Chitosan/Kollicoat SR 30D Film-Coated Pellets of Aminosalicylates for Colonic Drug Delivery

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ABSTRACT: The purpose of the study was to (i) prepare the chitosan/Kollicoat SR 30D film-coated pellets for colonic drug delivery, and (ii) evaluate the colonic delivery and efficacy of these coated pellets in the rat. The pellets were coated to different film thickness with chitosan/Kollicoat SR 30D formulations. *In vitro* drug release was assessed in simulated gastrointestinal (GI) tract conditions. Biodistribution of aminosalicylates (5-ASA) in GI tract and plasma was measured after oral administration of coated or uncoated 5-ASA pellets. Efficacy of the coated or uncoated 5-ASA pellets was tested in 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced rat colitis model. Healing of induced colitis was assessed by measuring the myeloperoxidase activities, colon wet weight/body weight, and damage score. The coating was susceptible to bacteria digestion, resulting in an increase in the release of 5-ASA from the coated pellets. After administration of the coated pellets, the drug concentration in the large intestine was higher than those of uncoated pellets. In plasma, the observed mean C_{max} from the coated pellets was significantly lower than that of the uncoated pellets. Chitosan/Kollicoat SR 30D film-coated pellets could deliver the 5-ASA to the targeted site, providing effective treatment for inflammatory bowel disease. © 2009 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 99:186–195, 2010

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INTRODUCTION

Inflammatory bowel disease (IBD) encompasses several chronic inflammatory conditions of the gastrointestinal (GI) tract, which can impact the

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small or large bowel.[1] The general principle of drug treatment in IBD is to induce remission of outbreaks and to prevent outbreaks during remission.[2] Aminosalicylates (5-aminosalicylic acid, 5-ASA) represent the drugs of first choice in the treatment of IBD.[3] However, 5-ASA itself is not adequate to be used for treatment of the IBD since it is absorbed rapidly and extensively through the upper intestine, but poorly absorbed from the colon.[4,5] Besides serious adverse effects, such as hepatitis, blood dyscrasias, pancreatitis, pleuropericarditis nephrotic syndrome would also be induced by the systemic absorption of 5-ASA.[6,7] Thus, it would be ideal to target the 5-ASA directly to the large intestine for the treatment of IBD.

Different therapeutic approaches have been employed to target the active 5-ASA to the colon. While excluding some approaches, it is convenient to categorize the targeted delivery systems into one of four categories[8]: (1) time-based systems, (2) pH-based systems, (3) pressure-based systems, and (4) enzyme-based systems. However, except for the enzyme-based systems, other systems were not reliable because of the variability in intestinal pH, pressure, or transit times.[9] Microbially activated delivery system to the colon relies on the unique enzymatic ability of the colonic bacteria.[10] The predominant species of anaerobic bacteria in the colon are the *bacteroides*, *bifidobacteria*, *eubacteria*, *clostridia*, and Gram-positive cocci.[11] These bacteria produce a wide range of enzymes, such as β-glucuronidase, β-xylosidase, α-arabinosidase, β-galactosidase, nitroreductase, azoreductase, deaminase, urea hydroxylase, etc.[9,10] The produced enzyme is able to degrade the undigested polysaccharides, which are not digested in the upper GI tract.[12] Many natural polysaccharides are resistant to degradation in the upper GI tract (above the colon), but degraded by the colonic bacteria.[13] Thus, the polysaccharides have the potential to obtain colonic drug delivery. In fact, a number of colonic delivery systems based on the polysaccharides have been designed and developed by various research groups.[14]

Chitosan is a functional linear polymer derived from chitin, the most abundant natural polysaccharide on the earth after cellulose, and it is not digested in the upper GI tract by human digestive enzymes.[15,16] Chitosan is a copolymer consisting of 2-amino-2-deoxy-D-glucose and 2-acetamido-2-deoxy-D-glucose units linked with β-(1 → 4) bonds. 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.[17] Being soluble in gastric acid, the chitosan is not able to shield its drug load effectively during its passage through the upper GI tract in the colonic drug delivery. In order to reduce the solubility of the chitosan, a water-insoluble polymer Kollicoat SR 30D (composed of 27% polyvinyl acetate (PVAc)) was selected to combine with chitosan as a film-coating material in our previous report.[18] The results indicated that the free films not only possessed good mechanical properties, but also were susceptible to digestion by rat colonic bacterial enzyme. Thus, the chitosan/Kollicoat SR 30D films coating has a potential as a coating system for colonic delivery.

The purpose of the current work was to (i) prepare chitosan/Kollicoat SR 30D film-coated pellets, (ii) study the profiles of *in vitro* drug release, (iii) assess the distribution of drugs in intestinal tracts and pharmacokinetics (PK) in rats and (iiii) finally evaluate the therapeutic efficiency of this drug carrier system using the experiment colitis rat model. 5-ASA was used as the model drug.

MATERIALS AND METHODS

Materials

Kollicoat SR 30D 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). 5-ASA was obtained as gift sample from Laifu Pharm&Chem Co., Ltd. (Zhoushan, China).

Preparation of Chitosan/Kollicoat SR 30D Film-Coated Pellets

Pellets were prepared by the process of extrusion–spheronization. The formulation comprised 20% 5-ASA, 30% lactose, and 50% microcrystallisate cellulose (Avicel® PH101). The pellets were dried in a fluidized bed dryer (Jiangsu Jiafa Granulating drying equipment, Changzhou, China) for 30 min at 60°C. The dried pellets were then sieved and those ranging from 0.8 to 1.0 mm were used in further studies.

Chitosan solutions (2.5 wt. %) were prepared by dissolving chitosan 0.5% in acetic acid solution at ambient temperature with stirring for overnight. The pH value of the solution was adjusted to 4.0–