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Gastro-floating tablets of cephalexin: Preparation and *in vitro*/*in vivo* evaluation

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ABSTRACT

Gastro-floating tablets of cephalexin were developed to prolong the residence time in major absorption sites. Gastro-floating tablets were prepared and optimized using hydroxypropyl methylcellulose (HPMC K100M) as matrix and sodium bicarbonate as a gas-forming agent. The properties of the tablets in terms of floating lag time, floating time and *in vitro* release were evaluated. Furthermore, in *vivo* pharmacokinetic study in fed and fasted beagle dogs was performed. The gastro-floating tablets had short floating lag time and exhibited a satisfactory sustained-release profile *in vitro*. Compared with conventional capsules, the gastro-floating tablets presented a sustained-release behavior with a relative bioavailability of 99.4%, while the reference sustained-release tablets gave a relative bioavailability of only 39.3%. Meanwhile, the food had significant effect on the pharmacokinetics of sustained-release tablets. It was concluded that the gastro-floating tablets had a sustained-release effect *in vitro* and *in vivo*, as well as desired pharmacokinetic properties in both fed and fasted conditions.

1. Introduction

Oral delivery is the most widely used and most readily accepted route of drug administration, because of its high patient compliance and flexibility in formulation. However, several factors often impact the absorption of orally administered drugs. These factors include unfavorable physico-chemical characteristics of the drug, high and frequent doses, and physiological conditions such as limited gastric emptying and retention time (Streubel et al., 2006b; Strusi et al., 2008). The latter, in particular, refers to the fact that the upper gastrointestinal (GI) tract (*i.e.*, stomach and upper small intestine) is often the most critical absorption site for many drugs. The residence time of the dosage forms at or prior to the absorption site is therefore crucial to drug bioavailability (Bardonnet et al., 2006; Hou et al., 2003; Streubel et al., 2006b). Thus, prolonging the residence time of dosage form in the stomach is an important strategy to enhance the drug bioavailability (Kotreka and Adeyeye, 2011).

To extend the residence time of dosage form in the stomach, gastroretentive drug delivery systems can be adopted. The systems not only improve the bioavailability of drugs characterized by a narrow absorption window in the upper GI tract, but also provide multiple pharmacokinetic–pharmacodynamic advantages over conventional immediate-release and sustained-release dosage forms (Kotreka and Adeyeye, 2011; Zhang et al., 2012). For example, local treatment for *Helicobacter pylori* infections, which can lead to severe diseases such as gastric cancers and mucosa-associated lymphoid tissue lymphomas, can also be achieved (Badhan et al., 2009; Kotreka and Adeyeye, 2011). Additionally, due to the prolonged gastric residence time, these systems can also be used as sustained-release devices with a reduction of administration dose and frequency, resulting in improved patient compliance (Bardonnet et al., 2006; Streubel et al., 2006b). Several approaches have been attempted in the preparation of gastroretentive systems, including mucoadhesive delivery systems, which adhere to mucosal surfaces; swelling and expanding delivery systems, which rapidly increase in size once they are in the stomach to retard the passage through the pyloru; and floating delivery systems, which float on gastric fluids (Kotreka and Adeyeye, 2011; Pawar et al., 2011; Reddy and Murthy, 2002; Streubel et al., 2006a). Floating drug delivery systems are considered preferable and promising since they do not adversely affect the motility of the GI tract (Kotreka and Adeyeye, 2011; Reddy and Murthy, 2002; Strusi et al.,

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Table 1
Formulations of the gastro-floating tablets and their floating lag time (all quantities are given in grams).

Formulation	Cephalexin	HPMC K100M	HPMC K15M	Stearyl alcohol	$NaHCO_3$	FLT(s)
S1	500	60	–	60	30	0
S2	500	60	–	125	–	5.3
S3	500	120	–	60	–	10.7
S4	500	–	–	60	30	0
S5	500	60	–	–	30	4.9
S6	500	100	–	100	15	15.1
S7	500	100	–	100	50	5.7
S8	500	60	60	–	40	126.0
S9	500	50	60	–	40	60.0
S10	500	60	50	–	40	12.8
S11	500	50	50	–	40	15.6

2008; Zhang et al., 2012). The reliability of gastro-floating drug delivery systems can also be evidenced by the fact that many floating dosage forms have been marketed (Arora et al., 2005; Bardonnet et al., 2006; Kotreka and Adeyeye, 2011).

Cephalexin (CPL), a β-lactam antibiotic, is a broad-spectrum antibiotic for the treatment of a wide range of bacterial infections, including urinary tract infections and respiratory tract infections (Chattopadhyay et al., 1983; Sammeta et al., 2009). It is a lipophilic weak acid with pK_a values of 5.2 and 7.3, and is stable in gastric conditions but degrades in intestinal conditions (pH 6.5) (Davies and Holt, 1972). It is absorbed completely with a short biological half-life of approximately one hour (Davies and Holt, 1972; Griffith, 1983). Thus, to maintain therapeutic range, its conventional dosage forms need to be administered 3–4 times a day (Wise, 1990), leading to a sawtooth kinetics and thus an ineffective therapy. In order to reduce the frequency of administration, several conventional sustained-release products were developed (Agnihotri et al., 2006; Saravanan et al., 2002, 2003). However, the drug bioavailability yielded (35%) is lower due mainly to its instability in intestine and its narrow absorption widow at the upper GI tract (Davies and Holt, 1972; Griffith, 1983; Soback et al., 1987).

To improve the bioavailability of conventional sustained-release dosage forms, we herein present a floating delivery system for cephalexin. In this study, gastro-floating tablets of CPL were prepared and optimized in terms of buoyancy properties and *in vitro* drug release. The pharmacokinetics of floating tablets was performed in beagle dogs.

2. Materials and methods

2.1. Materials

Cephalexin raw material was purchased from Guangzhou Baiyunshan Pharmaceutical Co., Ltd. (Guangdong, China). Hydroxypropyl methylcellulose (HPMC, METHOCEL® K100M, METHOCEL® K15M) was supplied by Colorcon Coating Tech., Ltd. (Shanghai, China). Povidone (PVP, PLASDONE® K29/32) was from ISP Tech., Ltd. (Shanghai, China). Microcrystalline cellulose (MCC, Avicel® PH 101) was supplied by JRS Pharma Tech., Ltd. (Rosenberg, Germany). Lactose monohydrate (Tablettose® 80) was the product of Meggle Pharma Tech., Ltd. (Wasserburg, Germany). Magnesium stearate, stearyl alcohol and xanthan gum were purchased from Yunhong Excipients Co., Ltd. (Shanghai, China). Sodium hydrogen carbonate, sodium alginate and calcium sulfate were supplied from Shanghai Chemicals Co., Ltd., (Shanghai, China). Cephalexin sustained release tablets CEFF-ER® were purchased from Lupin Pharmaceuticals, Inc. (Mumbai, India). Cephalexin capsules were purchased from Zhejing Deruide Pharmaceutical Co., Ltd. (Zhejiang, China). Acetonitrile and other reagents were of chromatographic grade.

2.2. Preparation of gastro-floating tablets

Gastro-floating tablets of cephalexin were prepared by wet granulation method. The drug and other inactive ingredients in each formulation were mixed homogeneously for 30 min in a mortar with pestle, and then granulated using 5% (w/w) PVP K-30 ethanol solution as granulating agent. The granules were dried at 50 °C in an oven. Dry granules were sieved and mixed with 1% (w/w) magnesium stearate before being compressed into tablets. Table 1 shows the detailed formula compositions tested for gastro-floating tablets.

2.3. In vitro buoyancy study

The time (floating lag time, FLT) that gastro-floating tablets take to emerge on the surface of medium and the time that the tablets constantly float on the surface of medium (duration of floating) were determined by the USP type II Apparatus (RCZ-8A, Tiandatianfa Tech., Ltd., Tianjin, China) filled with 900 mL of artificial gastric fluid without pepsin (pH = 1.2, 37 ± 0.5 °C, paddle rotation = 100 rpm). The FLT and the total floating time were determined for each formulation of gastro-floating tablets (n = 3).

2.4. In vitro release study

The *in vitro* release study was carried out with USP type II Apparatus (RCZ-8A, Tiandatianfa Tech., Ltd., Tianjin, China). Nine hundred milliliters of artificial gastric fluid (pH = 1.2) was used as the dissolution medium for gastro-floating tablets and maintained at 37 ± 0.5 °C with the paddle rotation speed of 100 rpm. At predetermined time intervals, aliquots of 10 mL were withdrawn from the dissolution apparatus and filtered through a 0.45 μm cellulose acetate membrane. The drug released was assayed using an UV spectrophotometer (UV-2401PC, Shimadzu Co., Ltd., Jiangsu, China) at 262 nm.

The similarity factor (f_2) adopted by the U.S. Food and Drug Administration was used to evaluate the similarity in release profiles between these two pharmaceutical preparations (Ocana et al., 2009). The similarity factor as a logarithmic transformation of the sum-squared error of differences between the test preparation and reference preparation was calculated by the following equation:

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{i=1}^{n}(\bar{R}_t - \bar{T}_t)^2\right]^{-0.5} \times 100\right\} \quad (1)$$

where R_t and T_t are the accumulated release rates of the reference preparation and test preparation at the predetermined time points respectively, and n is the number of the time points. The similarity factor fits the result between 0 and 100. It is 100 when the test and