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ORIGINAL ARTICLE

Formulation and evaluation of new long acting metoprolol tartrate ophthalmic gels

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IOP

Abstract The rationale of the present work is to formulate and evaluate metoprolol tartrate (MT), which is a beta-1 selective adrenergic blocking agent in a new ocular gel delivery system; this is our way and method to increase its contact to the cornea, giving a longer time of drug contact to the eye and slow possible release from the preparation. Metoprolol tartrate is chosen as a candidate for gel formulation because although it has been available for a few years as ophthalmic solutions, it has not been marketed as an ocular gel yet. Two polymers; Carbopol 934 and Pluronic F127 (PF127) were used in two different concentrations in this study. Metoprolol tartrate was used in two concentrations, 0.5% and 1% (w/w). All formulations were exposed to visual examinations, pH measurement, in vitro release, rheological study and differential scanning calorimetry (DSC). Results showed that all formulations were clear, showed pH within the acceptable range suitable to be administered in the eye, and exhibited pseudoplastic flow behavior. DSC results concluded that, MT was compatible with different polymers used. In vitro release results showed that the release rate of metoprolol tartrate from gel preparations decreased as an inverse function of polymer concentration, and the release rate of the drug increased as the initial concentration increased. Intraocular pressure (IOP) measurements of rabbit's eye treated with 1% (w/w) metoprolol tartrate in gel formulations with different concentrations of the polymer were determined. Carbopol 934 gel formulations showed that this polymer extended the duration of pressure reducing effect of MT

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to more than 5hr when compared with Pluronic F127 gel formulations. The area above the curve (AAC), maximum response, time of maximum response (t_{max}), and the duration of the drug action were also calculated.

1. Introduction

It is often assumed that drugs administered topically to the eye are rapidly absorbed and are available at a desired site in the globe of the eye to exert their therapeutic effect. Indeed, this is generally not the case. Were this true we would not see drug products containing as much as 5–10% of such systemically active drugs as atropine, homatropine, and pilocarpine. When a quantity of a topical ophthalmic dosage form is applied to the eye, generally to the lower cul-de-sac, several factors immediately begin to affect the availability of the drug contained in that quantity of the dosage forms (Habib and Attia, 1984).

Although many methods of instilling drugs to the eye have been experimented with the use of drops has emerged and still remains the major method of administration for the topical route. Poor bioavailability of drugs from ocular dosage forms is mainly due to tear production, transient residence time, and impermeability of corneal epithelium (Kaur and Kanwar, 2002). Due to these physiological and anatomical constraints only a small amount of drug, effectively 1% or less of the instilled dose, is absorbed ocularly. So far, many attempts have been made to improve ocular bioavailability by extending drug residence time in the conjunctival sac and improve drug penetration across the cornea, the major pathway of drug entry into the internal eye (Kaur and Kanwar, 2002).

Several ways of prolonging the presence of drugs in precorneal area consist of increasing the viscosity of the dosage form by adding a number of viscosity imparting agents such as water soluble or insoluble, natural, synthetic, and semisynthetic polymers (El-Kamel, 2002). Many studies reported that the aqueous-base gels appear to offer several advantages over the other traditional ophthalmic dosage forms, either in terms of improved ocular bioavailability or enhanced therapeutic response (Zaki et al., 2011). Many of the ophthalmic gels investigated to date have been formulated with either Carbopols or Poloxamers. Poloxamers are a class of gel forming polymers that have been evaluated as semisolid vehicles for the ophthalmic use (Ma et al., 2008; Gratieri et al., 2010).

Poloxamer 407 (Pluronic F127) possesses several properties which appear to make it particularly suitable for use in the formulation of ophthalmic dosage forms, including its low toxicity, mucomimetic properties, and optical clarity (Waring and Harris, 1979). Carbopol is a polyacrylic acid polymer, which shows a sol-to-gel transition in aqueous solution as the pH is raised above its pka of about 5.5 and it is widely used in ophthalmology to enhance precorneal retention to the eye (Deshmukh and Gattani, 2013). Moreover, Carbopol exhibits excellent mucoadhesive properties when compared with other polymers.

Metoprolol tartrate, MT (Fig. 1) is a selective beta-1 blocking agent and because of its ability to lower the elevated intraocular pressure (IOP), it is used clinically to treat patients with ocular hypertension or glaucoma, primarily of the open angle type (Luch, 1983).Treatment with metoprolol tartrate as 0.5%, 1%, 2%, 3%, 4%, 5%, and 8% eye drops was clinically studied. It was found that, the IOP was significantly lowered by the drug in all patients throughout the study but a short-lasting reduction in IOP was obtained with 0.5% eye drops. In addition, the concentrations over 1% were less well tolerated (Alm and Wickström, 1980; Krieglstein, 1981). The Metoprolol eye drops had no effect on the diameter of the pupil of the eye, blood pressure or resting pulse and moreover, the reduction in intraocular pressure and duration of action showed no diminution (Bucheli et al., 1980).

The aim of this work is the formulation and evaluation of a new gel ocular delivery system of metoprolol tartrate using Carbopol 934 and Pluronic F127. The rheological behavior of the studied formulations was carried out. The formulation variables that could affect the release rate and absorption of the drug in the topical formulations, such as the polymer type, concentration of gelling agent, and the initial drug concentration in the formulations were studied. In addition, the in vivo performance of gel formulations of MT was assessed on the basis of the influence of the drug on the intra-ocular pressure of rabbit's eye, and the duration of the pressure reducing effect. The effect of the drug on the pupil diameter of the eye was also visually examined.

2. Materials and methods

2.1. Materials

Metoprolol tartrate was kindly donated by (Sid. Co., for Pharmaceutical and Chemical Industry, Egypt). Carbopol 934 (CP 934) was purchased from (Goodrich Chemical Company, OH, USA), Pluronic F127 (PF127) was obtained from (BASF Corp., Wyan-dotte, MI). All other chemicals were of analytical grade.

2.2. Methods

2.2.1. Preparation of metoprolol tartrate gels

The gel formulations containing two different concentrations of the drug (0.5% and 1% w/w) were prepared according to the polymer used and the composition is shown in Table 1.

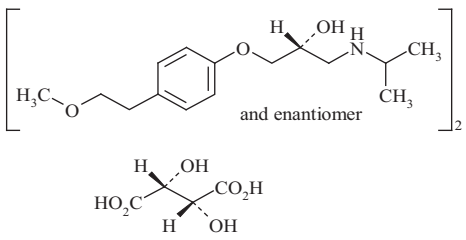

Figure 1 Chemical structure of metoprolol tartrate (Luch, 1983).