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Design and evaluation of an innovative floating and bioadhesive multiparticulate drug delivery system based on hollow structure

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ABSTRACT

In this study a gastric-retentive delivery system was prepared by a novel method which is reported here for the first time. An innovative floating and bioadhesive drug delivery system with a hollow structure was designed and prepared. The floating and bioadhesive drug delivery system was composed of a hollow spherical shell, a waterproof layer (Stearic acid), a drug layer (Ofloxacin), a release retarding film (the novel blended coating materials) and a bioadhesive layer (Carbomer 934P) prepared by using a liquid multi-layering process. A novel blended coating material was designed and investigated to solve the problem of the initial burst release of the formulation and the release mechanism of the novel material was analyzed in this study. The optimized formulation provided the sustained release characteristic and was able to float for 24 h. The SEM cross-section images showed that the particulates were hollow with a spherical shell. X-ray images and pharmacokinetic studies (F_{rel} = 124.1 ± 28.9%) in vivo showed that the gastric-retentive delivery system can be retained in the stomach for more than 6 h. The floating and bioadhesive particulate drug delivery system based on a hollow structure with a dual function presented here is a viable alternative to other for gastroretentive drug delivery system.

1. Introduction

Oral delivery system is the predominant and most preferable route for drug administration, due to the excellent patient compliance, dose reliability and formulation flexibility. However, drug absorption is unsatisfactory and highly variable in many individuals despite excellent in vitro release patterns (Davis, 2005; Streubel et al., 2006a). One important factor is the gastric residence time (GRT) of these dosage forms. A short gastric emptying time results in an incomplete release of the drug from the drug delivery system leading to reduced efficacy of the administered dose (Chueh et al., 1995). Recently, scientific and patent literature has shown increasing interest in novel dosage forms that can be retained in the stomach for a prolonged and predictable period of time. As reported, these gastric-retentive delivery systems are of particular interest for drugs which:

- are locally active in the stomach (Whishead et al., 1996);
- have an absorption window in the stomach or in the upper small intestine (Hoffman et al., 2004; Lippold and Günther, 1991);
- are unstable in the intestinal or colonic environment (Matharu and Sanghavi, 1992);
- exhibit low solubility at high pH values (Soppimath et al., 2001).

A gastro-retentive dosage form (GRDF) can overcome these problems and is particularly useful for drugs with the properties mentioned above. The classification of different modes of gastric retention has been listed by Hwang et al. (1998) and Bardonnet et al. (2006). These involve:

- Density-controlled delivery systems, which either float or sink in gastric fluids;
- Delivery systems that rapidly increase in size to slow the passage through the pylorus expandable systems;
- Bioadhesive delivery systems, which adhere to mucosal surfaces.

Proposed gastric-retentive delivery systems to increase local drug delivery mainly employ either floating or bioadhesive systems. Use of a hollow multiparticulate, a type of floating drug

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delivery system, has attracted a great deal of attention because of its properties of low density, high specific surface area, and good flowability (Liu et al., 2011). Many drugs have been reportedly delivered by hollow microspheres including riboflavin, aspirin, nifedipine, ibuprofen and many others (Jain et al., 2008). However, there are no relevant studies about the use of hollow floating pellets due to the technological difficulties of preparation.

Bioadhesive drug delivery systems are one way to prolong the gastric residence time of drug formulations (Varshosaz et al., 2006). Several types of dosage forms have been proposed to allow prolonged residence within the stomach based on bioadhesive polymers such as carbopol 934P and chitosan (Streubel et al., 2006b; Varshosaz et al., 2006). Bioadhesive polymers are usually macromolecular, hydrophilic gelling substances with numerous hydrogen-bond forming groups, such as carboxyl, hydroxyl, amide and sulfate groups. In addition to hydrogen bondings, covalent and electrostatic interactions are known to play an important role. However, both systems have limitations. Floating systems are unable to retain the drug in the gastric mucous layer while in bioadhesive systems, the mucoadhesive polymers interact non-specifically with the mucus (Liu et al., 2011). Therefore, a synergic drug delivery system combining buoyancy and mucoadhesion may overcome these problems and prove more effective in treating gastric disease (Umamaheswari et al., 2002).

Ofloxacin is a fluoroquinolone antibacterial agent, which has a broad antimicrobial spectrum of activity against both Gram-positive and Gram-negative bacteria. It is approved for use in the treatment of gastrointestinal, respiratory tract and urinary tract infections (Zivanovic et al., 2006). The higher bioavailability and only minor degree of biotransformation ensure a high therapeutic effect (Marier et al., 2006). Ofloxacin exhibits pH- dependent solubility (Chavanpatil et al., 2006) and is freely soluble in acid medium but poorly soluble at an alkaline pH. The absorption site is in the upper part of the gastrointestinal tract and due to its poor solubility in the intestinal tract and the narrower absorption window, ofloxacin gastro-retentive sustained release tablets have been developed by one research group (Chavanpatil et al., 2006). The aim of the present investigation was to design and develop a novel gastro-retentive dosage form.

Response surface methodology (RSM) is a widely practiced approach used in the development and optimization of drug delivery systems (Furlanetto et al., 2003). In principle, the methodology encompasses the use of various experimental designs, generation of polynomial equations and mapping of the response over the experimental domain to optimize the formulation as well as the processing conditions (Joshi et al., 2008). The advantages of such methodology are that it provides a rationale for simultaneous evaluation of several variables and it has been proved to be more efficient than conventional methods.

The aim of this study was to develop a floating and bioadhesive system for gastric-specific drug delivery based on hollow structure, and to evaluate the in vitro and in vivo properties of these hollow-bioadhesive pellets. A water-soluble excipient was completely released from core beads coated with novel blended materials. The washed hollow spherical shell was freeze dried for 24 h. Then the dry hollow spherical shell was sequentially coated with four different layers: a waterproof layer (Stearic acid), a drug layer (Ofloxacin), a release retarding film (the novel blended coating materials (Surelease® E-7-19040 and Eudragit® NE 30D)) and a bioadhesive layer (Carbomer 934P) using a standard manufacturing process (fluidized-bed technology). The air entrapped in the hollow spherical shell confers buoyancy allowing it to be retained in the stomach for a prolonged period of time. The coating level, in vitro and in vivo buoyancy, pellet characteristics, release properties and in vivo pharmacokinetics were investigated. A novel blended coating material for controlling release was designed and investigated. The effect of this novel coating material on release and the properties of the novel blended coating materials were characterized in a series of experiments. A three-level three-factorial central composite rotatable design was employed in the drug release optimization experiments. The responses were studied in a series of experiments. The hollow gastro-retentive dosage form was subjected to in vivo X-ray analysis and a pharmacokinetics study was carried out using UPLC/MS/MS. Until now, there have been no relevant literature reports about the above described material.

2. Materials and methods

2.1. Materials

Ofloxacin (CAS: 82419-36-1) was purchased from Zhejiang Kangyu Pharmaceutical Co. Ltd (H33021162). (Zhejiang, China). Suglets®((Sugar Spheres) Colorcon) was used to prepare the core pellets (Shanghai, China). Surelease® E-7-19040 was a gift from. HPMC E5 (Huzhou Zhanwang, ZheJiang, China) was used as a binder for the drug. PEG 6000 (Bodi, Tianjin, China) was used as a pore-foaming agent. Eudragit® NE 30D was a gift from Röhm Pharma, Darmstadt, Germany. Barium sulfate was China Pharmacopoeia grade. Carbomer 934P was purchased from the Lubrizol Corporation. Stearic acid (Bodi, Tianjin, China) was used as a waterproof layer. Methanol and acetonitrile were HPLC grade and dichloromethane was analytical grade. Ciprofloxacin (internal standard) was purchased from Zhejiang Jiangnan Pharmaceutical Co., Ltd. (Zhejiang, China) Ofloxacin tablets (0.1 g, Shuanghe, Beijing, China) were chosen as the reference preparation.

2.2. Preparation of floating sustained-release pellets

The spherical shell coating materials, the waterproof layer, the model drug (Ofloxacin), the release retarding film and the bioadhesive layer were coated in order.

2.2.1. Preparation of hollow core pellets

A bottom-spray fluidized bed coater (FD-MP-01, Powrex, Japan) was used to modify pellets on a laboratory scale. Sugar spheres (Suglets® 840–710 μm) were used as the core. Eudragit® NE 30D and Surelease® E-7-19040 were blended as the first layer coating materials. Pellets coated with combinations of Eudragit® NE 30D and Surelease® E-7-19040 (in a ratio of 1:1) were used to achieve a weight gain of 15% (w/w) to obtain the optimal core pellets. The process parameters were as follows: temperature = 40 ± 2 °C, spray rate = 4–5 ml/min, and atomization pressure = 1.2 bar. After coating, the pellets were cured at 40 °C, for 24 h then 200 g of coated pellets was washed in purified water and the water was changed every hour until 8 h. The washed pellets were freeze dried for 24 h.

2.2.2. Coating of waterproof layer

A waterproof layer was the second coating of the floating pellets. Stearic acid was dissolved in 87.5% alcohol at a concentration of 1.25% (w/v). Soluble stearic acid (with the weight gain of 20% (w/w)) was sprayed onto the surface of the hollow pellets forming a barrier film coating to improve the water-proofing effect of the pellets. The coating parameters were as follows: temperature = 30 ± 2 °C, spray rate = 2.5–3 ml/min, atomization pressure = 1.2 bar. After coating, the pellets were further cured at 40 °C, for 8 h.

2.2.3. Ofloxacin layering

The model drug (Ofloxacin) was added to HPMC E5 aqueous solution (0.5% w/w) with a pH of 1 (HCl) to prepare the drug solution. The amount of drug loaded was fixed at 60%. After