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Matrix tablets based on carrageenans with dual controlled release of doxazosin mesylate

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ABSTRACT

The use of polymeric polyelectrolytes as matrix-forming agents is far from optimally or fully understood. Polyelectrolyte carrageenan (CARR) matrices loaded with oppositely charged active substance doxazosin mesylate (DM) were investigated according to their water-uptake/erosion properties, *in situ* complexation ability of CARR with DM, and the possibility to achieve dual drug release control. Interactions between different CARR types (ι-, κ-, and λ-) and DM were confirmed by differential scanning calorimetry (DSC), scanning electron microscopy (SEM), and zeta potential measurements. Combination of water-uptake/erosion with *in situ* complexation prolonged DM release from CARR matrices for more than 24 h. The rate order of drug release was in accordance with the number of ester sulfate moieties per disaccharide unit of CARRs (κ (1) > ι (2) > λ (3)). The higher the charge on the CARR backbone, the higher the number of interactions with DM and the slower the drug release. Low pH, more vigorous hydrodynamics, and higher ionic strength resulted in faster drug release. Based on zeta potential measurements of DM and CARRs, proposed influence of counterion condensation and its effect on screening polyelectrolyte–drug interactions was confirmed to lower *in situ* DM–CARR complexation. Dual drug release control from polyelectrolyte matrices by water-uptake/erosion and *in situ* complexation offers many new approaches for designing controlled-release systems.

1. Introduction

Hydrophilic, swellable polymers are the main functional matrix excipients for the majority of modified-release tablet preparations (Omidian and Park, 2008). Cellulose ethers have been the most thoroughly investigated of all of the semi-synthetic polymers (Alderman, 1984; Baumgartner et al., 1998). Nevertheless, polymers of natural origin widely used in the food and cosmetics industry are now coming to the fore of pharmaceutical research (De Ruiter and Rudolph, 1997; Bhardwaj et al., 2000; Coviello et al., 2007).

For hydrophilic polymers, it is generally accepted that upon contact with water they hydrate and swell, forming a gel layer around the dry core that regulates the penetration of water into the matrix and the release of the active ingredient incorporated. Swelling and erosion of the functional polymers are therefore the two main mechanisms governing the release of the drug from the hydrophilic polymer matrices (Colombo et al., 2000; Baumgartner et al., 2002). However, the term "swelling" is often reserved for polymers that form a gel upon contact with water. Because some polymers such as λ-carrageenan do not form gels but rather very viscous solutions (Rees, 1977; Rochas et al., 1986; Yuguchi et al., 2002), "swelling" is denoted as a "water-uptake mechanism."

When ionic polymers (polyelectrolytes) are used as excipients in pharmaceutical formulations, the release of oppositely charged drugs may be strongly affected by the occurrence of charge–charge interactions or possible complex formation (Lelham and Sundelöf, 1995). In some cases, these events are considered negative and should be avoided because they represent drug–excipient incompatibility. On the other hand, polyelectrolyte–drug interactions (complexation) can also be exploited for controlled drug release (Bonferoni et al., 2000).

The polyelectrolytes that have attracted much attention due to their variations in ion specificity, charge density, and possibility of helix–coil transition, thus offering a large number of different applications, are carrageenans (CARRs).

CARRs are linear, anionic, partially sulfated galactans extracted from many species of red algae, the Rhodophyceae. They are composed of D-galactose residues linked alternately with α-(1→3) and β-(1→4) linkages. These sulfated galactans are classified according to the presence of 3.6-anhydrogalactose on the 4-linked residue and the position and number of sulfate groups (Rowe et al., 2005). The most important types of carrageenans are κ-, ι- and λ-carrageenan (Fig. 1). In theory and in the ideal case, κ-CARR has only

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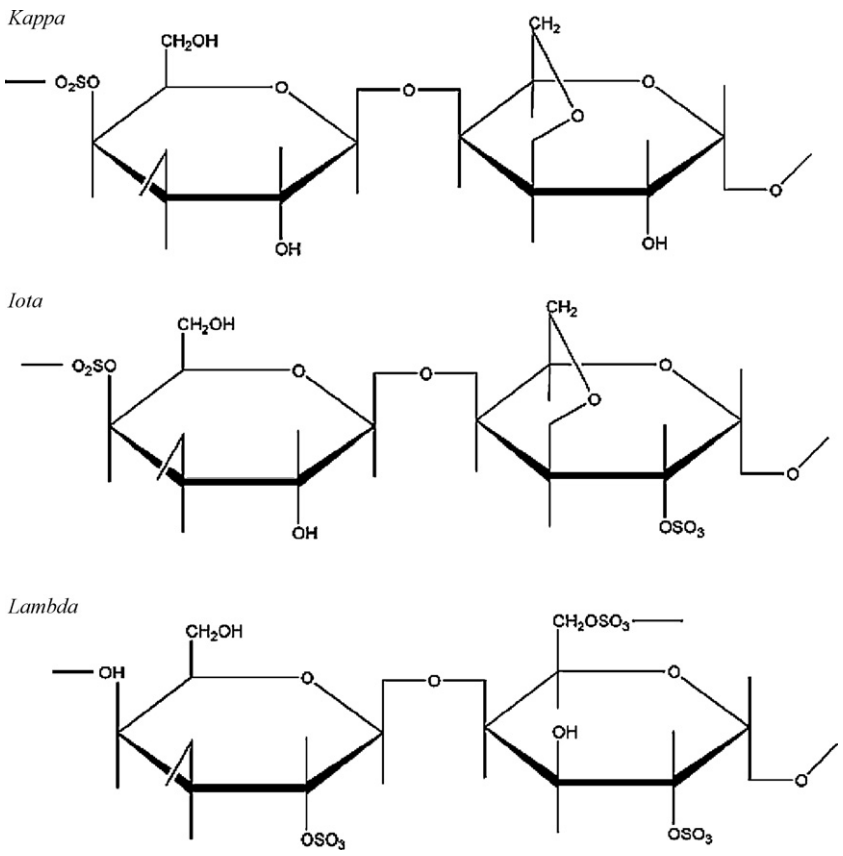

Fig. 1. The repeating unit structure of the carrageenan family (Rowe et al., 2005).

one sulfate moiety per disaccharide repeating unit, ι-CARR two, and λ-CARR can bear three sulfate moieties per disaccharide unit. κ- and ι-CARR contain the 3.6-anhydrogalactose unit and are gelling polymers, but λ-CARR has only galactose residues and is considered a non-gelling, water-soluble polymer, which forms very viscous solutions (Rees, 1977; Rochas et al., 1986; Yuguchi et al., 2002). CARRs are very often used in food products as thickeners and stabilizers; however, their usage is also increasing in pharmaceutical formulations. They are GRAS and are also of pharmaceutical grade. The polyanionic nature of CARRs was shown to have a possible crucial influence on drug release behaviour as well (Singh and Lelham, 1998).

Drug release from CARR matrices was prolonged up to 12 h (Picker, 1999a,b; Naim et al., 2004). CARRs were also combined with other well-established excipients for controlled release, such as cellulose ethers, to additionally prolong drug release (Nerurkar et al., 2005). Combinations of different CARRs themselves (Gupta et al., 2001) or with inert excipients (Picker, 1999a) were also studied. These investigations have shown that CARRs may interact with some basic drugs (Hugerth, 2001), which can lead to additional decreases in the drug release rate (Hariharan et al., 1997). A special method for preparation of a diltiazem hydrochloride–λ-CARR complex was proposed (Aguzzi et al., 2002) and almost all further CARR studies with a basic drug focused on the preparation of the complex before tablet preparation. To the best of our knowledge, no comparison of characteristics of prepared complexes with all three CARR types and a basic drug has been done to date, and no *in situ* complexation (instead of special complex preparation) has been evaluated. Detailed explanation of processes controlling drug release from matrices achieved by a combination of complexation and water-uptake/erosion mechanisms and the environmental impacts on these processes is still lacking.

Doxazosin mesylate (DM) is a cationic drug and selective α_1-antagonist used to treat hypertension. It also blocks α_1-receptors in the prostate gland and alleviates the symptoms of benign prostatic hyperplasia. The therapeutic dose is between 1 and 16 mg, also available as once-daily dosing in controlled-release formulations, which lead to increased patient compliance (Williams and Lemke, 2002).

The aim of our study was to focus on achieving dual drug release control from CARR matrices based on water-uptake and erosion on the one hand, and drug–polyelectrolyte complexation on the other. To accomplish this, various polyelectrolyte behaviours of all three major CARR types were exploited to achieve *in situ* complexation with the cationic drug DM. Complexes were characterized by DSC, SEM, and zeta potential measurements. Water-uptake and erosion mechanisms of CARR matrices were also studied. The magnitude of polymer–drug interactions can completely change the release profile and offers fine-tuning of the release profile in a desirable manner. An understanding of these interactions together with the impact of ionic strength and hydrodynamics is valuable in elucidating the effects of drug release *in vivo*.

2. Experimental

2.1. Materials

Carrageenan (CARR) ι (Gelcarin GP 379 NF), κ (Gelcarin GP 911 NF), and λ (Viscarin GP 209 NF) were obtained from FMC Biopolymers (USA). The average molecular weight (MW) for ι- and κ-CARR was in the range of 400–600 kDa and for λ-CARR it was 400–800 kDa. The active substance doxazosin mesylate (DM) with a MW of 547.58 g/mol was supplied by Krka (Slovenia). The saturated solubility of DM was determined experimentally in the following