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Solubility and release modulation effect of sulfamerazine ternary complexes with cyclodextrins and meglumine

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ABSTRACT

This study investigated the effect on solubility and release of ternary complexes of sulfamerazine (SMR) with β-(βCD), methyl-(MβCD) and hydroxypropyl-β-cyclodextrin (HPβCD) using meglumine (MEG) as the ternary component. The combination of MEG with MβCD resulted the best approach, with an increased effect (29-fold) of the aqueous solubility of SMR. The mode of inclusion was supported by 2D NMR, which indicated that real ternary complexes were formed between SMR, MEG and MβCD or HPβCD. Solid state analysis was performed using Fourier-transform infrared spectroscopy (FT IR), differential scanning calorimetry (DSC) and powder X-ray diffraction (XRD), which demonstrated that different interactions occurred among SMR, MEG and MβCD or HPβCD in the ternary lyophilized systems. The ternary complexes with βCD and MβCD produced an additional retention effect on the release of SMR compared to the corresponding binary complexes, implying that they were clearly superior in terms of solubility and release modulation.

1. Introduction

Cyclodextrins (CDs) (Fig. 1a) are cyclic torus-shaped molecules, consisting of 6–8 D-(+)-glucopyranose units with a hydrophilic outer surface and a lipophilic central cavity, and are among the most widely used hosts due to their ability to bind organic molecules in aqueous solutions and in the solid state by non-covalent interactions [1,2]. The inclusion complex normally exhibits a higher aqueous solubility [3–6], and a greater chemical stability than the pure drug [7–11], and also affects the release rate of drugs in physiological fluids [12–14].

However, the high molecular weight, cost, production capability and possible parenteral toxicity have hindered the use of CDs in pharmaceutical formulations, leading their concentrations being minimized whenever [15,16]. The total solubility of a drug in the presence of CDs can be highly enhanced by pH adjustment or the use of an appropriate third component, including the addition of polymers to the complexation media [15,17], drug ionization and salt formation [7,18,19] or the addition of organic salts [16].

N-acetyl glucamine, also known as meglumine (MEG) (Fig. 1b), is a polyhydroxy organic amine that has been demonstrated to raise solubility [20,21], drug release rate [21–24] and stabilization [24] of weakly acidic molecules. In a previous work developed in our laboratory, meglumine showed a significant solubilization enhancement of sulfamerazine (SMR) (Fig. 1c), which is a very slightly water-soluble (0.22 mg/ml) [21] sulfonamide, compared with the free drug and with the SMR-CD complexes, and was demonstrated to be responsible for a solubility improvement via multiple factors rather than just providing a favorable pH. Moreover, it was demonstrated that the complexation with βCD, MβCD, HPβCD and MEG resulted in a decrease in the release rate of the drug through cellulose acetate membrane, thereby enabling sustained drug delivery systems. [21] Other formulation strategies have been applied to SMR, such as the use of co-solvent mixtures [25], nanocrystals [26], amorphous solid dispersions containing polymers [27], pectin films [28], chitosan membranes [29,30] and phase transformation [31,32], with Rajendiran et al. also describing the binary complexes of this drug with βCD and αCD [33]. In

Abbreviations: SMR, sulfamerazine; MEG, meglumine; K_c, apparent stability constant; PSS, phase solubility studies; S_0, intrinsic solubility of the drug; δ_S, δ_T, δ_B, δ_M, chemical shifts of SMR alone, in the ternary and binary complexes with CD or MEG, respectively; FDBS, freeze-dried binary system; FDTS, freeze-dried ternary system; TPM, ternary physical mixtures; S_{max}, maximum solubility; $K_{c\,TER}$, K_c value of the ternary system; $K_{c\,BIN}$, K_c value of the binary system; BPM, binary physical mixture.

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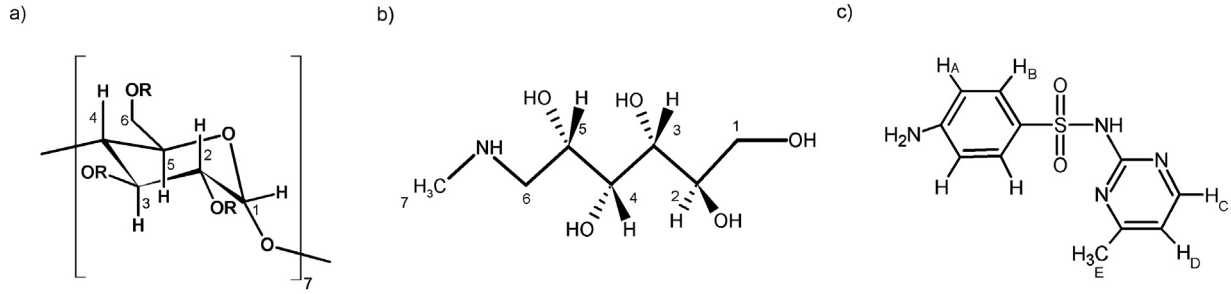

Fig. 1. Chemical structure of: (a) βCD, MβCD or HPβCD with R = H; —CH_3 or —$CH_2CH(OH)CH_3$, respectively; (b) MEG and (c) sulfamerazine.

addition, it is important to note that the preparation of multicomponent inclusion complexes has been previously described in a patent of Chiesi et al. (1998). By using a drug bearing an acidic group, a CD and a basic compound, they found that the simultaneous salt formation with the suitable basic counter-ions and complexation with CDs dramatically increased the aqueous solubility of the drug [34]. In another study, Redenti et al. showed that complexation and simultaneous salt formation resulted in a higher solubility of a drug in comparison with simple binary complexes [35], thereby permitting the production of oral formulations with an increased dissolution rate and bioavailability of the complexed drug over a wider pH range [36]. Recently, in our laboratory, the solubility and dissolution profile of sulfisoxazole was improved by the development of a ternary system with HPβCD and triethanolamine (TEA) as the co-solubilizing agent [37]. Furthermore, the formation of an inclusion multicomponent complex of acetazolamide with HPβCD and TEA significantly enhanced the water solubility and the dissolution rate of the drug, resulting in a powerful strategy for ocular formulations, since this was able to reduce the intraocular pressure in rabbits [38].

Following on from these studies, we now aimed to examine various formulation approaches, namely ternary cyclodextrin complexes made with three different CDs, with varying abilities to improve the solubility of poorly soluble SMR and using meglumine as the ternary component to intensify the solubilization by cyclodextrins. Also, the ability of the ternary complexes to deliver SMR and to sustain its release was examined.

2. Materials and methods

2.1. Materials

Sulfamerazine was obtained from Parafarm®, Argentina. Meglumine was purchased from Sigma–Aldrich®, USA, with βCD, MβCD KLEPTOSE® CRYSMEB (DS = 0.5) and HPβCD (DS = 0.45–0.95) being kindly supplied by Ferromet® (agent in Argentina of Roquette®). All the other materials and solvents were of analytical reagent grade, and the water used in these studies was generated by a Millipore Milli-Q Water Purification System.

2.2. Phase solubility studies (PSS)

Solubility diagrams were obtained according to the Higuchi and Connors method [39], and each experiment was performed in triplicate. Excess amounts of SMR, to create saturation conditions, were added to aqueous or buffered solutions containing a 3 mM concentration of MEG and βCD (0–16 mM), MβCD (0–100 mM) or HPβCD (0–18 mM), in relation to their aqueous solubilities. The suspensions formed were sonicated in an ultrasonic bath for 15 min every 12 h to favor solubilization before being placed in a 25.0 ± 0.1 °C constant temperature bath [HAAKE DC10 thermostat (Haake®, Paramus, NJ, USA)] for 72 h. After equilibrium was reached, the suspensions were filtered through a 0.45 μm membrane filter (Millipore®, USA) and analyzed in a *Shimadzu® UV-160* spectrophotometer. The equilibrium pH of each solution was measured (*Hanna® HI 255* pH-meter) and the apparent stability constants (K_c) of the SMR:CD:MEG complexes were determined as a function of the CD concentration (CD) added [12]. From A_L-type isotherms or from the linear portion of the A_N or A_P phase solubility diagrams, the apparent stability (or formation) constants K_c were calculated assuming a 1:1 drug–CD stoichiometry and taking into account the value of the slope using the following equation:

$$K_c = \frac{\text{slope}}{S_0(1 - \text{slope})}$$

where S_0 is the solubility of the pure drug.

2.3. Nuclear magnetic resonance (NMR) studies

Heteronuclear single quantum coherence (HSQC) and heteronuclear multiple bond coherence (HMBC) 2D NMR experiments were performed at 298 K in a Bruker® Advance II High Resolution Spectrometer equipped with a broad band inverse (BBI) probe and a variable temperature unit (VTU) using 5 mm sample tubes, with spectra being obtained at 400.16 MHz. Equimolar ratio complexes (1:1:1) and pure substance solutions were prepared in D_2O by incorporating an excess amount of the drug with a fixed concentration of each ligand, which were then sonicated for 1 h to favor the maximum SMR solubilization in order to obtain a measurable concentration of the drug and to form complexes. All suspensions were filtered before their analysis and the NMR data were processed with the Bruker TOPSPIN 2.0 software. The residual solvent signal (4.80 ppm) was used as the internal reference. Induced changes in the ^{1}H NMR chemical shifts ($\Delta\delta$) for SMR originating from their interactions with the ligands were calculated according to the following equations:

$$\Delta\delta = \delta_T - \delta_S; \quad \Delta\delta = \delta_T - \delta_B \quad \text{and} \quad \Delta\delta = \delta_T - \delta_M$$

where δ_S, δ_T, δ_B and δ_M are the chemical shifts of SMR alone, in the ternary and binary complexes with CD or MEG, respectively.

2.4. Solid sample preparations

Freeze-dried binary (FDBS) and ternary (FDTS) systems were obtained by the freeze-drying technique using a Labconco® Freeze Dry 4.5 apparatus. Equimolar ratio systems (1:1:1) and pure substance aqueous solutions were prepared by incorporating an excess amount of the drug with a fixed concentration of the ligands, which were sonicated for 1 h. The suspensions were filtered and then frozen at −40 °C until their complete solidification had been achieved for the freeze-drying procedure. In contrast, ternary physical mixtures (TPM) were prepared using the same molar ratios, by simple mixing in an agate mortar.