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A novel gastro-floating multiparticulate system for dipyridamole (DIP) based on a porous and low-density matrix core: *In vitro* and *in vivo* evaluation

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ABSTRACT

The study was aimed to develop a novel gastro-floating multiparticulate system based on a porous and low-density matrix core with excellent floatability.

The gastro-floating pellets (GFP) were composed of a porous matrix core, a drug loaded layer (DIP and HPMC), a sub-coating layer (HPMC) and a retarding layer (Eudragit® NE 30D). The porous matrix cores were evaluated in specific. EC was chosen as the matrix membrane for its rigidity and minimal expansion to large extent. The porous matrix core was achieved by the complete release of the bulk water soluble excipient from the EC coated beads, and mannitol was selected as the optimal water soluble excipient. SEM photomicrographs confirmed the structure of porous matrix cores. The compositions of GFP were investigated and optimized by orthogonal array design. The optimized formulation could sustain the drug release for 12 h and float on the dissolution medium for at least 12 h without lag time to float. The pharmacokinetic study was conducted in beagle dogs, and the relative bioavailability of the test preparation was 193.11 ± 3.43%.

In conclusion, the novel gastro-floating pellets can be developed as a promising approach for the gastro-retentive drug delivery systems.

1. Introduction

The oral controlled drug delivery system is the most preferable and most reliable route for drug administration, benefiting from excellent patient compliance, low cost of therapy and flexibility in formulation. But for drugs that act locally in the proximal gastrointestinal tract, exhibit good solubility at an acidic pH but poor solubility at an alkaline pH, or have a narrow absorption in the stomach or in the upper small intestine, the conventional oral controlled drug delivery system cannot provide satisfactory therapeutic efficiency (Davis, 2005; Streubel et al., 2006). In these cases, the gastro-retentive systems show super advantages in enhanced bioavailability by releasing drug in a controlled and prolonged manner.

The main approaches to achieve gastro-retention include:

(a) High density systems, which can settle in the lower part of the antrum for a prolonged period of time by employing a heavy inert material such as barium sulphate, titanium dioxide, zinc oxide to increase the total density (Clarke et al., 1993; Guan et al., 2010).
(b) Swelling and expanding systems, which after swallowing, imbibe lots of water before swell or unfold to prevent their passage through the pyloric sphincter (Johnson et al., 1997; Klausner et al., 2003).
(c) Muco-adhesive systems, which are usually hydration, bonding or receptor mediated by adhering to the gastric epithelial cell, thereby prolonging the gastric retention time (Chun et al., 2005; Park and Robinson, 1984).
(d) Floating systems, which can be effervescent or none effervescent in nature to reduce the bulk density to float on the surface of the gastric fluid (Gröning et al., 2007; Sungthongjeen et al., 2008).

Among all the gastro-retentive systems, floating drug delivery systems (FDDS) are considered preferable and promising, since they do not adversely affect the motility of the gastrointestinal tract (GIT) (Kotreka and Adeyeye, 2011; Reddy and Murthy, 2002; Strusi et al., 2008). The fact can also confirm the superiority and reliability of the FDDS that many floating dosage forms have been commercialized and marketed (Bardonnet et al., 2006; Arora et al., 2005; Udaya and Kotreka, 2011). The wide range of dosage forms

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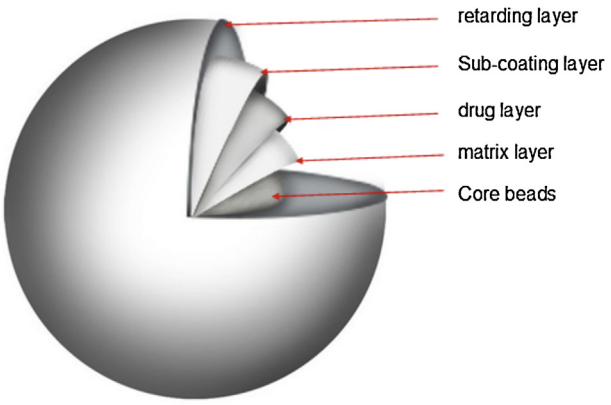

Fig. 1. The schematic diagram of the novel gastro-floating pellets (GFP).

developed as FDDS include single unit FDDS and multiparticulate FDDS, and the multiparticulate FDDS are more advantageous than the single unit FDDS for the absence of "all or none" emptying pattern and minimized variation in distribution in the GIT.

Dipyridamole (DIP) inhibits thrombus formation when given chronically and causes vasodilation when given at high doses over a short time. DIP is a weakly basic drug with a pK_a value of 6.4 (Zhou et al., 2005), and thereby exhibits a pH-dependent solubility with good solubility at a low pH value and poor solubility at a high pH value (Zhang et al., 2009). Since DIP is classified as class II drug (high permeability and low solubility) according to the Biopharmaceutics Classification System (BSC) (Butler and Dressman, 2010), it shows a narrow absorption in the stomach and duodenum (Zhang et al., 2012). In addition, DIP has a short biological half-life of 2–3 h. Research data indicated that the individual difference in drug absorption and bioavailability of DIP is significant (Mahony et al., 1982; Terhaag et al., 1986). Recently, there are some searches on the DIP gastro-retentive dosage forms (Senthil et al., 2011; Birajdar Shivprasad and Darveshwar Jagdeep, 2005). All characterizations mentioned above make DIP an ideal drug to develop into a gastro-retentive dosage form.

In this study, multi-layered gastro-floating pellets (GFP) of DIP were designed to provide sustained drug release in the stomach. Fig. 1 showed a schematic diagram of the novel gastro-floating pellets. Water soluble excipient, possessing 80% in weight, were completely released from the cellulose (EC) coated core beads. After dried at 40 °C, the matrix cores were achieved and then sequentially coated with three different layers: a drug loaded layer (DIP and HPMC), a sub-coating layer (HPMC) and a retarding layer (Eudragit® NE 30D) by using the fluid bed coater. The air entrapped in the matrix cores confers buoyancy to retain in the stomach for a prolonged period of time. The composition of the porous matrix cores and the three layers were investigated. The porous matrix cores were evaluated for the final weight, mechanical strength and morphology, and the gastro-floating pellets were tested for *in vitro* floatability, *in vitro* drug release and morphology. Orthogonal array design was employed to clarify the significance of the influencing factors: the particle size of the matrix cores, the coating levels of the sub-coating layer (HPMC E5) and the retarding release layer (Eudragit® NE 30D), and then to optimize the formulation. The pharmacokinetic study was conducted in beagle dogs.

2. Material and method

2.1. Materials

Dipyridamole (DIP, the purity of which was over 99.9%) was presented by Shenyang No. 1 Pharmaceutical Factory, Shenyang, China; microcrystalline cellulose (MCC, Avicel PH-101) was a gift from FMC, USA; lactose, mannitol, sucrose, sodium chloride (NaCl) and sodium acetate anhydrous were purchased from Tianjin Bodi Chemical Industry, Tianjin, China; ethyl cellulose (EC, 10cp) and hydroxylpropyl methylcellulose (HPMC, E5) were gifts from Colorcon, shanghai, China; polyvinyl pyrrolidone (PVP k30) was a gift from BASF, Germany; Eudragit® NE 30D (B111112096) was a gift from Evonik Röhm Pharma, Darmstadt, Germany; sodium taurocholate and pepsin (1:3000) were purchased from Beijing Biotopped Science & Technology Co. Ltd., Beijing, China; Lipoid S 75 was a gift from Lipoid GmbH, Ludwigshafen, Germany; methanol, glacial acetic acid and ethyl acetate were purchased from Jiangsu Hanbon Sci. & Tech. Co. Ltd., Jiangsu, China. All the others were of either analytical grade or HPLC grade.

Conventional sustained release pellets (CP) with the similar release profile were prepared as the reference preparation in the pharmacokinetic study.

2.2. Preparation of GFP

2.2.1. Preparation of the porous matrix cores

The core beads were prepared by using extrusion/spheronization technique (E-50/S250, Chongqing Enger Granulating & Coating Technology Co., Ltd., China). Water soluble excipient (NaCl, mannitol, lactose or sucrose) and MCC (4:1, w/w) were uniformly mixed by passing through an 80 mesh screen. Moderate amount of distilled water was added to make damp mass, and then it was extruded through a 1.0 mm screen at 35 rpm. The extrudates were spheronized at 700 rpm for 20 min. The collected beads were dried overnight at 40 °C in an oven, and then they were sieved for next study.

The beads were coated with a coating solution which prepared by dissolving EC and PVP k30 in alcohol–water (80:20, v/v), and the mass ratios of EC to PVP k30 were 10:1, 7:1, 5:1 and 4:1. The PVP k30 was added as pore forming agent. The coating solution was sprayed onto the beads in a fluid bed coater (FD-MP-01, Powrex, Japan). The levels of the coating weight gain were 10%, 20% and 30%, separately. The coating conditions were as follows: temperature: 30 ± 2 °C, spray rate: 1.0 ml/min, atomization pressure: 0.2 bar, air flow frequency: 35 Hz. After coating, the pellets were dried at 40 °C for 12 h.

The matrix cores were achieved by using the USA TypeI (basket) dissolution test apparatus (RCZ-6B, Shanghai Huanghai Drug Inspection Instrument Co., Shanghai, China) in 1000 ml distilled water at 50 rpm and room temperature (25 °C). After 6 h, the distilled water was replaced by fresh distilled water. Pellets were picked out at 12 h and dried at 40 °C to constant weight. They were weighed accurately before and after dissolution.

2.2.2. Coating of the three successful layers: drug layer, sub-coating layer (HPMC) and retarding layer (Eudragit® NE 30D)

Firstly, a drug-binder suspension was sprayed onto the matrix core using the fluid bed coater. DIP passing through a 200 mesh sieve was dispersed in the HPMC solution. The PEG6000 (10%, w/w of HPMC) was added as plasticizer. The bottom spray technique was optimized for different parameters, such as atomization pressure, spray rate and air flow frequency. During the optimization process, each parameter was varied while the others were kept constant. The process parameters were as follows: temperature: 35 ± 2 °C, atomization pressure: 0.2 bar, spray rate: 0.7 ml/min, air flow frequency: 25 Hz. After coating, the pellets were fluidized in the fluid bed coater for 15 min to remove the residual moisture.

Then HPMC solution plasticized by PEG6000 was sprayed onto the drug-layered matrix cores as a sub-coating in the fluid bed coater. The coating parameters were as follows: temperature: