RESEARCH ARTICLE

Elucidation of Release Characteristics of Highly Soluble Drug Trimetazidine Hydrochloride from Chitosan–Carrageenan Matrix Tablets

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ABSTRACT: The aim of this study was to better understand the underlying drug release characteristics from matrix tablets based on the combination of chitosan (CS) and different types of carrageenans [kappa (κ)-CG, iota (ι)-CG, and lambda (λ)-CG]. Highly soluble trimetazidine hydrochloride (TH) was used as a model drug. First, characteristics of drug release from different formulations were investigated, and then *in situ* complexation capacity of CG with TH and CS was studied by differential scanning calorimetry and Fourier transform infrared spectroscopy. Erosion and swelling of matrix were also characterized to better understand the drug-release mechanisms. Effects of pH and ionic strength on drug release were also studied. It was found that not only ι-CG and λ-CG could reduce the burst release of TH by the effect of TH–CG interaction, CS–ι-CG- and CS–λ-CG-based polyelectrolyte film could further modify the controlled-release behavior, but not CS–κ-CG. High pH and high ionic strength resulted in faster drug release from CS–κ-CG- and CS–ι-CG-based matrix, but drug release from CS–λ-CG-based matrix was less sensitive to pH and ionic strength. In conclusion, CS–λ-CG-based matrix tablets are quite promising as controlled-release drug carrier based on multiple mechanisms. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: chitosan; carrageenan; trimetazidine hydrochloride; release characteristics; tablet; complexation; oral drug delivery; controlled release; drug-excipient interation; biodegradable polymers

INTRODUCTION

Hydrogels are hydrophilic, three-dimensional polymeric networks capable of imbibing large amounts of water or biological fluids.[1] In recent years, a number of studies have greatly contributed to the understanding of polysaccharide-based hydrogel networks, with numerous systems being proposed.[2] Polysaccharide-based hydrogels that swell in an aqueous medium have been widely used to formulate controlled-release tablets.[2,3] The release of drug from these systems usually depends on one or more of the following processes: wetting of the polymer matrix by solvent, swelling of the polymer, diffusion of drug through the hydrated polymer, dissolution of drug in the solvent, and erosion of the polymer.[4]

Among the polysaccharide-based hydrogels reported so far, anionic carrageenan (CG) and cationic chitosan (CS) present great potential for achieving well-controlled drug release.[3,5] CGs are linear, sulfated polysaccharides extracted from red algae with a pK_a value of about 2.0.[6] They are composed of D-galactose residues linked alternately in 3-linked-β-D-galactopyranose and 4-linked-α-D-galactopyranose units, and they are classified according to the degree of substitution that occurs on their free hydroxyl groups. There are three basic types of CGs, namely kappa (κ)-CG, iota (ι)-CG, and lambda (λ)-CG.[7] Different types of CGs (κ, ι, and λ) have varied characteristics in controlling drug release.[8] CS is the most abundant natural amino polysaccharide composed of β-1,4-linked glucosamine (deacetylated units) and N-acetyl-D-glucosamine (acetylated units),[9] with different degree of deacetylation (70%–95%) and molecular weight (10–1000 kDa). CS is also a weak base with a pK_a value of 6.2–7.0.[10] CS has already been the subject of interest as pharmaceutical excipients because

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of its appealing properties such as biocompatibility, biodegradability, low toxicity, and relatively low production cost from abundant natural sources.[3]

At present, the main applications of CS in oral controlled release are concentrated on mixed matrix of CS with other hydrophilic polymers. As CS is positively charged at low pH values (below its pK_a value), it can spontaneously associate with negatively charged polyions in solution to form polyelectrolyte complexes.[9] Their physical mixture or polyelectrolyte complexes as the matrix of modified release dosage forms for oral administration have been reported, such as CS–sodium alginate,[11] CS–xanthan gum,[12] CS–carboxymethylcellulose,[13] CS–hyaluronic acid,[14] and CS–carbopol.[15] Compared with single polymer, physical mixture, or polyelectrolyte complexes as the matrix of tablets have many advantages, such as increasing the controlled-release capability[11] and reducing the pH dependence.[15] CGs, because of the presence of sulfate groups in the structure, have strong negative charge under certain pH conditions.[6] Therefore, polyelectrolyte complexes might also be formed between negatively charged CG and positively charged CS, which can be used for the preparation of sustained-release tablets,[16] beads,[17] and nanoparticles.[18] Different types of CGs can control drug release by different mechanisms.[7,8] Therefore, it is assumed that the combination of CS with different types of CGs as tablet matrices may show varied controlled-release characteristics. However, to the best of our knowledge, there is no report about comparative studies of extended-release tablets based on mixed matrix of CS and different types of CGs so far, which are expected to have better controlled drug release for the foreseen formation of polyelectrolyte complex on the surface of the tablets based on the charge properties of CS and CG. Moreover, analysis of release characteristics from CS–CG-based systems was also absent.

Thus, the objective of this paper is to study the feasibility of using the physical mixture of CS and CGs (κ, ι, and λ) as the tablet matrices to achieve sustained release and elucidate the corresponding drug-release mechanism in detail. In this study, trimetazidine hydrochloride (TH) was chosen as a model drug, which has two pK_a values, 4.54 and 9.14, respectively.[19] TH is a cardiovascular drug for the prophylactic treatment of anginapectoris, adjuvant symptomatic treatment of vertigo and tinnitus, and visual disorders of circulatory origin.[20] Because of its short half-life and application in chronic diseases, it is considered as an ideal drug candidate for the design of oral controlled-release dosage forms. However, because of its high water solubility (>1 g/mL), commonly used hydrophilic polymers were difficult to control its release.[21] Here, different types of drug-loaded CS–CG matrix tablets were prepared; drug release characteristics were studied in detail by investigating *in situ* complexation capacity of CG with TH and CS, the erosion and swelling of the matrices. Moreover, effects of dissolution media and ionic strength on drug release were also elucidated for furthering the current understanding of fundamental release mechanisms based on CS–CG matrix tablets.

MATERIALS AND METHODS

Materials

Trimetazidine hydrochloride was purchased from Hubei–Sihuan Pharmaceutical Company, Ltd. (Wuhan, Hubei, China). CS (400 kDa) was purchased from Weifang Kehai Chitin Company, Ltd. (Weifang, Shandong, China) with a degree of deacetylation of 86.5%. κ-CG (GelcarinGP-812 NF), ι-CG (GelcarinGP-379NF), λ-CG (ViscarinGP-209NF), and microcrystalline cellulose (Avicel PH-101) were kindly provided as a gift by FMC (Philadelphia, Pennsylvania). Magnesium stearate was from Tianjin Bodi Chemical Company, Ltd. (Hexi, Tianjin, China). Silica was from Huzhou Zhanwang Pharmaceutical Company, Ltd. (Huzhou, Zhejiang, China). All other chemicals were of analytical grade.

Formulation and Preparation of Tablets

The formulations studied are shown in Table 1. Tablets containing CS and CG as polymeric carriers, microcrystalline cellulose as filler, and colloidal silicon dioxide and magnesium stearate as lubricants were prepared by direct compression. The model drug (35 mg per tablet) and the excipients used were all passed through 80-mesh sieve and blended for at least 10 min. Tablets were prepared using a single-punch tabletting machine (DP30A; Beijing Gylongli Company, Ltd., Beijing, China) equipped with an 8 mm diameter flat-faced punch. Hardness of all the tablets was adjusted to 40–80 N (hardness tester; $n = 6$; Shanghai Huanghai Instruments Company, Ltd., Shanghai, China). The weight of each tablet was 250 mg.

In Vitro Release Studies

All drug release tests were carried out using a dissolution apparatus (ZRD6-B, Shanghai Huanghai Instruments Company, Ltd.) with basket method (USP Apparatus I), rotating at 100 rpm at 37 ± 0.5°C. Unless specially indicated, the tablets were submerged into 900 mL of simulated gastric fluid (SGF: pH 1.2, enzyme free) for 2 h, and then the tablets were transferred to 900 mL of simulated intestinal fluid (SIF: phosphate buffer, pH 6.8, enzyme free) for additional 10 h. Aliquots of 5 mL were withdrawn at different time intervals (1, 2, 4, 6, 8, 10, and 12 h) and were replaced with equal amounts of fresh release medium.

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