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Ketoroloac tromethamine loaded nanodispersion incorporated into thermosensitive in situ gel for prolonged ocular delivery

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ABSTRACT

The present study was designed to improve the ocular availability of ketorolac tromethamine and to prolong its precorneal residence time for the treatment of postoperative ocular inflammation. Ketorolac tromethamine nanodispersions were successfully prepared by nanoprecipitation method using Eudragit® RL100. These nanodispersions were characterized in terms of particle size, zeta potential, entrapment efficiency and in vitro release. Consequently, the optimum nanodispersion was incorporated into thermosensitive in situ gel. The optimum gelling capacity was obtained by 20% Pluronic® F-127 and 14% Pluronic® F-127/1.5% HPMC K4m. The gelling temperature and gelation time of the in situ gels increased by decreasing the concentration of Pluronic® F-127. The mucoadhesive strength was significantly improved by the addition of HPMC. Incorporation of ketorolac tromethamine loaded nanodispersions into in situ gel bases sustained the release of ketorolac tromethamine, improved its ocular availability and prolonged its residence time without causing irritation to eye.

1. Introduction

The ideal treatment of ocular diseases, especially when the drug is required to display a localized action on the cornea and/or anterior segment, would be the topical administration of ophthalmic preparation. Unfortunately, in several cases, topical treatment is not effective due to protective mechanisms of the human eye e.g. lacrimal secretion and blinking reflex, which cause rapid drainage of the formulation. The short pre-corneal contact time combined with corneal impermeability result in low bioavailability, and as a result, frequent dosing is usually needed (Wei et al., 2002).

Several ophthalmic delivery systems have been developed to prolong the pre-corneal drug contact time for enhancing diffusion and to improve ocular bioavailability including the use of bioadhesive polymers, liposomes and nanoparticles. Nanoparticles have the unique property to accumulate at the site of inflammation and, therefore, are very suitable for targeted drug delivery (Sahoo and Labhasetwar, 2003; Parveen and Sahoo, 2008).

One of the cationic polymers that are used for production of nanoparticles is the synthetic acrylic copolymers (Eudragit®). The simplest method to prepare drug loaded-Eudragit nanoparticles is the solvent displacement method, also known as nanoprecipitation method, which was developed by Fessi et al. (1989). One of the requirements of this method is that, both polymer and drug have to be insoluble in continuous phase (Gao et al., 2006; Dhoka et al., 2011). However, entrapment of hydrophilic drug substances is very difficult in this technique and several methods were reported to improve drug entrapment efficiency of the nanoprecipitaion method. These methods include changing the pH of the internal/external phase, addition of excipients (fatty acids, oligomers), replacing the salt form of the drug with the base form and the addition of salt to the aqueous phase (Peltonen et al., 2004). Typical nanodispersions have low viscosity, which leads to a low drug ocular bioavailability due to the rapid precorneal mechanism of elimination. To avoid this drawback, these systems could be incorporated into different delivery systems to increase their viscosity and stability (Silva et al., 2012).

Nevertheless, it was reported that viscous solutions do not have enough mechanical strength to resist ocular clearance mechanism and only offer a transient improvement in ocular residence time (Davies et al., 1991). Also, the use of preformed gels still has a number of drawbacks which limit their use in ophthalmic drug

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delivery as they do not allow accurate and reproducible administration of drugs and after administration their high viscosity often produce blurred vision and malted eyelids which substantially reduce patient acceptability (Agarwal, 2012).

From the point of view of patient compliance, a liquid dosage form that can sustain drug release and remain in contact with the cornea of the eye for extended periods is ideal. Such properties can be achieved by delivery systems based on in situ gel-forming solutions (Gupta et al., 2010).

In situ gel system is a recent approach, which combines the advantages of both gels and solutions so that an accurate dose can be administered with ease of administration (Srividya et al., 2001). Various systems are employed to cause sol to gel phase transition on the ocular surface (Rathore, 2010) including pH sensitive systems, ion activated systems and temperature sensitive systems. Temperature sensitive in situ gelling can be achieved by using a polymer that forms a solution at room temperature (<25 °C) and converts to a semisolid gel at precorneal temperature (35 °C). At increased temperatures the sol-gel transition may be due to desolvation of the polymer, increased micellar aggregation and increased entanglement of polymeric network (Shastri et al., 2006).

Poloxamers (commercially available as Pluronics®), the most commonly used thermosensitive polymers in pharmaceutical formulations, are amphiphilic synthetic copolymers consisting of a central hydrophobic polyoxypropylene oxide (PPO) block surrounded by hydrophilic polyoxyethylene oxide (PEO) blocks (Talasaz et al., 2008). At low temperature, poloxamer molecules can readily self-assemble to form small micellar units due to their amphiphilic nature. An increase of temperature results in packing of the micellar structure to form large micellar cross linked network (Rajoria and Gupta, 2012). Pluronic F-127 was reported to be the least toxic among all commercially available poloxamers (Laughlin, 1994).

Though pluronics are widely employed, they suffer from a major drawback of having weak mechanical strength, which leads to rapid erosion (i.e. dissolution from the surface) (El-Kamel, 2002). Thus, one interesting approach focuses on blending pluronics with other bioadhesive polymers like carbopol, alginate or HPMC (Qi et al., 2007).

The objective of the present study was to develop KT-loaded Eudragit nanodispersion to improve the ocular availability of the drug. To overcome rapid drainage of the drug from the eye and prolong its ophthalmic residence, the nanodispersion was incorporated into thermosensitive in situ gelling system using pluronic F-127. The impact of combining hydroxypropyl methyl cellulose, on the physicochemical properties of the in situ gelling system was also investigated.

2. Materials and methods

2.1. Materials

Ketorolac tromethamine was kindly supplied by European Egyptian Pharmaceutical Industrial Company, Egypt. Eudragit RL100 (EG) and polyvinyl alcohol (PVA, MW 14000) were purchased from Rhom Pharma, GMBH (Germany). Hydroxypropyl methyl cellulose (HPMC K4m, 4000 cps) was kindly supplied by Colorcon (England). Poloxamer 407 (Pluronic F-127) was obtained from BASF (Germany). All other reagents were of analytical grade. Cellophane membrane (Spectra/Por® Membrane, molecular porous MWCO: 6–8000) was obtained from Spectrum Laboratories (USA).

2.2. Methods

2.2.1. Preparation of KT-loaded Eudragit RL100 nanodispersions

Polymeric nanodispersions with different KT: Eudragit RL100 ratios (1:1, 1:3 and 1:5) were prepared using solvent displacement technique (Das et al., 2010). Briefly, the weighed amount of Eudragit RL 100 (100, 300 or 500 mg) and KT (100 mg) were first dissolved by sonication in specified volume of organic phase (anhydrous ethanol or acetone/methanol). This organic phase was slowly poured with constant speed (0.5 ml/min) into calculated volume of different aqueous phases (distilled water or citrate-phosphate buffer of pH 3) containing 1% polyvinyl alcohol (PVA), as hydrophilic surfactant, under moderate magnetic stirring at 800 rpm, where the nanoparticles were formed spontaneously. Finally, the nanoparticle dispersions, with constant volume of 30 ml and different ratios (1:2, 1:3 and 1:4) of organic/aqueous phases, were stirred for 24 h at room temperature until the complete evaporation of the organic solvent. The composition of the different formulae is shown in Table 1.

2.2.2. Evaluation of KT-loaded nanoparticles

2.2.2.1. Particle size, polydispersity index and zeta potential. The mean particle size, size distribution and zeta potential of freshly prepared nanoparticle dispersions were determined using a Malvern Zetasizer 2000 (Malvern Instruments Ltd., UK). The measurements were performed after diluting samples by 100-fold with water at ambient temperature.

2.2.2.2. Entrapment efficiency (EE%). The amount of drug entrapped in the nanoparticles (NPs) was determined by calculating the difference between the total amount of KT used to prepare the NPs and the amount of non-entrapped drugs remaining dissolved in the aqueous dispersion medium. Five milliliters of KT-loaded nanodispersions were centrifuged at

Table 1
Composition of ketorolac tromethamine-loaded Eudragit R100 nanodispersions.

Formula	Composition			
	Drug: polymer	Organic phase	Aqueous phase	Organic: Aqueous
E1	1:1	ethanol	distilled water	1:2
E2	1:1	ethanol	CP buffer[a]	1:2
E3	1:3	ethanol	CP buffer	1:2
E4	1:5	ethanol	CP buffer	1:2
E5	1:1	ethanol	CP buffer	1:3
E6	1:1	ethanol	CP buffer	1:4
E7	1:1	acetone/methanol (3:1)	CP buffer	1:2

[a] Citrate phosphate buffer pH 3.