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β-Cyclodextrin-dextran polymers for the solubilization of poorly soluble drugs

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ABSTRACT

The aim of this study was to assess the potential of novel β-cyclodextrin (βCD)-dextran polymers for drug delivery. The size distribution of βCD-dextrans (for eventual parenteral administration), the influence of the dextran backbones on the stability of the βCD/drug complex, the solubilization efficiency of poorly soluble drugs and drug release properties were investigated. Size analysis of different βCD-dextrans was measured by size exclusion chromatography (SEC) and asymmetrical flow field-flow fractionation (AF4). Stability of drug/βCD-dextrans was assessed by isothermal titration calorimetry (ITC) and molar enthalpies of complexation and equilibrium constants compared to some commercially available βCD derivatives. For evaluation of the solubilization efficiency, phase-solubility diagrams were made employing hydrocortisone (HC) as a model of poorly soluble drugs, whereas reverse dialysis was used to detect potential drug supersaturation (increased molecularly dissolved drug concentration) as well as controlled release effects. Results indicate that all investigated βCD-polymers are of appropriate sizes for parenteral administration. Thermodynamic results demonstrate that the presence of the dextran backbone structure does not affect the stability of the βCD/drug complex, compared to native βCD and commercially available derivatives. Solubility studies evidence higher solubilizing abilities of these new polymers in comparison to commercially available βCDs, but no supersaturation states were induced. Moreover, drug release studies evidenced that diffusion of HC was influenced by the solubilization induced by the βCD-derivatives.

1. Introduction

Poor solubility of active pharmaceutical ingredients (API) is one of the biggest challenges in drug development: a large number of drugs on the market (approximately 40%), and even more those under development (approx. 70%), belong to class II, or respectively class IV of the Biopharmaceutics Classification System (BCS) and are therefore associated with solubility issues and as a consequence, poor oral bioavailability (Williams et al., 2013; Fahr and Liu, 2007; Amidon et al., 1995). In the last few years, a number of techniques have been suggested to increase bioavailability of such APIs (Williams et al., 2013; Fahr and Liu, 2007; Zhang et al., 2008). Amongst these, the use of cyclodextrins (CDs) has emerged as an efficient approach for solubilization. Cyclodextrins are cyclic oligosaccharides consisting of (α-1,4)-linked α-D-glucopyranose units. CD molecules are shaped like truncated cones, with a hydrophobic cavity inside and a hydrophilic surface outside. For many years CDs have been intensively investigated for pharmaceutical use due to their ability to spontaneously complex poorly soluble drug molecules, inducing solubilization (enhancement in apparent solubility) (Loftsson et al., 2002, 2004; Connors, 1997). For pharmaceutical purposes, β-cyclodextrins (βCDs, 7 glucose units in the ring) are mostly studied. Although βCDs are hydrophilic (as well as their complexes), their aqueous solubility is comparably low. The reason for this fact is associated with the high crystal lattice energy (Loftsson and Brewster, 2010) as well as intramolecular hydrogen bond formation that compromise the interaction with water molecules (solvation). To overcome this limitation, derivatives of the βCDs with higher aqueous solubility have been developed by introducing substituents at specific positions of the glucose rings, breaking the intramolecular net of hydrogen bonds and thereby enhancing aqueous solubility. The

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most commonly used derivatives are methyl-β-cyclodextrin (MβCD), hydroxypropyl-β-cyclodextrin (HPβCD), and sulfobutylether-β-cyclodextrins (SBEβCD) (Brewster et al., 2008). Some of these βCD derivatives are of high solubility (e.g., methyl-derivatives), but were found to have strong systemic toxicity. Among the different derivatives, hydroxypropyl and sulfobutylether βCDs were found to have the lowest hemolytic effect and are therefore regarded suitable for parenteral administration (as well as some α- and γ-cyclodextrin derivatives with 6 and 8 glucose units, respectively) (Loftsson and Brewster, 2010). Moreover, it has been shown that pharmacokinetic parameters of a number of drugs are not significantly modified after parenteral co-administration with these specific types of βCD derivatives (Kurkov et al., 2012). The general mechanism of the complexing reaction comprises exothermic interaction between the drug molecules and the CD cavity (negative enthalpy value), and the replacement of water from the cavity by the drug molecule (negative entropy). Furthermore, the presence of small quantities of hydrophilic polymers (such as PVP) or specific salts (e.g., sodium acetate or sodium salicylate) together with βCDs has previously been shown to stabilize drug/CD complexes through increased drug/CD interaction (enthalpy) or by formation of water-soluble drug/CD aggregates (Loftsson et al., 1994; Loftsson and Brewster, 2012). It has also been described that hydrophilic polymers can induce supersaturation states (increased molecularly dissolved drug concentration) (Di Cagno and Luppi, 2013). In order to overcome low aqueous solubility of native βCD and to take advantage of the stabilizing effect that hydrophilic polymers may have on the complex drug/CD, a new series of polymers based on hydrophilic backbones (i.e., dextrans) with conjugated βCD units have been synthetized and studied (Nielsen et al., 2010, 2009). The advantages of these CD-modified polymers are their much higher aqueous solubility compared to native βCD and the absence of substituents that may lead to steric hindrance at the CD opening. It should also be mentioned that FDA acknowledges dextran as GRAS when in use as food additives. Dextran is in pharmaceutical use as a plasma expander (Roberts and Bratton, 1998) and it is biodegraded by enzymatic activity. Considering all these facts, βCD-dextran polymers appear very promising as solubilizing agents for poorly soluble drugs and drug delivery vehicles. In the present work, we studied the suitability of some new βCD-dextran polymers for drug delivery purposes. We investigated size distribution of different βCD-dextrans to evaluate their potential for parenteral administration, the influence of the dextran backbones on the stability of the βCD/drug complexes, solubilization efficiencies of a selected poorly soluble drug and drug release properties.

2. Materials and methods

2.1. Materials

Three βCD modified dextrans (Fig. 1) were synthetized as described earlier (Nielsen et al., 2010). βCD, HPβCD with a number of substituent per glucose unit (molar degree of substitution (MS)) of 0.87 and MβCD (MS of 0.57) were a generous gift from Roquette Freres (Lestrem, France). Dextrans of different molecular weights (10, 20 and 25 kDa) were purchased from Pharmacosmos A/S (Holbaek, Denmark). Sodium di-hydrogen phosphate (NaH_2PO_4), di-sodium hydrogen phosphate (Na_2HPO_4) and sodium chloride (NaCl) (Sigma–Aldrich Chemie GmbH, Steinheim, Germany) were used for the preparation of the isotonic (275–285 mOsm, Semi-Micro Osmometer K-7400, Herbert Knauer GmbH, Berlin, Germany) and isohydric (pH 7.4, pH meter Lab 827, Metrohm AG, Herisau, Switzerland) buffer saline (73 mM). Ibuprofen (IBP, Caesar & Lorenz GmbH, Hilden, Germany) and hydrocortisone (HC, Sigma–Aldrich) were employed as model drugs (Fig. 1).

2.2. Molecular mass determination

2.2.1. Size exclusion chromatography (SEC)

Size exclusion chromatography was performed employing a TSK-gel column type SW 4000-3000, and polymer sizes were detected by a Wyatt miniDAWN 3 angle light scattering detector (MALS) (Wyatt Technology Inc., Santa Barbara, USA) and RI-detector (Optilab rEX, Wyatt) using a refractive index increment (dn/dc) of 0.15 mL/g. A 0.1 mM lithium nitrate ($LiNO_3$) solution preserved with 0.05% sodium azide was used as eluent at a flow rate of 1 mL/min.

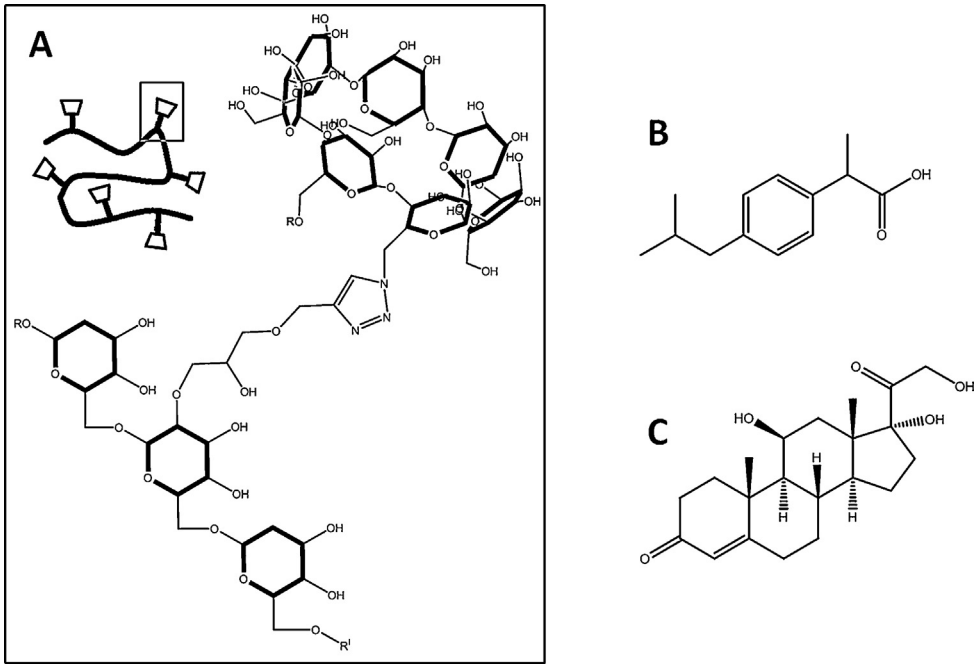

Fig. 1. Chemical structures of βCD-dextran derivatives (A), ibuprofen (B) and hydrocortisone (C).