respectively. Its two batteries enable a continuous measurement over a period of at least five days. An integrated energy saving mode gradually reduces the sampling frequency of each sensor beginning after 24 h. For data analysis, we used the baseline compensated pressure data and did all of analysis with aid of OriginPro 8.5.1.G (OriginLab Corporation, Northampton, MA, USA).

2.2. Standard methods

For evaluation of the occurring forces acting on a dosage form during compendial testing, several methods were investigated. The SmartPill® was tested under different conditions and served as a reference system to compare obtained data to in vivo measured pressure events.

2.2.1. Disintegration tester

The disintegration tester (ZT 222, ERWEKA GmbH, Heusenstamm, Germany) was used at 30 dpm. The test medium was water at 37 °C. The influences of the SmartPill® orientation within the basket (upright or downright) and the use of disks were investigated. Furthermore, we investigated whether significant pressure events occur if the SmartPill® fully emerges from the water during upward movement.

2.2.2. USP apparatus 2 and mini paddle apparatus

Tests in the paddle apparatus (USP apparatus 2, PT-DT70, Pharma Test Apparatebau AG, Hainburg, Germany) were carried out at 37 °C in water. The rotational speed of the paddle was increased by 25 rpm from 25 rpm up to 250 rpm. Tests in the mini paddle apparatus (modified DT 600, ERWEKA GmbH, Heusenstamm, Germany) were carried out at 37 °C in water. The rotational speed increased by 50 rpm from 50 rpm up to 150 rpm.

2.2.3. USP apparatus 3

To study the effect of up and downward movement of the reciprocating cylinder apparatus (USP apparatus 3, RRT 10, ERWEKA GmbH, Heusenstamm, Germany) on the SmartPill® measurement, tests were carried out at 37 °C. For the tests, a volume of 200 mL or 100 mL and a mesh size of 74 µm up to 840 µm for both sieves were used. The dip rate was increased by 5 dpm from 5 dpm up to 40 dpm. The direction of the pressure sensor remained downwards throughout all tests.

2.3. Dynamic open flow through test apparatus

The dynamic open flow through test apparatus was used to simulate the pressure profiles obtained in vivo for three healthy subjects. These subjects swallowed the SmartPill® together with 240 mL of water after an overnight fast of 10 h. A thorough description of the in vivo study is given elsewhere (Schneider et al., 2016).

2.3.1. Setup

Fig. 1 shows a schematic of the dynamic open flow through test apparatus as used in this study. This in vitro dissolution device was developed by Garbacz et al. in order to mimic gastric conditions arising after fasted state administration of solid oral dosage forms.

The main vessel can contain about 80 mL of dissolution media and is designed to guide the probe chamber, a spherical steel mesh, during its movement. The spherical probe chamber contains the dosage form and is able to perform pendulum motions within the main vessel. These motions are enabled by a stepping motor on one side of the central axis that is linked to the probe chamber. The other side of the hollow central axis contains a connection for compressed air supply. This allows to inflate a balloon inside the probe chamber via a nozzle that is connected with the central axis. The pressure to be exerted on a dosage form is regulated by a valve. The performed motions of the motor as well as balloon inflation are programmable and automated via a personal computer. Furthermore, two channels enable the perfusion of the main vessel with liquid media in horizontal direction. The media flow is enabled by an external programmable peristaltic pump (Ismatec IPC 16, Cole-Parmer GmbH, Wertheim, Germany). A water bath ensures correct temperature regulation.