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Development of a bio-relevant dissolution test device simulating mechanical aspects present in the fed stomach

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ABSTRACT

A novel bio-relevant in vitro dissolution device was designed to mimic intragastric conditions after food intake paying particular consideration to mechanical aspects: the *Fed Stomach Model* (FSM). The FSM represents a fully computer-controlled dynamic flow-through system, in which dosage forms are hosted in so-called gastric vessels. Dosage form movement profiles as well as pressures can be simulated in a physiologically relevant manner. This proof-of-concept study aimed at the investigation of the effects of individual parameters and complex test programs on the drug delivery behavior of diclofenac sodium bilayer extended release tablets. Magnetic marker monitoring experiments demonstrated the applicability of the FSM to simulate intragastric movement velocities of solid oral dosage forms equivalent to in vivo data. Dissolution experiments revealed the relevance of all simulated parameters (i.e. pressure, dosage form movement and pump rate). Moreover, three different test scenarios with test programs specific for fundus, antrum and gastric emptying considered the variability of intragastric transit of solid oral dosage forms after food intake and were confirmed to be reasonable. Dissolution rates were low under conditions specific for fundus owing to low shear stresses. In contrast, higher amounts of the drug were released under high stress conditions simulating antral transit and gastric emptying. Concluding, the FSM can be a valuable tool for bio-relevant dissolution testing due to its potential of precise and reproducible simulation of mechanical parameters characteristic for the fed stomach.

1. Introduction

During the transit of solid oral dosage forms through the human gastrointestinal (GI) tract, several mechanical, enzymatical and physico-chemical factors may affect the drug delivery behavior in vivo. These parameters are distributed regionally, which implies that transit conditions are not homogeneous and differ along the GI tract. Different techniques such as magnetic resonance imaging (MRI), magnetic marker monitoring (MMM) or telemetric capsules (e.g. Intellicap® or SmartPill™) help to gain an insight into the complex GI physiology (Tran et al., 2012; Weitschies and Wilson, 2011). Furthermore, the design of bio-relevant in vitro test methods that are able to simulate critical aspects of human GI physiology is another prerequisite for the comprehension of the in vivo drug release behavior from solid oral dosage forms.

Due to low fluid volumes and short transit times in oral cavity and esophagus, the dissolution of solid oral dosage forms typically starts in the stomach. The human stomach is a complex organ, which can be divided into regions of different functionality as illustrated in Fig. 1. The proximal part of the stomach, the fundus, represents a reservoir for incoming contents and can gain up volumes of higher than 1 L (Geliebter and Hashim, 2001). In terms of mechanical aspects, this part is mainly characterized by low stress conditions (i.e. low mechanical activity), whereas in the distal part, the antrum, higher shear stresses are generated by the gastric motility in order to prepare gastric contents for intestinal absorption ("antral mill"). The gastric peristalsis accounts for homogenization and particle fragmentation. Gastric secretions containing several components such as enzymes or hydrochloric acid contribute to these processes (Schulze, 2006; Schwizer et al., 2006). The last step of intragastric transit is the emptying into the duodenum via the pylorus. At this point, solid dosage forms can experience high pressures of up to 300 mbar followed by high velocities of up to 50 cm/s during the passage of the C-shaped duodenal segment. Hence, intense shear stresses act on the dosage form at this point and may influence the drug release (Weitschies et al., 1999; Willis et al., 2011).

Meal ingestion changes numerous aspects of intragastric conditions such as gastric content volume, pH value, secretory activity or motility (Camilleri, 2006; Dressman et al., 1990; Koziolek et al., 2013b; Malagelada et al., 1976; Sauter et al., 2012). Furthermore,

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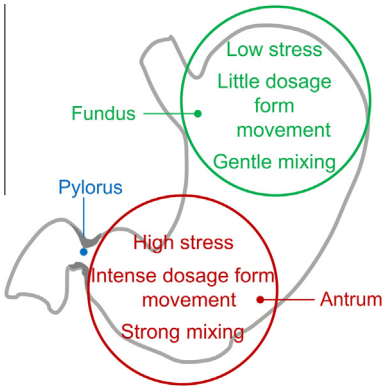

Fig. 1. Functional characteristics of intragastric regions.

the gastric residence time (GRT) of large non-disintegrating monolithic objects such as hydrogel matrix tablets or telemetric capsules is extended up to several hours. These dosage forms are usually emptied in phase II or III of the migrating motor complex, which is a GI motility pattern present under fasting conditions. Meal intake induces the disruption of the MMC and therefore accounts for longer GRT of non-disintegrating objects (Sarosiek et al., 2010; Weitschies et al., 2005; Willis et al., 2011). To date, little attention was paid to mechanical processes characteristic for the fed stomach such as the generation of antral contraction waves (ACW) with a frequency of 3 min^{-1}, intragastric flow pattern (e.g. retropulsive flow with velocities higher than 10 cm/s) as well as pressures of up to 300 mbar generated by the stomach walls during peristalsis (Boulby et al., 1999; Cassilly et al., 2008; Kwiatek et al., 2006). Furthermore, regional differences of the intragastric conditions have to be considered (Pal et al., 2004). Weitschies et al. demonstrated in magnetic marker monitoring (MMM) studies that the intragastric location of a solid dosage form affects its drug delivery behavior. Based on the study results, we calculated intragastric velocity profiles of the magnetically labeled tablets prevailing in different sections of the postprandial stomach. The movement pattern of the dosage form located in fundus is characterized by long phases of rest interrupted by events of slow movement. In contrast, tablets located in the antro-pyloric region underlie frequent and intense transport events (Weitschies et al., 2005).

For the reasons presented, food given concomitantly with medication may change one or more pharmacokinetic parameters and hence, drug plasma levels. Severe consequences for the patient such as therapy failure or increased risk of adverse drug reactions in case of drug plasma levels above the therapeutic range can result (Garbacz et al., 2008).

It is obvious that this physiological intricacy cannot be depicted by compendial in vitro methods like the USP apparatus I or II. Consequently, the complex in vivo dissolution behavior of solid oral dosage forms is poorly predictable by these methods. Therefore, complex bio-relevant test devices such as the TNO TIM-1 or the Dynamic Gastric Model (DGM) were introduced recently with the aim to simulate the postprandial conditions of the proximal GI tract (Koziolek et al., 2013a; McAllister, 2010; Wickham et al., 2012). Their usability in studies of food digestion and bioavailability was widely demonstrated. However, their application for routine dissolution testing of solid oral dosage forms is limited due to high complexity and often low effectiveness with respect to costs and time. Based on literature data presented in two previously published reviews, we aimed to design an in vitro dissolution device for the bio-relevant simulation of critical parameters present under postprandial intragastric conditions: the Fed Stomach Model (Koziolek et al., 2013a and b).

This novel bio-relevant dissolution test device shall enable the explanation of different drug release phenomena such as dose dumping or presence of lag phases that are related to galenic issues and/or meal ingestion. By its abstract design and full computer control, the dissolution test environment can be varied specifically and thus, the effects of the simulated parameters can be individually investigated. The aim of the present proof-of-concept study was to investigate the applicability of the FSM for dissolution testing of modified release formulations. Therefore, the effect of single parameters (e.g. application of pressure, dosage form movement) regarded as critical for the drug delivery behavior of solid oral dosage forms was evaluated. Moreover, the interplay was considered in complex programs based on literature and MMM data.

2. Materials and methods

2.1. Fed Stomach Model

The Fed Stomach Model is a modified paddle apparatus, which can be used for the investigation of the dissolution testing of up to six solid oral dosage forms under simulation of different mechanical aspects present during intragastric transit. Parameters that can be simulated are pressures and transport events generated by gastric peristalsis as well as different hydrodynamics. In different studies it was shown that these factors can be critical mechanical parameters that affect the drug delivery behavior. The key parts of the FSM are the gastric vessels, in which the dosage forms are hosted during the experiments (Fig. 2A). The gastric vessels represent dynamic flow through cells with a maximum fill volume of 100 mL. Two blades connected to a central axis at an angle of 90° are located in each cell. By a computer-controlled stepping motor, the central axis and thus the blades can be moved with certain driving velocities. Small glass beads (d = 1 mm) at the bottom of

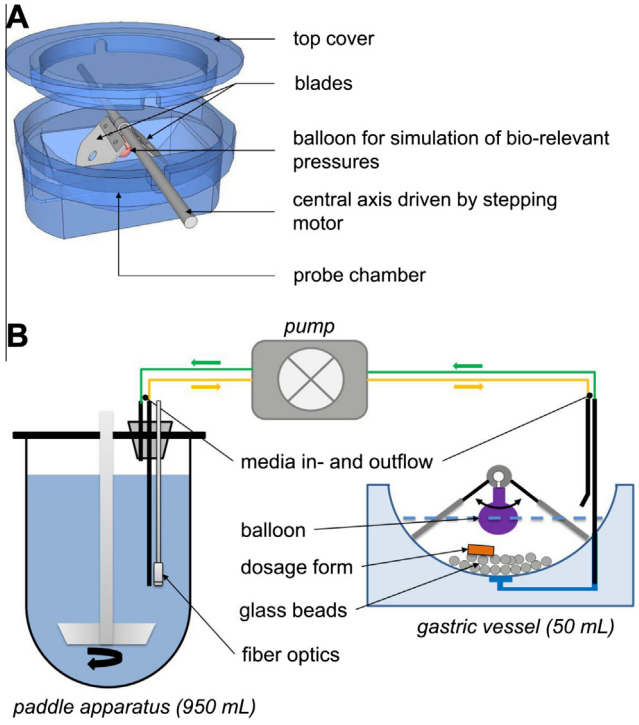

Fig. 2. Fed Stomach Model: A – FSM gastric vessel and B – closed loop test configuration.