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Cyclodextrin-based telmisartan ophthalmic suspension: Formulation development for water-insoluble drugs

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ABSTRACT

In this study, cyclodextrin-based aqueous eye drop suspension of the water insoluble drug telmisartan was developed. Formation of a drug/γ-cyclodextrin complex was enabled by preventing formation of a poorly water-soluble zwitterion using a volatile base that was removed upon drying of the complex powder. Hydroxypropyl methylcellulose was shown to have the overall best effect, stabilizing the complexes without hampering the drug release from the formulation. Two strategies for preparing cyclodextrin-based aqueous eye drop suspensions of telmisartan were investigated, one where hydroxypropyl methylcellulose was added to the medium during preparation of the drug/γ-cyclodextrin complex powder (ternary complex) and the other where hydroxypropyl methylcellulose was added to the complex powder after preparation of the complex (binary complex). The complexation was characterized by DSC, FT-IR and ^{1}H NMR and the eye drop suspensions formed were examined regarding their stability and *in vitro* mucoadhesion property. The ternary complex exhibited inferior mucoadhesive property compared to the binary complex. However, the ternary complex was more stable as no notable change in particle size and particle size distribution was observed during storage at 4 °C over 6 months ($p < 0.05$) with the mean particle size determined between 2.0 and 2.5 μm.

1. Introduction

Topical drug administration in the form of eye drops is the preferred means of drug administration to the eye due to its convenience and safety in comparison to other forms of ophthalmic drug administration such as intravitreal injections and implants (Le Bourlais et al., 1998). Drugs are mainly transported by passive diffusion from the eye surface into the eye where, according to Fick's law, it is driven by the gradient of dissolved drug molecules. The passive drug diffusion into the eye is hampered by three major obstacles (Gan et al., 2013; Loftsson et al., 2008a; Urtti, 2006). First is aqueous drug solubility. Only dissolved drug molecules are able to diffuse into the eye and, thus, drugs must possess sufficient solubility in the aqueous tear fluid to diffuse into the eye. The increasing solubility of poorly soluble drugs will increase their concentration gradient and consequent passive diffusion into the eye. The second obstacle is the rapid turnover rate of the tear fluid and the consequent decrease in concentration of dissolved drug molecules. The precorneal half-life of topically applied drugs administered in simple aqueous eye drop solutions is a couple of minutes and this hampers topical bioavailability of ophthalmic drugs. As a result, the precorneal half-life of topically applied drugs needs to be increased in order to enhance their bioavailability. Third, the slow drug permeation through the membrane barrier, i.e. cornea or conjunctiva/sclera. The drug molecules have to partition from the aqueous exterior into the membrane before they can passively permeate the membrane barrier. Nano- and microparticle-based formulations have been vigorously investigated in ophthalmic drug delivery systems. These formulation technologies can not only enhance the physiochemical properties of the drug but can also offer therapeutic advantages over conventional products. The particle size in the nanometer to micrometer-size range increases drug accumulation in the targeted tissue and, in some cases, enhances drug permeation through biomembranes (Ensign et al., 2012; Johannesson et al., 2016). Pharmaceutical formulations containing nano- and microparticles have allowed sustaining drug delivery, for instance, dexamethasone/γ-cyclodextrin nano- and

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microparticles provide high drug concentration on eye surface and are able to deliver the drug to the posterior segment of the eye (Jóhannesson et al., 2014; Loftsson et al., 2007b).

In this study, a novel method for preparation of aqueous eye drop suspension containing cyclodextrin (CD) complexes of poorly water-soluble and highly lipophilic drugs is proposed. Telmisartan (TEL) is selected as a model drug. TEL is a non-peptide angiotensin II (AT1) receptor blocker that is widely used to treat cardiovascular diseases. It has superior therapeutic effect in comparison to other drugs in the same therapeutic class due to its long biological half-life and consequent long duration (Wienen et al., 2000). Recently, there has been an increasing interest in TEL due to its ability to suppress corneal neovascularization (Usui et al., 2008). When administered orally TEL belongs to Biopharmaceutics Classification System (BCS) class II drugs (low solubility, high permeability). According to the European Pharmacopoeia 8th Edition TEL is practically insoluble in water due to zwitterion formation, and only slightly soluble in organic solvents like methanol but it is somewhat soluble under strongly basic conditions. Hence, alkalizing agents such as sodium hydroxide and meglumine are employed to increase its solubility (Tran et al., 2008). Several technologies have been investigated in order to enhance dissolution and absorption (i.e. bioavailability) of TEL and related drugs for oral tablets including preparation of amorphous solid forms and formation of CD inclusion complexes (Al Omari et al., 2011; Brough and Williams Iii, 2013; Dukeck et al., 2013; Loftsson et al., 2008b; Marasini et al., 2013; Sangwai and Vavia, 2013; Yuvaraja and Khanam, 2014). The dissolution and bioavailability of TEL have been improved by β-cyclodextrin (βCD) complexation through mechanical grinding and high pressure homogenizing process (Borba et al., 2015; Sangwai and Vavia, 2013), and the encapsulation of TEL with 2-hydroxypropyl-βCD (HPβCD) has improved both TEL solubility and its release rate from solid dosage forms (Godugu et al., 2013; Kaur et al., 2014).

CDs are a truncated cone oligosaccharide macromolecule with a somewhat lipophilic inner cavity and hydrophilic exterior. The natural α-cyclodextrin (αCD), β-cyclodextrin (βCD) and γ-cyclodextrin (γCD) are on FDA's generally recognized as safe (GRAS) list of food additives and are frequently used in pharmaceutical industry to improve physicochemical properties of lipophilic and poorly water-soluble drugs through formation of water-soluble inclusion complexes (Brewster and Loftsson, 2007; Loftsson and Brewster, 2013; Loftsson and Duchene, 2007; Loftsson et al., 2007d). In ophthalmic drug delivery, CDs have been used as drug carriers capable of controlling drug release, to increase mucoadhesion and to deliver dissolved drug molecules to the surface of biological membranes (Loftsson et al., 2007c; Uekama, 2004). The natural γCD has a relatively large central cavity that can accommodate a wide range of drug molecules. Furthermore, γCD has a very favorable toxicological profile and is digested by α-amylases that can be found in both tear fluid and saliva as well as in the gastrointestinal tract (Gannimani et al., 2015; Munro et al., 2004). Thus, the natural γCD was selected as a model CD for this study.

In CD chemistry complexation efficiency (CE) is the product of the intrinsic solubility (S_0) and the stability constant (K) of a drug/CD complex (Loftsson et al., 2005a, 2007a). CE can, in some cases, be increased by addition of polymers, organic acids and/or bases to aqueous complexation media. Although drug ionization can cause some decrease in the K value (i.e. formation of less stable complexes), the increase in S_0 is frequently much greater than the decrease in K resulting in overall enhanced complexation (Loftsson et al., 2004). Here the CE of TEL/γCD complex is increased by preparation of the complexes in an aqueous solution containing ammonium hydroxide that is by increasing the apparent S_0 of TEL through ionization. TEL possess amphoteric properties, both amine and carboxylic moieties that enable TEL to form hydrogen bonds with adjacent molecules (Laad et al., 2013). At physiological pH, the carboxylic moiety on the biphenyl ring forms an anion while the two protonated benzimidazole moieties carry cations. According to the pH-solubility profile in Fig. 1A, addition of an excess ammonium hydroxide increases the pH of the aqueous complexation medium and consequently the solubility (i.e. the apparent S_0) of TEL. This increases the CE and, thus, larger fraction of the drug forms a γCD complex. Due to its high vapor pressure ammonium hydroxide can be completely removed from the TEL/γCD complex by lyophilization and the aqueous TEL/γCD eye drop microsuspension was stabilized through the addition of water-soluble polymers (Fig. 1B).

2. Materials and methods

2.1. Materials

Telmisartan (TEL) was purchased from Beijing Mesochem Technology (Beijing, China) γ-cyclodextrin (γCD) was purchased from Wacker (Surrey, UK). Disodium edetate dihydrate (EDTA) was purchased from Merck (Darmstadt, Germany). Poloxamer 407 (P407), poly(vinyl alcohol) (PVA, MW 30,000–70,000), hydroxypropyl methylcellulose (HPMC, viscosity 2600–5600 cP), benzalkonium chloride (BAK) and tyloxapol were purchased from Sigma-Aldrich (St. Louis, MO). Cellophane membranes (Spectra/Pore®) with molecular weight cutoff (MWCO) of 3500 and 12,000–14,000 Da were purchased from Spectrum Laboratories Inc. (Rancho Dominquez, USA). All other chemicals and reagents used during this study were commercial products of analytical or high performance liquid

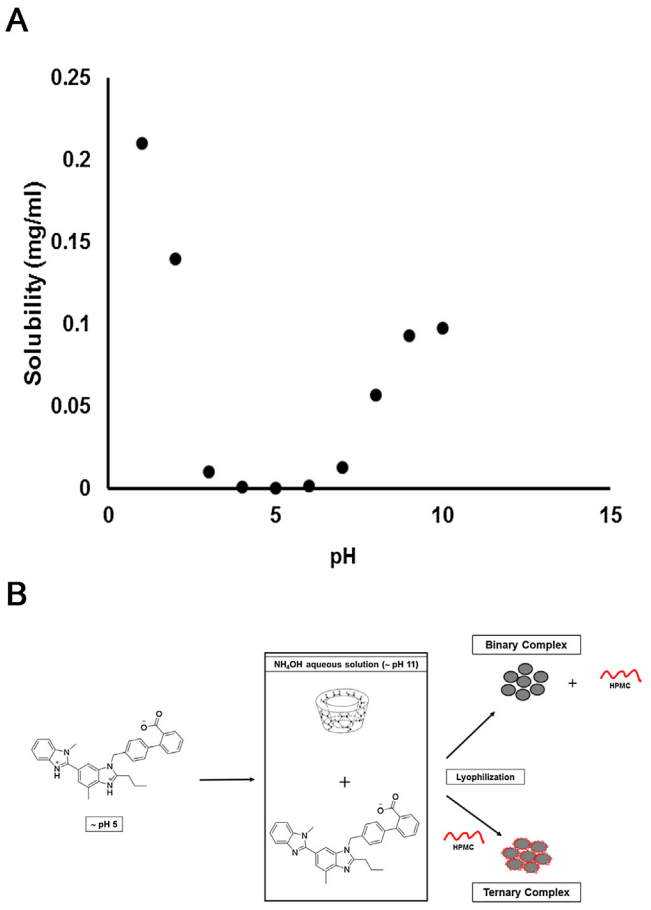

Fig. 1. The pH-solubility profile of telmisartan (A) and schematic diagram showing formation of TEL/γCD complexes (B).