



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 ¹H 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 .

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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; Urtili, 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 physicochemical 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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