International Journal of Pharmaceutics 461 (2014) 296–300

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Development of a pressure-sensitive glyceryl tristearate capsule filled with a drug-containing hydrogel

Lisa Wilde[a], Mona Bock[a], Gunnar Glöckl[a], Grzegorz Garbacz[b], Werner Weitschies[a,*]

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

ARTICLE INFO

Article history:
Received 9 October 2013
Received in revised form
28 November 2013
Accepted 30 November 2013
Available online 11 December 2013

Keywords:
Pressure-sensitive
Drug-targeting
Dissolution stress test
Pylorus
Gastric emptying

ABSTRACT

The purpose of this work was to develop a new pressure-sensitive dosage form that breaks and releases its content in a fasted stomach at the predominant pressure at the pylorus. The content of the dosage form should be liquid so that the active pharmaceutical ingredient quickly reaches maximum absorption in the upper small intestine. For this purpose glyceryl tristearate capsules were developed, consisting of an extremely brittle shell, with a crushing behavior that can be controlled by modification of the shell thickness. The capsules were filled with a hydroxyethyl cellulose gel containing paracetamol. Dissolution testing using USP apparatus 2, performed for simulating the resting time in the stomach, did not show any release. Studies using a texture analyser showed a correlation between the glyceryl tristearate filling volume and the necessary force to break the capsule. Physiological conditions in dissolution testing, such as movement, pressure and discontinuous medium contact, were set in a stress test device and showed that the dosage forms did not break and release its pharmaceutical ingredient until a pressure of 300 mbar was applied which served as a threshold limit for physiological pressure occurring during gastric emptying of large solids.

1. Introduction

Site-specific drug delivery to the small intestine and the colon requires an "intelligent" approach that determines or even senses the arrival of the delivery system at the intended delivery site in the intestines. Typically, this is achieved by using pH sensitive delivery systems, as the different regions of the GI tract show differences in the pH profile (Evans et al., 1988). Further mechanisms are time-controlled systems, enzyme-based systems or pressure controlled systems. Interindividual variations in pH, similarity of pH between small intestine and colon and high variations in gastric emptying times complicate the prediction of location for time- or pH-dependent drug release. Enzymatically triggered release may also underlay great variability since different disease patterns may influence local bacteria and the enzymatic degradation is generally a very slow process (Yang et al., 2002). Up to date only pH-based systems are widely used.

Therefore, another trigger mechanism should be taken into account. The different pressures conditions in the GI tract, especially at the sphincters could be used to create a pressure sensitive dosage form that releases its content due to a defined pressure. Kamba et al. developed the "destructive force dependent release system" (DDRS) to evaluate the mechanical destructive force in the stomach. A highly hydrophobic Teflon mantle of a defined crushing strength around an acid-soluble core containing a model drug was the principle of this system. In vivo studies indicate that the pressure from the gastric wall was lower than 1.5 N in fasted state (Kamba et al., 2000, 2001, 2002).

The "pressure-controlled colon delivery capsule" (PCDC) presented by Hu et al. is a system representing pressure-sensitive release. It consists of a capsule that was coated with ethyl cellulose on the inside and filled with polyethylene glycol (PEG). After intake, the PEG melts under body temperature and creates a pressure-sensitive balloon, breaking at defined forces in the colon. Investigations with different active agents, modified preparation and capsule fillings resulted in a pressure-sensitive dosage form that is suitable for colon targeting (Hu et al., 1998, 1999, 2000; Matsuda et al., 1996; Niwa et al., 1995; Takaya et al., 1995).

Non-digestible solids empty from the stomach as a result of the phase III contractions of the interdigestive migrating motor complex (IMMC) in the fasted state. It consists of several minutes of contractions that lead to the emptying of undigested food out

* Corresponding author at: Ernst-Moritz-Arndt-Universität Greifswald, Institut für Pharmazie, Biopharmazie & Pharmazeutische Technologie, C_DAT Center of Drug Absorption and Transport, Felix-Hausdorff-Straße 3, D-17487 Greifswald, Germany. Tel.: +49 03834 86 481; fax: +49 03834 86 4886.
E-mail address: werner.weitschies@uni-greifswald.de (W. Weitschies).

0378-5173/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ijpharm.2013.11.062

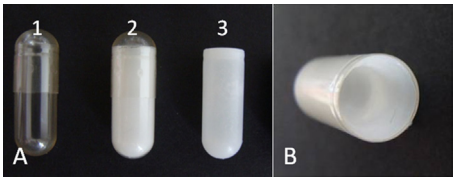

Fig. 1. (A) Preparation of GTS capsule: (1) Hard gelatine capsule, (2) inner GTS coating, (3) complete GTS capsule with removed gelatine. (B) View on top of empty GTS capsule.

of the stomach into the small intestine. Following this, phase I is characterized by relaxation and lasts 10–15 min. Subsequently Phase II, which precedes phase III, consists of intermittent contractile activity. This cycle ceases with food intake and gets replaced by several hours of forced and more frequent antral and intestinal contractions (Cassilly et al., 2008; Ouyang et al., 1989). *Sarosiek et al.* investigated the regional gut transit times with the help of a wireless motility capsule and thereby collected information about the pressure characteristics in the small and large intestine. In the fasted state, pressure in the stomach is about 130 mbar and may occasionally reach values of up to 200 mbar. During the gastric emptying, the pressure raises up to 300 mbar (Sarosiek et al., 2010).

Pressure-controlled drug release at the pylorus provides the drug in a burst release to the duodenum. Since the small intestine with its high effective surface area is the main site for absorption, a complete drug disposal may enhance absorption and bioavailability (Davis et al., 1986). Especially drugs like metformin, levodopa or acyclovir having their absorption window at the very beginning of the duodenum might benefit from a complete drug release at the pylorus (Davis, 2005; Murphy et al., 2012).

The aim of the present work is to develop a new dosage form that releases its model drug due to pyloric pressure with a threshold of 300 mbar fortitude. It should be crushed during IMMC phase III and the content with the dissolved active pharmaceutical ingredient (API) should be immediately provided for absorption as a solution at the upper small intestine.

The developed capsule consists of an extremely brittle glyceryl tristearate (GTS) shell, a hard fat with a melting range at 70–73 °C that stays intact when reaching the body temperature after intake. In our experiments it was filled with a hydrogel containing paracetamol as a model API. The capsules were characterized using compendial dissolution test as well as under biorelevant test conditions. Additionally the crushing strength of the capsules was characterized using a texture analyser.

2. Materials and methods

2.1. Materials

Glyceryl tristearate was purchased from Sasol Germany GmbH (Hamburg, Germany). Hydroxyethyl cellulose (330 mPa s at 2.0% (m/m)) was obtained from Fagron GmbH & Co KG (Barsbüttel, Germany) and Paracetamol was obtained from Caesar & Loretz GmbH (Hilden, Germany).

2.2. Preparation of GTS capsules

The GTS capsules (preparation steps are seen in Fig. 1) were manufactured using molds of hard gelatine capsules (size 0). GTS was melted on a water bath at 90 °C and the intended volume was filled into the bottom part of the capsules with the help of an automatic pipette. The capsules were rotated horizontally to allow the liquid hard fat to solidify uniformly. A 5% hydroxyethyl cellulose gel containing 1.33% paracetamol as API was filled into the empty GTS capsules which were then sealed with 85 μL of melted glyceryl tristearate. The hard gelatine dissolves rapidly (<10 min) at body temperature after intake and releases the GTS capsule containing the paracetamol hydrogel. For the test with a texture analyser, the hard gelatine coat was dissolved in warm water to not adversely affect the crushing behavior.

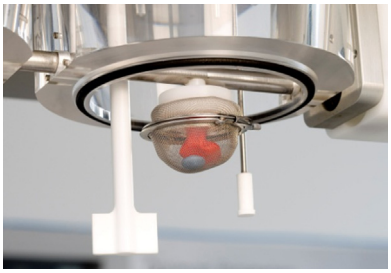

Fig. 2. Netting probe chamber of the dissolution stress test device with balloon and model dosage form.

The content of the GTS capsules was determined by putting a capsule in an Erlenmeyer flask and filling it up to 100.0 g with SGFsp pH 1.8. After complete crushing of the capsule with the help of a glass rod, the solution was mixed on a magnetic stirrer for 30 min at 300 rpm. Afterwards, the solution was diluted tenfold and measured spectrophotometrically in differential mode at wavelengths of 242 nm (signal) and 450 nm (noise).

2.3. Evaluation of mechanical properties

The crushing strength was measured by texture analyser (Stable Micro Systems, Surrey, UK) and the dissolution stress test device (Erweka, Heusenstamm, Germany) (Garbacz et al., 2008). The texture analyser consists of a base table for the dosage form and a movable probe with a 100 N load cell. The penetration velocity amounted to 0.5 mm/s. The load is continuously monitored at a rate of 200 Hz as a function of both time and distance until the probe again returns to its starting position when a preset maximum load of 20 N is reached. The GTS capsules were incubated in 37 °C warm water for removing the hard gelatine capsule before they were tested. The evaluation of the experimental data was detected and analyzed by the "Exponent" Data Analysis Software and plotted as load (N)-distance (mm) profiles.

The dissolution stress test device, whose design is demonstrated in Fig. 2, enables a more physiological investigation of the dissolution behavior including movements, pressure waves and phases of rest. Thereby, the biorelevant stress test is believed to be at least partly able to simulate physiological conditions. The detailed construction was described elsewhere (Garbacz and Klein, 2012; Garbacz et al., 2008, 2010).

The dissolution stress test device was used for analysis of the crushing behavior and dissolution. For the determination of the crushing behavior, the dosage forms were stressed with a gradually increasing pressure from 100 up to 500 mbar in order to estimate the minimal crushing pressure. Therefore, the dosage forms were separately placed in the probe chambers and were incubated in SGFsp pH 1.8 for 5 min for adaption of the temperature and removal of the hard gelatine coat. Afterwards, a pressure wave affected the dosage forms for 10 s. When they did not break, which was detected visually, the next higher pressure was chosen to stress the capsules again.

2.4. Standard dissolution test

Standard dissolution tests of the dosage forms were carried out in the USP dissolution apparatus 2 (Erweka, Heusenstamm, Germany) to simulate the residence time in a fasted stomach. The