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Studies of chitosan/Kollicoat SR 30D film-coated tablets for colonic drug delivery

Fan Li-Fang[a,b], He Wei[c,d,*], Chang Yong-Zhen[e], Xiang Bai[c], Du Qing[c], Wang Feng[f], Qin Min[g], Cao De-Ying[c,**]

[a] Hebei Yiling Pharmaceutical Group, Medicine Institute, Beijing, China
[b] Department of Pharmaceutical Analysis, School of Pharmaceutical Science, Hebei Medical University, ShiJiaZhuang, China
[c] Department of Pharmaceutics, School of Pharmaceutical Science, Hebei Medical University, ShiJiaZhuang, China
[d] CSPC Pharmaceutical Technology Co., Ltd, ShiJiaZhuang, China
[e] Department of Pharmaceutics, XingTai Medical School Facial Feature & Medical Treatment Technic Faculty, XingTai Medical College, XingTai, China
[f] Department of Hepatitis, National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China
[g] Department of Gastroenterology, Liuzhou Worker Hospital, 8, Guangchang Road, Liuzhou, China

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ABSTRACT

The aim of the study was to define in vitro and in vivo characteristics of chitosan/Kollicoat SR30D film-coated tablets of theophylline for colonic delivery. The tablet cores were coated to different film thicknesses with blends of Kollicoat SR30D and chitosan (2.5:1, 3.5:1, and 5:1, w/w). Swelling and drug release studies were carried out in simulated gastric fluid, simulated intestinal fluid and simulated colonic fluid, respectively. The mechanism of drug release was determined using the Korsmeyer–Peppas model. The in vivo degradation of the tablets was also studied in rats. The swelling behavior and drug release depended on the composition of the coating, as well as the ratio of Kollicoat SR30D to chitosan. The coating was susceptible to enzymatic action, and more accessible to bacterial enzymes than β-glucosidase enzyme. The extent of swelling and digestion correlated with the amount of chitosan within the coating. The drug release data fit well into the Korsmeyer–Peppas equation, indicating that the drug release was controlled by polymer relaxation. The in vivo pharmacokinetic studies of the coated tablets showed delayed T_{max}, decreased C_{max} and prolonged *MRT*. Chitosan/Kollicoat SR30D coated tablets could deliver the drug to the targeted site for local action.

1. Introduction

Colonic drug delivery is recognized to be advantageous in the treatment of disorders of the large intestine, such as irritable bowel syndrome, colitis, Crohn's disease, colon cancer, and infectious diseases where it is necessary to attain a high concentration level of active agent in the large intestine (Jain et al., 2007). Various strategies are currently available to target the release of drugs to the colon: (1) pH-dependent systems, (2) time-dependent systems, (3) prodrugs, (4) pressure-dependent systems and (5) colonic microbiota-activated systems.

Microbially activated delivery systems for colon targeting are being developed to exploit the potential of the specific nature of diverse and luxuriant microbiota associated with the colon compared to other parts of the gastrointestinal (GI) tract (Kosaraju, 2005). These colonic microbiotas produce a large number of hydrolytic and reductive enzymes (Rowhmd, 1988) which can potentially be utilized for colonic delivery. Prodrugs (Ryde, 1992) and coatings based on azoaromatic polymer (Saffran et al., 1986) and matrices (Brondsted and Kopecek, 1991) containing azoaromatic cross-links are examples of systems that are degradable by reductive enzymes released by colonic bacteria (Jain et al., 2006). Apart from azo reductase enzyme, the colonic bacteria release other polysaccharidases like glucosidases which are responsible for the degradation of polysaccharides (Larsen et al., 1989). Hence, drug delivery systems based on polysaccharide can be used for colonic delivery. Many natural polysaccharides, such as amylose, pectin, guar gum and chitosan, have been investigated for their potential to obtain colonic delivery. Especially, the blend of amylose/ethylcellulose film has been shown to have great potential as colonic targeting carries (Cummings et al., 1996; Milojevic et al., 1996a,b; Basit et al., 2004; McConnell et al., 2008). Currently, the amylose/ethylcellulose coating system for colonic targeting, which is known as COLAL, is in

* Corresponding author at: Department of Pharmaceutics, School of Pharmaceutical Science, Hebei Medical University, ShiJiaZhuang, China.
** Corresponding author.
E-mail addresses: hhewwei@126.com (H. Wei), caody3@163.com (C. De-Ying).

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late stage clinical trials for the local treatment of ulcerative colitis.

Chitosan, a natural polymer obtained by alkaline deacetylation of chitin, is non-toxic, biocompatible, and biodegradable. It is susceptible to glycosidic hydrolysis by microbial enzymes in the colon since it possesses glycosidic linkages similar to those of other enzymatically depolymerized polysaccharides (Kosaraju, 2005). As a result, this compound could be promising for colonic delivery if its solubility is reduced in gastric acid conditions (Tozaki et al., 1997; Shimono et al., 2002). This could be accomplished by combining water-insoluble polymers to produce an insoluble film coating. In fact, the method of film coating by the use of aqueous dispersion of chitosan–polymer composite appears to be more effective than that of other coating methods (e.g. compression–coating) using a blend of chitosan–polymer composite. However, no suitable hydrophobic polymer is successfully selected to combine with chitosan as a film-coating material for colonic delivery until now. In our previous investigation, the characteristics of chitosan/Kollicoat SR 30D (composed of 27% polyvinyl acetate (PVAc) free films were studied (He et al., 2008c). The results indicated that the chitosan/Kollicoat SR30D films could be successfully prepared by casting/solvent evaporation method. The free films not only had good mechanical properties, but also were susceptible to digestion by colonic bacterial enzymes. Thus, the application of such chitosan/Kollicoat SR30D films as coatings to oral dosage forms could direct solid dosage forms to the large intestine, where the component of the polysaccharide chitosan, incorporated into the blend film, would be digested. This digestion would allow the delivery of the drug(s) present in the dosage form in the colon. Single-unit systems provide an alternative and more common platform for oral modified-release drug delivery because of their ease and cost of manufacture (Wilson and Basit, 2005). The purpose of current work therefore was (i) to prepare chitosan/Kollicoat SR30D film-coated tablets for colonic delivery; (ii) to investigate the effects of the polymer blend ratio and coating level on the resulting drug release; (iii) to study the in vivo degradation of tablets in rats; and (iv) to assess the pharmacokinetics in dogs. Theophylline is useful in the treatment of nocturnal asthma and falls under Class I (high solubility-high permeability) drug according to the Biopharmaceutical Classification System and is well absorbed in the whole GI tract (Han et al., 2008), thus it was chosen as the model drug in our study.

2. Method and materials

2.1. Materials

Kollicoat SR30D was a gift from BASF (Ludwigshafen, Germany). Chitosan (molecular weight of 45 kDa, 85% degree of deacetylation) was obtained from Luyang Chemical Co., Ltd. (Rongcheng, China); β-glucosidase enzyme was from Yusen Bio. Ltd. (Shanghai, China). Theophylline was purchased from Xinhua Pharm. Co., Ltd. (Zibo, China).

2.2. Preparation of chitosan/KollicoatSR30D film-coated tablets

Tablets were prepared by wet granulation to the following formula: 35% theophylline, 40% lactose, 19% microcrystalline cellulose, 5% polyvinyl pyrrolidone and 1% magnesium stearate. The tablets were manufactured using a single punch tabletting machine (Gylongli Co., Ltd., Beijing, China). The tablets were bi-convex in design, 8 mm in diameter and 200 mg in mass.

Chitosan solutions (2.5 wt.%) were prepared by dissolving chitosan in 0.5% acetic acid solution at ambient temperature with stirring for overnight. The pH value of the solution was adjusted to 4.0–4.5 before use. Then, predetermined amounts of Kollicoat SR30D (2.5:1, 3.5:1 and 5:1, Kollicoat SR30D to chitosan, w/w) were added to this solution with stirring and stirred for a further 3 h to produce coating formulations.

The tablets were coated using a rotary tablet machine (Huanghai Machinery Co., Ltd., Shanghai, China). Drying air was introduced into the front of the pan approximately perpendicular to the tablet bed and the extract was located at the top of the coating pan. The coating conditions were as follows: atomizing pressure of 3.0 bar, inlet temperature of 50 °C, a bed temperature of 30 °C, a pan rotation speed of 20 rpm and a spray rate of 10–12 g/min (NO-2B spray gun, Youda Co., Ltd., Shanghai, China). The coated tablets were further dried in a coating pan for 15 min at 40 °C after the coating process was completed. Furthermore, the tablets coated with Kollicoat SR30D (15%, w/v solids content) were also prepared to obtain a predetermined weigh gain. A series of coated products were produced with different film thicknesses and quantified by the total weight gain (%TWG).

2.3. Swelling test

Chitosan/Kollicoat SR30D coated tablets were accurately weighed and immersed in a flask of dissolution test containing 250 ml of different medium at 37 °C. At specific intervals, the swollen tablet was withdrawn from the medium and weighed after removal of excess surface water by light blotting with a filter paper. The swelling behavior of the coated tablets was calculated using Eq. (1)

$$SD = \frac{W_t - W_o}{W_o} \quad (1)$$

where SD is the swelling degreed of tablet, W_t is the weight of tablet at appropriate intervals in buffer saline and W_o is the absolutely dried weight of tablet. Swelling tests were separately carried out in simulated gastric fluid (SGF, 0.1 M HCl, pH 1.2), simulated intestinal fluid (SIF, phosphate buffer, pH 6.8) and simulated colonic fluid (SCF). The SCF was SIF to which was added rat cecal contents (4%, w/w) (He et al., 2008a) or β-glucosidase enzyme (4%, w/w) (Nunthanid et al., 2008). Three parallel measurements were performed in each case.

2.4. In vitro release studies

The drug release from the chitosan/Kollicoat SR30D coated tablets was determined as follows: the coated tablets were placed into conical flask with 100 ml of release medium and incubated at 37 °C under shaking 100 strokes/min. The release media was SGF (pH 1.2), SIF and SCF with adding of rat cecal contents (4%, w/w) (He et al., 2008a) or β-glucosidase enzyme (4%, w/w), prepared according to the Chinese Pharmacopoeia 2005, respectively. At appropriate intervals, five milliliters of the solutions was replaced by fresh medium. The amount of theophylline released from the tablets was measured using an HPLC method described below.

Mean dissolution time (MDT) reflects the time for the drug to dissolve and is the first statistical moment for cumulative dissolution process that provides an accurate drug release rate. It is an accurate expression for drug release rate. A higher MDT value indicates great drug-retarding ability (Tanigawara et al., 1982; Patel and Patel, 2007). Each in vitro release dissolution testing was performed in triplicate. The MDT was estimated by Eq. (2):

$$MDT = \frac{n}{n+1} \cdot k^{-1/n} \quad (2)$$

where n is the release exponent and k is release rate constant (Mockel and Lippold, 1993) derived from exponential or Korsmeyer–Peppas equation.