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Development and characterization of in-situ gel for ophthalmic formulation containing ciprofloxacin hydrochloride

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ABSTRACT

In situ gels are systems which are applied as solutions or suspensions and are capable of undergoing rapid sol-to-gel transformation triggered by external stimulus such as temperature, pH etc. on instillation. The aim of the present study was to formulate and evaluate pH responsive *in-situ* gel for ophthalmic delivery. Ciprofloxacin hydrochloride is popularly used as a broad spectrum antibiotic in the treatment of corneal ulcers of ocular infections. However, rapid dilution on instillation, wash out, poor retention of drug concentration delimit the therapeutic benefits of the drug when used in form of conventional eye drops. Sodium alginate, an ophthalmic gel forming mucoadhesive polymer was chosen as polymer which undergoes instantaneous gel formation due to formation of calcium alginate by virtue of its interaction with divalent cation (Ca^{+2}) present in lachrymal fluid. Hydroxy Propyl Methyl Cellulose (HPMC K4M and E5 0LV) was further incorporated as a viscosity enhancer in order to achieve the desired consistency so as to facilitate sustained drug release. The developed formulations were evaluated for clarity, pH measurement, gelling capacity, drug content, rheological study, and in vitro drug release. Thus, in situ gel based systems containing gums can be a valuable approach for ophthalmic drug delivery when compared to conventional systems.

1. Introduction

One of the major limitations faced in ophthalmic delivery is the attainment and retention of optimum drug concentration at the site of action within the eye. Various ophthalmic dosage forms, like solutions, ointments, gels and polymeric inserts have been investigated in an attempt to extend the ocular residence time of medications for topical application to the eye [1]. The corneal contact time has been increased to varying degrees by these dosage forms. But, they have not been unanimously accepted, because of blurred vision (e.g. ointments) or lack of patient compliance (e.g. inserts).

The eye drops have very poor bioavailability due to their rapid washout during lachrymation in eyes. Most of the systems are applied as solutions or suspensions. The rapid pre-corneal elimination observed with conventional ocular formulations ends in poor drug bio-availability. Ease of administration in case of highly viscous solution and gel forms retard its use and patient compliance. The blurred vision and the lachrymation are associated with the dosage form involving hydrogel.

So, these may be overcome by fabricating the drug as a formulation that undergoes instantaneous in situ gel formation upon ophthalmic administration. They undergo gelation after instillation due to physico-chemical changes occurring in the eye. It increases the pre-corneal residence time and better bioavailability of drug can be achieved by formulating in situ gel. The present work describes the “formulation and evaluation of in situ gel forming ophthalmic formulation containing ciprofloxacin hydrochloride”. In which in situ phase transition occurs on the surface of the cornea. At time of instillation dosage form is in solution phase and soon later upon coming in contact with calcium ion with surrounding pH of 7.4 it turns into transparent gel depo. Thus, this type of formulation has benefit of both solutions as well gels they may improve the retention time of the formulation as well the drug, accuracy and ease of administration [1–4].

Ciprofloxacin hydrochloride is a pale yellow, crystalline powder which contains Fluoroquinolone group. Ciprofloxacin hydrochloride is used as an antibacterial agent in the treatment of corneal ulcers caused by susceptible strains of bacteria, including *Pseudomonas aeruginosa*, *Serratia marcescens*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumonia*, Streptococcus and conjunctivitis, bacterial (treatment) of conjunctivitis caused by *Haemophilus influenzae*, *S. aureus*, *S. epidermidis*, *S. pneumoniae*, and Streptococcus [5,6] (Fig. 1).

Ciprofloxacin's bactericidal action is due to interference with the enzyme DNA gyrase, which is needed for the synthesis of

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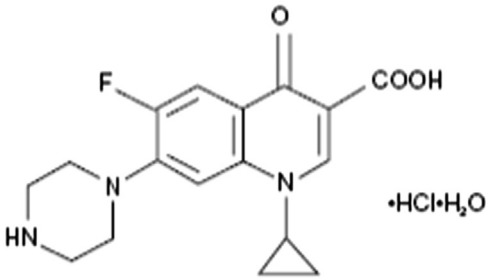

Fig. 1. Structure of ciprofloxacin hydrochloride.

bacterial DNA. It inhibits this enzyme hence will not allow multiplication of bacterial cell.

In situ gelling systems consist of polymer that exhibit sol-to-gel phase transitions in the cul-de-sac which improves patient compliance due to change in specific physico-chemical parameters like pH, temperature and ionic strength in the environment [8]. The sol-to-gel phase transition on the eye surface depending on the different methods employed which consist of thermo-sensitive, ion-activated and electric-sensitive, magnetic field-sensitive, ultrasonic-sensitive and chemical material-sensitive varieties. But above them the most commonly methods are as follows:

1. pH-triggered system (e.g. cellulose acetate hydrogen phthalate latex),
2. temperature dependent system (eg. pluronics and tetronics), and
3. ion activated system (eg. gelrite) [9,10].

The present work is based on the

1. pH triggered system and
2. ion activated system.

In situ gel based drug delivery systems consist of active pharmaceutical ingredients, polymer, co-polymer and excipients. Sodium alginate, an ophthalmic gel forming mucoadhesive polymer was chosen, as the polymer and Hydroxy Propyl Methyl Cellulose (HPMC) as copolymer.

Sodium alginate, family of linear un-branched polysaccharides, the sodium salt of alginic acid, is a natural hydrophilic polysaccharide containing two types of monomers, β-D-mannuronic acid (M units) and α-L glucuronic acid (G units) residues.

The polymer, Sodium alginate, which undergoes instantaneous gel formation due to formation of calcium alginate by virtue of its interaction with divalent cation (Ca^{+2}) present in lachrymal fluid (pH 7.4). Alginate can be ionically crosslinked in the presence of divalent cations.

Hydroxy Propyl Methyl Cellulose (HPMC) is incorporated as a viscosity enhancer to further aid in accomplishment of sustained drug delivery. HPMC is semisynthetic, inert, viscoelastic polymer which is non-ionic nontoxic, a good carrier for pharmaceutical application which exhibits high swelling capacity [11–14].

2. Materials and method

Ciprofloxacin hydrochloride was obtained from chitin chem (Vadodara), Sodium alginate and Hydroxy propyl methyl cellulose (HPMC E5 0LV and K4M) were obtained from Dutt enterprise, Renchem Company. All other chemicals and reagents were of analytical grade procured from CDH chemicals.

2.1. Analytical method development

2.1.1. Determination of λ_{max} of ciprofloxacin hydrochloride

For the determination of absorption maxima, stock solution (1000 μg/ml) was prepared by weighing 100 mg (0.1 g) drug and dissolving it in 100 ml volumetric flask and making the volume to the mark with Methanol. 10 ml of standard stock solution was taken in 100 ml volumetric flask and making the volume to the mark with methanol to make 100 μg/ml of ciprofloxacin. Serial dilutions with concentrations 2, 4, 6, 8 and 10 μg/ml were prepared by transferring 0.2, 0.4, 0.6, 0.8 and 1.0 ml of the stock solution in 10 ml volumetric flask and makeup the volume with phosphate buffer 7.4 up to the mark. The resulting solution was scanned between 200 and 400 nm using UV–visible spectrophotometer UV 1400, Shimadzu [15] (Figs. 2 and 3).

2.2. Formulation development and evaluation

2.2.1. Formulation of ciprofloxacin hydrochloride in situ gel

Table 1 and Figs 4 and 5.

2.3. Characterization of formulation

2.3.1. FT-IR studies

The IR spectra were recorded on Thermo Nicolet, Avatar 370. FTIR spectra of sodium alginate, HPMC and the drug (Ciprofloxacin

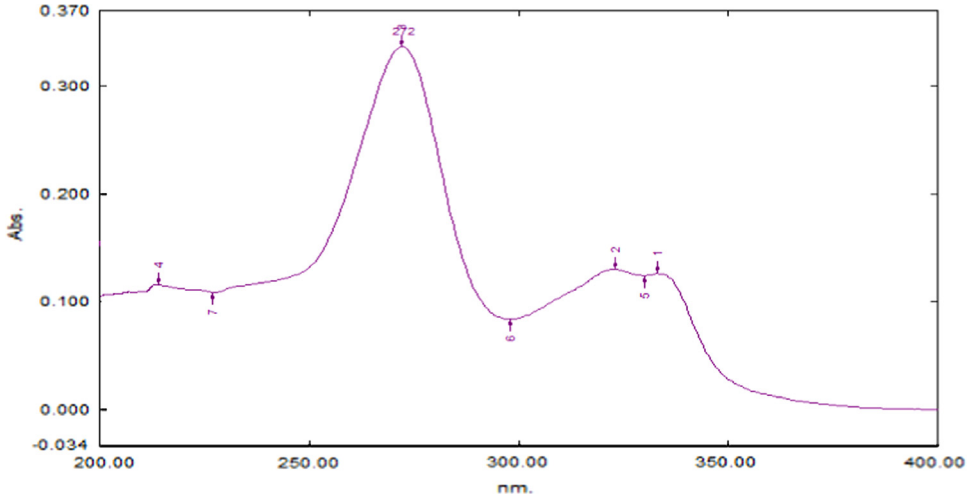

Fig. 2. UV visible spectra of ciprofloxacin hydrochloride at 272 nm.