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Research paper

A novel mechanical antrum model for the prediction of the gastroretentive potential of dosage forms

Marco Neumann[a], Felix Schneider[a], Mirko Koziolek[a], Grzegorz Garbacz[b], Werner Weitschies[a,*]

[a] Institute of Pharmacy, Department of Biopharmaceutics & Pharmaceutical Technology, Center of Drug Absorption and Transport, University of Greifswald, Felix-Hausdorff-Str. 3, D-17487, Greifswald, Germany
[b] Physiolution GmbH, Walther-Rathenau-Str. 49a, D-17489, Greifswald, Germany

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ABSTRACT

The development of gastroretentive dosage forms can be significantly enhanced by the reliable estimation of gastroretentive properties in vitro. In this context, it is mandatory to consider the propulsive contraction waves that occur in the antral region of the stomach, since they are regarded as the major physiological hurdle to overcome. Therefore, the aim of this study was to develop an in vitro model that allowed the evaluation of the gastroretentive potential of objects with different properties (e.g. size, shape and elasticity). The model enabled a realistic simulation of the human antrum and occurring contraction waves. We could demonstrate that larger objects made of elastic polyurethane foam were more rapidly emptied by the model than smaller objects having the same shape. Compared to this, rigid as well as slippery objects showed decreased gastroretentive properties. In contrast, a self-formed trichobezoar - an indigestible object known to remain in the stomach – showed the highest gastroretentive potential. We suggest that the gastroretentive potential of objects of a certain size increases if they exhibit compressible and elastic properties along with certain dimensions. The data showed that the development of novel gastroretentive dosage forms may be facilitated with the aid of the mechanical antrum model.

1. Introduction

A prolonged gastric residence time is considered to be advantageous for drugs that act locally in the stomach or exhibit an absorption window in the upper part of the small intestine (Kagan and Hoffman, 2008). Several groups have developed so-called gastroretentive systems based on different mechanisms with the aim to extend the therapeutic possibilities of various drugs (e.g. levodopa) (Pawar et al., 2011).

After oral intake, gastroretentive dosage forms are supposed to remain in the stomach over a long period of time while releasing their active pharmaceutical ingredient (Davis, 2005). Furthermore, gastroretention may also be suitable for drugs with very short plasma half-lives as well as for drugs with low solubility or stability under intestinal conditions (Streubel et al., 2006). By prolonging the gastric residence time, the dosing interval may be reduced and the oral bioavailability can be increased. Thus, the patient compliance can be significantly enhanced.

There are three major approaches that are typically applied to achieve gastroretention of solid dosage forms: (1) unfolding or expanding systems that enlarge in size and thus cannot pass the pylorus; (2) mucoadhesive systems that attach to the stomach wall and (3) floating systems that are able to float on top of gastric contents (Bardonnet et al., 2006; Lopes et al., 2016). However, it should be noted that none of these principles led to robust results in terms of their in vivo performance so far. Expanding dosage forms often show disappointing results in human clinical trials although previous animal studies have proven increased gastric residence time (Cargill et al., 1988; Fix et al., 1993). This can be explained by anatomic (especially maximum pyloric diameter) and functional (e.g. motility patterns) differences among the gastrointestinal tract of humans and the different animal species used for evaluation of solid oral dosage forms such as dogs or pigs (Hatton et al., 2015; Klausner et al., 2003). The major problem that mucoadhesive systems suffer from is the high secretion rate of gastric juices, which can amount up to 50 mL/min, depending on

* Corresponding author at: Institute of Pharmacy, Department of Biopharmaceutics & Pharmaceutical Technology, Center of Drug Absorption and Transport, University of Greifswald, Felix-Hausdorff-Str. 3, D-17487, Greifswald, Germany.
E-mail address: werner.weitschies@uni-greifswald.de (W. Weitschies).

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the prandial state and stimulation, which hampers the adhesion of such systems to the stomach wall over longer periods of time (Deshpande et al., 1996; Koziolek et al., 2013a). Floating dosage forms require solid or liquid contents for flotation, which are not present especially in the fasted state (Koziolek et al., 2016; Schiller et al., 2005).

The main physiological challenge of the stomach for all kinds of gastroretentive dosage forms is the fasted state motility, in particular the housekeeper waves that occur during phase III of the interdigestive migrating motor complex. Those strong propulsive contraction waves are able to clean the stomach from indigestible material that still remained after complete gastric emptying of ingested food (Cassily et al., 2008). By a further decrease of the small intestinal wall pressure with subsequent increase of the pyloric diameter, even large objects can be emptied from the fasted stomach during peristalsis. The intake of caloric liquids and food interrupts this gastric motility pattern and induces the postprandial motility (Deloose et al., 2012). Larger objects (e.g. non-disintegrating dosage forms) were shown to survive postprandial motility (Khosla and Davis, 1990; Willis et al., 2011) and thus for most systems prolonged gastric residence can be demonstrated by using a smart study design (i.e. dosing in fed state and applying high frequent feeding regimen). Ewe and co-workers demonstrated this effect for non-disintegrating tablets that were retained in the stomach for 509 min ± 220 min after co-administration with a large breakfast and subsequent food intake (lunch, dinner and snacks) (Ewe et al., 1991). Therefore, significant gastroretention is currently only achievable by administering gastroretentive dosage forms together with food. It should be noted that in this case the gastric residence time depends on the composition and the properties of the meal. However, the prerequisite for a reproducible and safe pharmacotherapy with gastroretentive dosage forms would be a prolonged gastric residence time irrespective of the prandial state.

For the successful development of such dosage forms, a realistic in vitro estimation of their gastroretentive properties is mandatory, but the explanatory power of the parameters that are typically investigated (e.g. floating behavior or swelling indices) is missing with respect to the resulting in vivo behavior, in particular under fasting conditions (Lopes et al., 2016). Based on the above mentioned problems, the accurate simulation of antral contraction waves should be in the center of the in vitro testing of gastroretentive dosage forms. Due to the fact that large objects are mainly emptied by the housekeeper waves, their correct simulation is of major importance.

Therefore, the aim of this study was the development of an in vitro model that allowed the evaluation of the gastroretentive potential of objects with different properties (e.g. size, shape and elasticity). This model should be able to simulate antral contraction waves in a realistic manner in order to identify crucial properties that can be used for the rational development of gastroretentive dosage forms.

2. Materials & methods

2.1. Materials

Different silicone types (AlpaSil® EH 10:1 components A + B and Protosil® RTV 240 components A + B) were purchased from Modulor GmbH, Berlin, Germany and used for the preparation of the tube and ring-shaped balloons. Impression material (Stylex GmbH, Nordhorn, Germany) and polypropylene tubes were used to form negatives. Polyvinyl alcohol (PVA, M_r = 145000, Merck, Darmstadt, Germany), Pluronic® F-68 (Sigma Aldrich Co., St. Louis, MO/USA), and croscarmellose sodium (Ac-Di-Sol®, FMC BioPolymer, Girvan, Scotland) were used for the preparation of the cryogel foam. All other reagents and chemicals were of analytical grade. Test objects made of polyurethane foam were formed using commercial sponges purchased from local supermarkets; the same applies to the tested glass marble.

2.2. Physiological background

The quality of an in vitro model depends on the correctness of the simulation of the physiological conditions. Therefore, a thorough understanding of the critical parameters is mandatory. A short physiological background that is important for the comprehension of the novel in vitro model shall be given in this chapter.

The stomach consists of three functional parts: fundus, corpus and antrum. In the proximal part, the fundus, food is mainly stored and only little movements and shear forces are present. The antrum represents the distal part of the stomach responsible for intensive food grinding and crushing. It is linked to the duodenum via the pylorus. The corpus is a connective part between the fundus and the antrum. In fasted state, the stomach can be seen as a collapsed tube with low liquid volumes (10–50 mL) (Fidler et al., 2009; Schiller et al., 2005). In the fed state, it can take up 800 mL to 1700 mL of food or liquids via extension of the gastric wall (Ferrua and Singh, 2010).

Under distended conditions the antrum has a conical shape, while during contraction it is shaped like a tube (Schulze, 2006). The antrum has a diameter of 3–6 cm over a length of up to 8 cm and can take up a maximal volume of about 180 mL (Liao et al., 2004; Schulze, 2006). Its surrounding muscle layer thickens

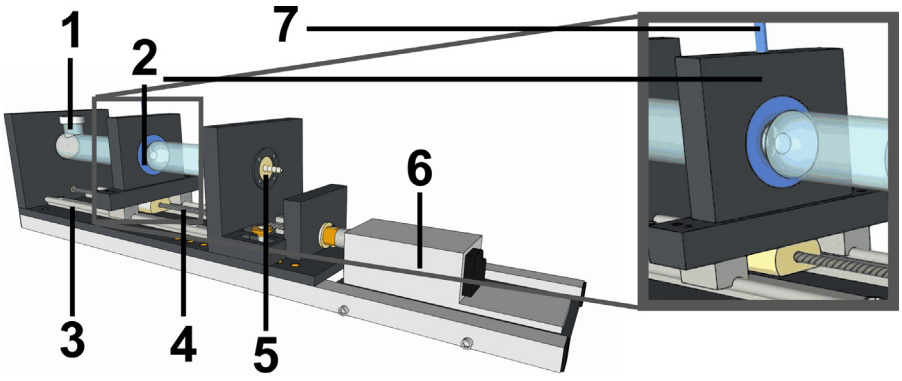

Fig. 1. 3D illustration of the mechanical antrum model. (1) sample inlet, (2) movable slide with inflatable balloon, (3) guide rails, (4) drive screw, (5) media supply via plug, (6) stepping motor, (7) compressed air supply.