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Research paper

Development of pressure-sensitive dosage forms with a core liquefying at body temperature

Lisa Wilde [a], Mona Bock [a], Marieke Wolf [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), Greifswald, Germany
[b] Physiolution GmbH, Greifswald, Germany

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ABSTRACT

Pressure-sensitive dosage forms have been developed that are intended for pulsatile delivery of drugs to the proximal small intestine. The novel dosage forms are composed of insoluble shell and either a hard fat W32 or polyethylene glycol (PEG) 1000 core that are both liquidizing at body temperature. The release is triggered by predominant pressure waves such as contractions of the pylorus causing rupture of the shell and an immediate emptying of the liquefied filling containing the active ingredient. In consequence immediately after the trigger has been effective the total amount of the drug is intended to be available for absorption in the upper small intestine. Both core types were coated with a cellulose acetate film that creates a pressure-sensitive shell in which mechanical resistance is depending on the coating thickness.

Results of the texture analysis confirmed a correlation between the polymer load of the coating and the mechanical resistance. The dissolution test performed under conditions of physiological meaningful mechanical stress showed that the drug release is triggered by pressure waves of $\geqslant$300 mbar which are representing the maximal pressure occurring during the gastric emptying.

1. Introduction

Site specific drug delivery can be realized using dosage forms in which drug delivery is initialized by one or more specific triggers such as time, pH, enzymatic activity or mechanical agitation. Based on the defined passage times for the different parts of the gastrointestinal tract Niwa et al. developed a time-controlled release capsule made of ethyl cellulose intended for colonic drug delivery. It consists of a drug container, a swellable substance (hydroxypropyl cellulose), a capsule body with micropores and a cap. As water penetrates through the pores, the hydroxypropyl cellulose swells, causing the water-insoluble ethyl cellulose to burst when it cannot withstand the swelling pressure [1].

Karrout et al. used the possibility of enzyme-controlled release to create bacteria-sensitive films for colon-targeting. They prepared ethyl cellulose films that were blended with different types of starch derivates which are substrates for enzymes secreted by bacteria in the colon of inflammatory bowel disease patients [2]. A combination of pH and time as release trigger was developed and investigated by Bott et al. They prepared a dosage form consisting of an API-covered pellet that was coated with two different films. The inner coating was a mixture of Eudragit® RL and RS causing sustained release while the outer layer of Eudragit® FS 30 D dissolves at pH > 7 [3]. After entering the colon, the outer layer dissolves and releases a dosage form that immediately liberates its API. However, the use of the pH as the sole trigger for the site specific drug delivery bears several problems. The pH is inter- and probably also intraindividual variable and the difference in pH between small intestine and colon is not always high [4–6]. Under fasting conditions the water content of the small intestine is typically very low and is scattered in a few "pockets" [7]. Dosage forms are not necessarily within these watery pockets, yielding to a further increase in variability in the time point and location of dissolution of enteric coatings. High variations in gastric emptying times make it also complicate to predict the location of time-dependent drug release [8]. Enzymatic-activated release is promising but the enzymatic degradation of polysaccharide matrices is a very slow process [4]. Besides time-, pH- and enzyme-controlled release for drug targeting to the small or large intestine, another trigger mechanism for the site-specific drug release could be pressure caused by the GI motility. The predominant pressures in the gastrointestinal tract were investigated by Sarosiek et al. using a wireless motility capsule. When swallowing the capsule in the fasted state, pH and pressure were monitored as a function of time. In the fasted state, the fortitude of the intragastric pressure waves amounted to about 130–150 mbar. The pressure waves were even higher during the gastric emptying and amounted up

* Corresponding author. 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. Tel.: +49 (0) 3834 86 4813.
E-mail address: werner.weitschies@uni-greifswald.de (W. Weitschies).

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to 300 mbar [9]. This is most likely to housekeeping waves that generate in phase III of the interdigestive migrating motor complex (IMMC) in the stomach [10,11].

A system to evaluate the mechanical destructive force in the stomach is the "destructive force dependent release system" (DDRS) presented by Kamba et al. The tablet like system consists of a highly hydrophobic Teflon mantle of a well-defined crushing strength with an acid-soluble coated core containing the model drug. They in vivo confirmed the presence of the mechanical destructive force that acts on the dosage forms during the GI transit. However, the study results indicate that only two of five subjects could crush a tablet with a crushing strength of 1.5 N in fasted state [12–14], which means that the forces from the gastric wall might be lower.

This work aimed at development of two dosage forms intended for pressure-sensitive drug targeting to the upper small intestine, namely hard fat W32 (Witepsol W32) spheres and polyethylene glycol 1000 (PEG) or macrogol 1000 spheres. The dosage forms contain a solid core of a base melting at body temperature. The core is coated with an insoluble, not swelling, but brittle film that is neither affected by the pH of the stomach nor the residence time in the gastric fluid. As soon as the core melts, the dosage form behaves like a balloon with a liquid center that is intended to burst due to the pressure forces at the pylorus. Consequently the dosage form releases its content immediately and completely in the upper small intestine where it should reach maximum absorption. Riboflavin phosphate (RFP) was used as a model drug and was homogenously dispersed in the core base. The API is characterized by good solubility in water, low toxicity and ease of analysis via spectrophotometry.

The dissolution behavior was characterized using USP apparatus 2 (Erweka, Heusenstamm, Germany) over 3 h and SGFsp pH 1.8. The test was intended to mimic only the physio-chemical conditions of the fasting stomach. The mechanical properties of the spheres were examined using a texture analyzer (Lloyd Instruments, Meerbusch, Germany) as well as the dissolution stress test device (Erweka, Heusenstamm, Germany) [15]. The stress test was used in order to investigate the dissolution under near physiological conditions, including movement, pressure and discontinuous medium contact.

2. Materials and methods

2.1. Materials

Witepsol W32 was purchased from Sasol Germany GmbH (Witten, Germany) and is now available from Cremer Oleo (Hamburg, Germany). PEG 1000 and PEG 6000 were purchased from Fagron GmbH & Co. KG (Barsbüttel, Germany) and Riboflavin phosphate and talcum from Sigma Aldrich Chemie GmbH (Taufkirchen, Germany). Cellulose acetate (pure) and acetone were obtained from Carl Roth GmbH & Co. KG (Karlsruhe, Germany) and Triacetin from Fluka Chemie AG (Buchs, Switzerland). Magnesium stearate and isopropyl alcohol were obtained from Caesar & Loretz GmbH (Hilden, Germany). MCC Vivapur Type 200 was purchased from JRS GmbH & Co. KG (Rosenberg, Germany).

2.2. Preparation of hard fat W32 spheres

For the preparation of the hard fat spheres Witepsol W32 was melted on a water bath at 40 °C. After slight cooling for about 10 min to obtain a creamy consistency, riboflavin phosphate was added at a concentration of 10 mg per sphere. After stirring, the suspension was poured into round steel molds with a diameter of 15 mm, which are usually used for the preparation of vaginal globules. The hard fat W32 spheres were allowed to completely cool down, were then removed from the steel molds and had a mass of 2 g. The batch size was about 50 spheres, depending on the way of pouring the melted hard fat into the molds. For the following coating process they were rounded at the seams with the help of a warm plate. The coating suspension was composed of 5% cellulose acetate solution with an addition of 20% talc and 10% macrogol 6000 (both referred to polymer dry weight) in a mixture of acetone/isopropyl alcohol (4:1). The hard fat W32 spheres for the tests in the stress test device were prepared in a coating pan at an angle of 30° with a diameter of 35 cm and a drum rotation speed of 22 rpm and a drive unit AR 400 (Erweka, Heusenstamm, Germany). The spheres were coated in one batch without heating in order to prevent melting of the base. The filling volume of the coating pan for the coating process was about 250 g. The coating solution was applied manually with the help of a spray gun in a manner that prevents sticking of the spheres and blocking of the spraying nozzle. Two sprays over the spheres were followed by a break of about 15–30 s to allow the coating solution to dry uniformly. Spheres for the breaking strength test in the texture analyzer were coated with a polymer load of 3–7 mg/cm^2, whereas spheres for the dissolution test in USP apparatus 2 and dissolution stress test device and for the breaking strength in the dissolution stress test device were coated with a polymer load of 2–4 mg/cm^2. A surcharge of 17% was included for the preparation in the coating pan. Hard fat W32 spheres that were tested in a USP apparatus 2 and a texture analyzer were coated in one batch in the GMPC I Mini-Coater (Glatt GmbH, Binzen Germany) with the same coating suspension and in the same way as the PEG 1000 spheres.

2.3. Preparation of PEG 1000 spheres

Similar to the preparation of the hard fat W32 spheres, the PEG 1000 spheres were produced by melting PEG 1000 on a water bath at 40 °C. After slight cooling for about 10 min to obtain a creamy consistency, the API riboflavin phosphate was added to the melted base in a concentration of 12.5 mg per sphere, was well suspended and poured into steel molds of same type as those for the hard fat W32 spheres. When the resulted spheres with a mass of 2.5 g cooled down to room temperature, they were removed from the steel molds and the seams were manually rounded with the help of a warm plate to obtain completely round spheres. Because of the high hygroscopicity, the PEG 1000 spheres had to be stored in tight containers until the coating process. The coating solution consisted a 5% cellulose acetate solution with 20% talc and 10% triacetin (both referred to the polymer dry weight) in a mixture of acetone/isopropyl alcohol (4:1) that was applied onto the spheres by the GMPC I Mini-Coater. The settings for the Mini-Coater were a flow rate of 9 g/min, a process air of 20 m^3/h, spray pressure of 1 bar, fine broad spray pressure of 0.8 bar, a process temperature of 17–20 °C and a drum rotation at 20 rpm. The PEG 1000 spheres for all tests with the exception of the crushing strength in the texture analyzer were produced in one batch. They were coated with the same polymer load for the different tests as the hard fat spheres and a surcharge of 50% was included for the preparation in the Mini-Coater. The duration of the coating process depended on the volume of the coating solution that had to be applied on the spheres to obtain different polymer loads. The optical difference between hard fat W32 and PEG 1000 spheres before and after coating is visible in Fig. 1.

2.4. Determination of drug load

The drug load was determined for $n = 6$ parallels of each formulation. For the determination of drug load the hard fat W32 spheres

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