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Release mechanism of doxazosin from carrageenan matrix tablets: Effect of ionic strength and addition of sodium dodecyl sulphate

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ABSTRACT

The polyelectrolyte matrix tablets loaded with an oppositely charged drug exhibit complex drug-release mechanisms. In this study, the release mechanism of a cationic drug doxazosin mesylate (DM) from matrix tablets based on an anionic polyelectrolyte λ-carrageenan (λ-CARR) is investigated. The drug release rates from λ-CARR matrices are correlated with binding results based on potentiometric measurements using the DM ion-sensitive membrane electrode and with molecular characteristics of the DM-λ-CARR-complex particles through hydrodynamic size measurements. Experiments are performed in solutions with different ionic strength and with the addition of an anionic surfactant sodium dodecyl sulphate (SDS). It is demonstrated that in addition to swelling and erosion of tablets, the release rates depend strongly on cooperative interactions between DM and λ-CARR. Addition of SDS at concentrations below its critical micelle concentration (CMC) slows down the DM release through hydrophobic binding of SDS to the DM-λ-CARR complex. On the contrary, at concentrations above the CMC SDS pulls DM from the complex by forming mixed micelles with it and thus accelerates the release. Results involving SDS show that the concentration of surfactants that are naturally present in gastrointestinal environment may have a great impact on the drug release process.

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1. Introduction

Polyelectrolyte-drug interactions have drawn the attention of many research groups in the field of pharmaceutical dosage form design because the presence of a polyelectrolyte can strongly interfere with drug release, stability and other processes (Kindermann et al., 2012; Ferstl et al., 2011; Park et al., 2013; Yang et al., 2012). In particular, polysaccharides have long been investigated from this perspective (Coviello et al., 2007; Persson et al., 2000; Baena et al., 2011) due to their favorable characteristics such as biocompatibility and biodegradability, renewability, acceptance by regulatory authorities and broad choices regarding their molecular weights and degrees of substitution (Rinaudo, 2008; Alderman, 1984). Among many polysaccharides, carrageenans (CARRs), which are widely used in food industry, have gained importance in pharmaceutical dosage forms (Bonferoni et al., 1994, 1998; Heinen et al., 2013). Different researchers have investigated interactions between CARRs and various amphiphilic drugs. For example, the relevance of mutual CARR-drug interactions was demonstrated for the drug release profile from matrix tablets containing lambda (λ)-CARR and a basic drug diltiazem (Bonferoni et al., 2000) or for systems containing amitriptyline, chlorpromazine and doxepin (CaramLelham and Sundelof, 1996; Caramlelham and Sundelof, 1995). Besides the advantageous swelling (water uptake) and erosion properties of charged polysaccharides, which are already favorably used in sustained drug release, the release of an oppositely charged drug from the drug-CARR formulation is affected also by the occurrence of charge–charge and other interactions, which in majority of cases lead to the formation of a strong drug-CARR complex and to additional prolongation of drug release (Bonferoni et al., 1994, 1998; Heinen et al., 2013).

In our previous study (Pavli et al., 2011), we evaluated the binding of doxazosin, a cationic drug with an amphiphilic character, to various CARRs in water by using a new experimental approach to examine the binding of ionic drugs by polyelectrolytes.

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This approach is based on a special ionic-drug-sensitive membrane electrode that enables the determination of the amount of drug that binds to the polysaccharide/polyelectrolyte chain. CARRs are negatively charged and partially sulphated galactans (Yuguchi et al., 2002). Herein, we focus on λ-CARR, a representative of the carrageenan family with the highest charge. It bears 2–3 (on average 2.7) negative charges per disaccharide repeating unit, in contrast to kappa (κ) and iota (ι)-CARRs with only one or two charges, respectively. λ-CARR is considered as a non gelling, water soluble polymer, which forms very viscous solutions (Kogej, 2007). Doxazosin is an antihypertensive α1-adrenoceptor antagonist (Alabaster and Davey, 1986), which can be considered as a cationic amphiphile/surfactant due to its hydrophobic character and nitrogen atoms that can bind protons (Kinsella et al., 2006). Protonation of doxazosin mesylate (DM) results in a positively charged doxazosin mesylate ion (DH^+). Due to this ionic character and simultaneous amphiphilicity, the binding of DM to CARRs proved to be cooperative (Pavli et al., 2011), in strong resemblance with the binding of conventional cationic surfactants to anionic polyelectrolytes (Kogej, 2012). Cooperativity implies that the initial strong electrostatic attraction between DH^+ and CARRs is followed by self-association of DH^+ ions in the vicinity of CARR chains due to so-called hydrophobic interactions between the bound DH^+ ions. This self-association resembles micellization, a phenomenon well-known for conventional surfactants.

In order to predict *in vivo* behaviour of dosage forms with poorly soluble drugs it is crucial to adequately simulate the gastrointestinal conditions. In our previous publication, all studies of DM binding by CARRs were performed in water at either room (25 °C) or body temperature (37 °C) (Pavli et al., 2011). The purpose of the present study is to investigate the effect of increased ionic strength of the medium/solvent, since the *in vivo* release behaviour is strongly dependent on conditions such as pH, the type of buffer, its ionic strength, and surface tension (Garbacz et al., 2014; Tolia and Li, 2013; Machado et al., 2013). We have therefore performed potentiometric measurements in phosphate buffer with pH = 7.0 at 37 °C using the DH^+ ion selective membrane electrode in order to determine the amount of DH^+ ions bound by λ-CARR. From these data, binding isotherms for DH^+ binding by λ-CARR were constructed and correlated with results of the drug release studies in the same phosphate buffer.

In recent years, the utilization of bio-relevant media in dissolution testing has rapidly increased (Dressman et al., 1998; Bergstrom et al., 2013; Koziolek et al., 2013). Media simulating the small intestinal contents in the fed (FeSSIF) and fasted (FaSSIF) state aim at mimicking the most relevant parameters of human intestinal fluids, such as osmolality, pH, surface tension, and the solubilisation capacity of the medium for drug release from dosage forms (Galia et al., 1998; Arndt et al., 2013). These media contain the most important physiological amphiphiles, the bile salts, such as phosphatidylcholine and sodium taurocholate, and lecithin (Boni et al., 2009). Although they have improved the IVIVC (*in vitro-in vivo* correlation) of poorly soluble drugs (Garbacz and Klein, 2012), their large-scale use in pharmaceutical industry is limited due to their complexity and high cost. Therefore, several studies were performed using various high permeability and low solubility Class II drugs (according to the Biopharmaceutics Classification System (BCS) guidance) (Amidon et al., 1995; Jogia et al., 2009; Lehto et al., 2011; Taupitz and Klein, 2010) to compare the physicochemical properties of synthetic aliphatic surfactants with those of uniquely structured naturally present ones. Dissolution media containing 24-phosphonobile acid, a tailor-made synthetic surfactant with a structure similar to bile acids, yielded comparable dissolution profiles to those from FeSSIF and FaSSIF states for three different BCS Class II drugs, dipyridamole, glimepiride, and ibuprofen (Jogia et al., 2009). Moreover, the suitability of two conventional surfactants, anionic sodium dodecyl sulphate (SDS) and non-ionic polysorbate (Tween 80) was evaluated for two BCS Class II drug tablet formulations (Danol® and Spiridon®) and similar dissolution profiles for physiological and for non-physiological surfactants were achieved (Lehto et al., 2011). However, it was revealed that bio-relevant concentrations of SDS and Tween 80 need to be evaluated specifically for each drug and each system. SDS and Tween 80 were applied also in studies involving different tamoxifen tablet formulations (Taupitz and Klein, 2010). It was emphasized that not only the type of the surfactant but also its concentration has a huge impact on the rate and extent of *in vitro* drug release. The aim of our study was thus to investigate the effect of a non-physiological surfactant SDS, in particular its concentration, on the complexation between DM and λ-CARR and on the release of DM from λ-CARR matrix tablets and ultimately to propose the release mechanism. In order to achieve this goal, drug release and binding studies were supplemented with dynamic light scattering measurements of hydrodynamic radii and size distributions of particles in various DM, λ-CARR and SDS mixtures.

2. Materials and methods

2.1 Materials

A commercial sample of λ-CARR (Viscarin GP 209 NF) was purchased from FMC Biopolymers (USA) and was used without further purification. Average molecular weight of λ-CARR was in the range from 400 to 800 kDa. The active substance doxazosin mesylate (DM; $C_{23}H_{25}N_5O_5 \times CH_3SO_3H$, molar mass M_{DM} = 547.6 g/mol) was supplied by Krka, d.d. (Slovenia). For the phosphate buffer with pH = 7.0, 1.7 g/L of $NaH_2PO_4 \times 2H_2O$ (Merck) was dissolved in water and pH was set to 7.0 ± 0.05 with 1 M NaOH. The ionic strength of the final buffer solution was 0.018 mol/L. Sodium dodecyl sulphate (SDS, $NaC_{12}H_{25}SO_4$, molar mass M_{SDS} = 288.37 g/mol) and NaOH were purchased from Merck (Germany). NaCl (Riedl-de-Haen, Germany) and SDS were of analytical grade.

2.2. Potentiometry

2.2.1. Galvanic cell and the membrane ion-sensitive electrode (MIE)

The active part of the electrode, a membrane selective to DH^+, was prepared and integrated into the electrode as described previously (Pavli et al., 2011). The saturated calomel electrode (SCE) was used as the reference electrode. The difference in potential (E) between MIE and SCE was measured with the pH-meter ISKRA MA 5740. The dependence of E on the total DM concentration (c^t_{DM}) was determined by a titration technique at 37 °C as described previously (Pavli et al., 2011) (see also Supplementary material, SM). For the determination of the degree of DM binding by λ-CARR, 10 mL of λ-CARR solution in triple distilled water or in phosphate buffer were allotted into the cell. The concentration of λ-CARR solution in the titration cell was 5×10^{-4} mol of polymer charges per volume, denoted as c_{ch} (in distinction with the usual unit for polymer concentration given in moles of repeat units per volume, designated as c_p). A 4×10^{-3} mol/L aqueous DM solution was added gradually to the λ-CARR solution and the dependence of E on c^t_{DM} in the presence of λ-CARR was measured. To keep the concentration of λ-CARR in the cell constant during the experiment, the same volume (compared to DM additions) of λ-CARR solution in water or in phosphate buffer with a two times higher concentration ($c_p = 1 \times 10^{-3}$ mol/L) compared to its concentration in the cell was added after each DM addition.

Potentiometric titrations were carried out also with the simultaneous presence of SDS in the dissolution medium. Because the membrane of the surfactant selective electrode contains a complex between the cationic drug doxazosin (DH^+) and the

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