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Oral sustained-release suspension based on a novel taste-masked and mucoadhesive carrier–ion-exchange fiber

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ABSTRACT

The purpose of this study was to evaluate the feasibility of ion-exchange fiber ZB-1 as a novel carrier in oral taste-masked mucoadhesive sustained-release suspensions. Propranolol (PPN) hydrochloride was selected as a model drug with good water solubility, short half life and bitter taste. The PPN-fiber complexes (PF) were prepared by a batch process and coated with Eudragit® RS100. Gamma scintigraphy was performed on fasted volunteers revealed about 30% ZB-1 and more than 50% coated ZB-1 were still remaining in the stomach at 6 h. *In vitro* results showed the releases of PF and coated PPN-fiber complexes (C-PF) were sustained. The release, drug content and particle size of C-PF were influenced by coat to core ratio, concentration of coating material and rotation rate. The suspension was stable after standing for 30 days in 0.5% Carbopol® with no release rate and taste changed. The administration of C-PF suspension to rats resulted a significant different ($P < 0.05$) improvement of the plasma drug level and prolongation of the release. However, because of the burst effect, the C_{max} values of PF suspension didn't differ from drug solution ($P > 0.05$). Furthermore, a linear relationship between *in vitro* dissolution and *in vivo* absorption was observed.

1. Introduction

Oral liquids are useful in patients with swallowing disorders, such as pediatric, geriatric and bedridden, because of their ease of swallowing and the flexibility of adjusting dosages. Recent years, attempts to develop liquid oral sustained-release formulation based on multiparticulates, such as coated pellets or microparticles, have been gained extensive attention. The large number of particles in the dosage unit may result in more reproducible release profiles, more predictable gastric emptying, more reproducible absorption, and minimized risk of dose dumping or local irritation. However, in general a large part of drugs have unpleasant taste, making the liquid formulation of a palatable product difficult. Meanwhile, the leakage of the drugs into the aqueous suspending medium and the change in release properties during storage are prevalent for ordinary liquid suspensions (Kawano et al., 2010; Khan et al., 2007; Torres et al., 1998).

The use of ion-exchange materials that manifest specific functions such as drug release only in ionic environment, taste-masked and mucoadhesive properties presents a robust alternative drug delivery system for achieving sustained-release. Ion-exchange materials are water-insoluble polymers containing exchange groups in repeating positions on the polymer chain. The drug is not let out from complexes in an ion-free aqueous medium during storage, but after oral use, it is released gradually through displacement of ions of same charge being present in gastrointestinal fluids. As contrasted to the other drug delivery systems based on physical principle, the elution of drugs from complexes depends only on the ion strength of the gastrointestinal fluids and not on complex physiological factors (e.g., pH and

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enzymes) (Guo et al., 2009; Junyaprasert and Manwiwattanakul, 2008; Sriwongjanya and Bodmeier, 1997; Sun et al., 2013). Previous studies have indicated that ion-exchange resin has potential mucoadhesive properties which would enhance the topical or site-specific drug delivery to target sites (Atyabi et al., 1996; Burton et al., 1995; Jackson et al., 2000; Jackson and Perkins, 2001; Park and Robinson, 1984; Thairs et al., 1998). Usually drugs delivered in tablet or capsule tend to fall to the base of the stomach and either empty quickly or remain in the antrum until the occurrence of the next migrating motor complex (Washington et al., 1989). When loaded on ion-exchange resins, potential topical drug can be delivered to the body and fundus of the stomach, where colonies of *H. pylori* are known to exist, or site-specific drug can be delivered to duodenum. Meantime, continuous drug release in a single region (stomach) may consistently match release *in vitro* with passive adsorption *in vivo*.

Different from resins, the structure of ion-exchange fibers is non-cross-linked. A much faster loading rate and larger loading amount are possible because of a lack of pores and channels. These characteristics facilitate the preparation of drug–fiber complex and improve patient compliance by markedly reducing the dose of material. In this study, we tried to evaluate the feasibility of ion-exchange fiber as a novel carrier in oral sustained-release suspensions. Propranolol (PPN) hydrochloride, a non-selective beta adrenergic blocking agent, has been widely used in the treatment of hypertension, angina pectoris, and many other cardiovascular disorders (Huang et al., 2004). It is highly soluble in water and has an intense bitter taste. Due to shorter half life (about 2–6 h), the drug has to be administrated 3 or 4 daily so as to maintain adequate plasma levels of the drug (Datta, 2013; Taylan et al., 1996). Propranolol-fiber complexes and coated propranolol-fiber complexes were used to prepare oral sustained-release suspensions with taste masked, and to examine the release characteristics of them *in vitro* and *in vivo*. The gamma scintigraphy was applied in order to assess gastro-retentive behavior of the ion-exchange fiber in healthy human volunteer.

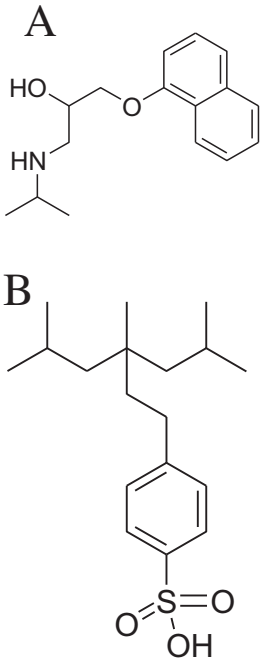

Fig. 1. The structure of propranolol (A) and ion-exchange fiber ZB-1 (B).

2. Materials and methods

2.1. Materials

The structures of propranolol and ion-exchange fiber are shown in Fig. 1. The fiber was stable in a high concentration of acid or alkali, like HCl, H_2SO_4 or NaOH, and all kinds of organic solvent. The working pH and temperature range were 0–14 and 0–120 °C. Some studies had reported on its morphology, load or release characteristics and application (Gao et al., 2014a,b; Yuan et al., 2014). The following chemicals were obtained from commercial sources and used as received: popranolol hydrochloride (Changzhou Yabang Pharmaceutical Co., Ltd., Jiangsu, China); sulfonic acid cation-exchange fibers ZB-1 in the H^+ form (Guilin Zhenghan Co., Ltd., Guangxi, China); Eudragit® RS100 (Röhmpharma, Darmstadt, Germany); Carbopol® 974NF (Lubrizol, Ohio, USA); Ceolus® RC-A591NF (a special mixture of microcrystalline cellulous and carboxymethylcellulose sodium, Asachi Kasei, Tokyo, Japan); liquid paraffin, Span 80, polyethylene glycol 400, dibutyl phthalate (Tianjin Bodi Chemical Co., Ltd., Tianjin, China); petroleum ether, 95% ethanol (Tianjin Fuyu Fine Chemicals Co., Ltd., Tianjin, China); ether absolute (Tianjin Kaixin Chemicals Co., Ltd., Tianjin, China); acetonitrile of HPLC grade (Yuwang Group, Shandong, China); Technetium-99m (as pertechnetate) $\left({}^{99m}TcO_4^-\right)$ was obtained from the Nuclear Medicine Department, The General Hospital of Shenyang Military Command (Liaoning, China). All other chemicals were of analytical grade.

2.2. Purification of the ion-exchange fibers

The fibers in staple form with the maximum ion-exchange capacity of about 3.03 mmol/g were washed with deionized water and 95% ethanol to remove impurities. Each stage of treatment took at least 4 h using a batch process with magnetic stirring and this procedure was repeated thrice. Activation was achieved by recycling the ion-exchanger thrice between its basic and acidic forms, respectively, with 0.01 M NaOH and 0.01 M HCl solution and washing after each treatment with deionized water. Then the fibers were immersed into 1 M NaCl solution in order to pre-load with sodium ions. Finally, they were recovered by vacuum filtration, washed thoroughly with deionized water, dried to constant weight at 50 °C. The diameter of the fiber was about 30–50 μm. Before use, they were cut into small unit.

2.3. Preparation of the drug–fiber complexes

The propranolol-fiber complexes (PF) were formed by a batch process, whereby the previously purified fiber (4 g dry weight) was immersed in a 24.24 mM solution of propranolol hydrochloride (500 ml) and stirred at 40 °C for 3 h. The complexes were harvested by vacuum filtration and washed free of any unbound drug and ions with deionized water and dried to constant weight. The fraction fine enough to pass through a 200-mesh screen and retain on a 300-mesh screen was the final product. To determine the actual loading capacity, the supernatant was assayed spectrophotometrically (UV-2000, Unico (Shanghai) instruments, China) at a wavelength of 289 nm. The amount of drug loaded into the fibers was calculated as the difference between the initial and the remaining amount of drug in the supernatant.

2.4. Characterization

The thermal behavior of drug, ZB-1, PF and physical mixture of drug/ZB-1 were conducted on a DSC instrument (DSC-60, Shimadzu, Japan). Sample was placed in an aluminum pan and