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Effect of formulation variables on *in vitro* release of a water-soluble drug from chitosan–sodium alginate matrix tablets

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ABSTRACT

The objective of this study is to investigate the feasibility of using chitosan–sodium alginate (CS–SA) based matrix tablets for extended-release of highly water-soluble drugs by changing formulation variables. Using trimetazidine hydrochloride (TH) as a water-soluble model drug, influence of dissolution medium, the amount of CS–SA, the CS:SA ratio, the type of SA, the type and amount of diluents, on *in vitro* drug release from CS–SA based matrix tablets were studied. Drug release kinetics and release mechanisms were elucidated. *In vitro* release experiments were conducted in simulated gastric fluid (SGF) followed by simulated intestinal fluid (SIF). Drug release rate decreased with the increase of CS–SA amount. CS:SA ratio had only slight effect on drug release and no influence of SA type on drug release was found. On the other hand, a large amount of water-soluble diluents could modify drug release profiles. It was found that drug release kinetics showed the best fit to Higuchi equation with Fickian diffusion as the main release mechanism. In conclusion, this study demonstrated that it is possible to design extended-release tablets of water-soluble drugs using CS–SA as the matrix by optimizing formulation components, and provide better understanding about drug release from CS–SA matrix tablets.

1. Introduction

Polymer-based monolithic matrix tablets are the most commonly used to fabricate oral extended-release dosage forms because of the economic benefits, the relative simplicity of process development and scale-up procedures. For decades, hydrophilic matrices have been widely utilized to prepare matrix tablets. In general, drugs are dispersed or dissolved in

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hydrophilic matrix and they are available for release as the matrix hydrates, swells (forms a gel), and dissolves [1]. Hydrophilic matrices have the capability to provide desired release profiles for a wide range of drugs using established and well-characterized excipients. So far, most commercially available controlled-release products are fabricated using nonionic polymers such as hydroxypropyl methylcellulose, hydroxypropyl cellulose and polyethylene oxide [1–3]. At present, a few anionic polymers, such as sodium carboxymethyl cellulose, carbomer, xanthan gum and sodium alginate (SA), also showed great potential for controlling drug release [2,4].

Among the anionic polymers, SA, a water-soluble salt of alginic acid, is a natural linear unbranched polysaccharide extracted from marine brown algae. It consists of different proportions of β-D-mannuronic acid (M) and α-L-guluronic acid (G) units and can be prepared with a wide range of molecular weight (MW 50–100,000 kDa) [5,6]. Due to its biocompatibility and ease of gelation, SA hydrogels are particularly attractive in oral drug delivery [5]. For example, verapamil hydrochloride extended-release matrices (Calan®SR, Pfizer) containing a combination of hydroxypropyl methylcellulose and SA produce desired drug release profile *in vivo* [1]. The presence of carboxylate groups that can accept or release protons in response to pH change makes SA pH sensitive. At pH values below the pK_a of the M (3.38) and G (3.65) monomers, the soluble sodium salt is converted to insoluble alginic acid. In the matrix tablets, pH sensitivity of SA could affect characteristics of the diffusion barrier and as a consequence drug release [1]. Cryogenic electron microscopy reveals the hydrated surface layer formed by SA matrices in simulated gastric fluid (SGF) was particulate and porous, which induced crack formation or lamination of SA matrix tablet, leading to burst release of drug in gastric environment. This compromised the integrity of drug diffusion barrier and resulted in loss of controlling release [7,8]. In contrast, a highly hydrated continuous swollen layer was formed in simulated intestinal fluid (SIF) [7]. However, SA-based matrix tablets usually could not extend drug release for more than 12 h due to its swelling and erosion in SIF [9,10]. To overcome this shortcoming, some innovative approaches have been attempted to modify SA matrices for better control of drug release, such as inclusion of pH-modifiers [8], incorporation of crosslinking agents [5,11] and combination with other hydrophilic matrices [12]. Among them, SA in combination with chitosan (CS) played a key role in controlling drug release.

CS, obtained by deacetylation of chitin from crustacean shells, is a cationic polysaccharide consisting of repeating D-glucosamine and N-acetyl-D-glucosamine units linked via (1–4) glycosidic bonds [13]. It was reported that CS–SA polyelectrolyte complexes could be used as the oral controlled-release matrix. Consequently, the integrity of SA matrices could be improved by the interaction with CS and the drugs entrapped were retained for a longer time. Meanwhile, CS also showed drug release controlling capacity due to gelling [14]. In previous reports, *in situ* polyelectrolyte complexes formation based on the physical mixtures of SA and CS were found, avoiding the complex process of preparing polyelectrolyte complexes [15]. The new mechanism updated CS–SA based drug delivery systems. SA has been attempted to control the release of highly water-soluble drugs such as chlorpheniramine maleate [8], diltiazem hydrochloride [11], and verapamil hydrochloride [12], but with some limitations. Thus, CS–SA matrix tablets loading a highly water-soluble drug draw more attention as they are easy and economical to prepare by using the common tableting procedures.

Therefore, in the present study, by using trimetazidine hydrochloride as the model drug, which has high aqueous solubility in both acidic and neutral media (both more than 1 g/ml at pH 1.2 and 6.8, respectively, at 20 °C) [16], influence of formulation variables on drug release from CS–SA matrix tables were investigated systemically, and drug release kinetics and transport mechanisms were elucidated using different mathematical models.

2. Materials and methods

2.1. Materials

Trimetazidine hydrochloride was purchased from Hubei-Sihuan Pharmaceutical Co., Ltd. (Wuhan, Hubei, China). Chitosan was purchased from Weifang Kehai Chitin Co., Ltd. (Weifang, Shandong, China) with a molecular weight of about 400 kDa and a degree of deacetylation of 86.5%. Sodium alginate (Table 1) [17] and microcrystalline cellulose (MCC, Avicel PH-200) were kindly provided as a gift by FMC Biopolymer (Philadelphia, Pennsylvania, USA). Lactose monohydrate (FlowLac® 100) was kindly provided by Meggle Excipients & Technology (Wasserburg, Germany). Pregelatinized starch and magnesium stearate were kindly provided by Anhui Shanhe Pharmaceutical Excipients Co., Ltd. (Huainan, Anhui, China). Aerosil was purchased from Huzhou Zhanwang Pharmaceutical Company, Ltd. (Huzhou, Zhejiang, China). All other chemicals were of analytical grade.

2.2. Preparation of matrix tablets

The formulations studied are shown in Table 2. Tablets containing CS–SA as polymeric carriers, microcrystalline cellulose, pregelatinized starch and lactose monohydrate as fillers, and magnesium stearate and aerosil as lubricants were prepared by direct compression method. The model drug and the excipients used were all passed through 80-mesh sieve. The model drug and excipients except for magnesium stearate were firstly blended for at least 10 min. Thereafter, magnesium stearate was added and mixed for another 2 min. Tablets were prepared using a single punch tableting machine (DP30A; Beijing Gylongli Company, Ltd., Beijing, China) equipped with

Table 1 – FMC biopolymer commercially available alginate products for controlled-release.

Trade name	Viscosity (mPa.s, 1% w/v SA sol., 20 °C)	M/G (%)
Protanal LF200M	200–400	55–65/35–45
Protanal LF120M	70–150	55–65/35–45
Protanal LF240D	70–150	65–70/30–35

M/G: manuronate/guluronate [17].