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Novel *in situ* gelling ocular films for the opioid growth factor-receptor antagonist-naltrexone hydrochloride: Fabrication, mechanical properties, mucoadhesion, tolerability and stability studies

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ABSTRACT

Naltrexone hydrochloride (NTX) is an innovative drug used in ophthalmology for treatment of ocular surface diseases such as impaired corneal wound healing and severe dry eye. Poor chemical stability has been a major limitation for development of NTX in solution form. The aim of this study was to develop and characterise NTX *in situ* ocular films for enhanced chemical stability and improved ocular tolerability. The films were prepared from different amorphous polymers and characterised for physicochemical compatibility, moisture-sorption, surface pH, mechanical properties, sterilisability, surface morphology, mucoadhesion, *in vitro* release, conjunctival irritation and accelerated stability at 40 °C/75% relative humidity for 3 months. Glycerin (GLY)-plasticised films exhibited significantly better mechanical properties, compared with polyethylene glycol (PEG) 400 and triethylcitrate (TEC)-plasticised formulations. Superior mucoadhesion was recorded for F7 and F9 plasticised with GLY and PEG 400, respectively. The stability of NTX was significantly enhanced more than 18-times, compared with the solution form. Combination of carboxymethylcellulose sodium (CMC) and sodium alginate (ALG) in a film formulation demonstrated minimal % moisture sorption, good mechanical properties, *in vitro* release, excellent chemical stability and minimal conjunctival irritation lending them as promising ocular formulations.

1. Introduction

Topical ocular drug delivery is the preferred route for treatment of disorders of the ocular surface and anterior segment, such as keratoconus, keratitis, conjunctivitis, glaucoma and diabetic keratopathy (Abdelkader et al., 2011a,b,b; Khutoryanskaya et al., 2014; Lang et al., 2002; Urtti, 2006). The lipophilic corneal epithelium is a significant barrier against the transport of water soluble drug molecules; both non-productive absorption due to absorption of drugs into conjunctival blood vessels and nasolacrimal drainage are not only responsible for major loss from the administered dose but have the propensity to cause systemic side effects. Serious cardiovascular and pulmonary side effects were observed with topical ocular administration of timolol (a widely used ocular hypotensive drug) (Nelson et al., 1986a,b,b). It has been reported that the nasal mucosa accounts for 70% of the timolol systemically absorbed (Chang and Lee, 1987). These are typical limitations of conventional eye drops due to exposure of the eye tissues to an abrupt and fluctuated drug release.

In situ gelling inserts/films are single-dose solid units intended for insertion into the nasal cavity (nasal inserts) that hydrate and gel quickly after contact with mucus membranes. These delivery systems demonstrated extended drug release, good stability and good acceptance mainly due to avoiding foreign body sensation (Bertram et al., 2010; Bertram and Bodmeier, 2006; Farid et al., 2013). Small drug molecules (*e.g.* nicotine, oxymetazoline hydrochloride and salbutamol sulphate) (Bertram and Bodmeier, 2006; Farid et al., 2013; McInnes et al., 2005) and macromolecules (*e.g.* insulin and influenza vaccine) (Bertram et al., 2010; McInnes et al., 2007) were loaded into these delivery systems. Many polymers such as carbopol 971P, polyvinyl alcohol, sodium alginate, sodium carboxymethylcellulose, hydroxypropylmethylcellulose (Bertram

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and Bodmeier, 2006; McInnes et al., 2005) have been utilised as drug-release retarding polymers to fabricate the so called *in situ* gelling inserts/films. Two simple and mild methods (not involving excessive heat) have been employed to prepare *in situ* gelling inserts, namely, lyophilisation and solvent casting (Bertram et al., 2010; Bertram and Bodmeier, 2006; Farid et al., 2013; McInnes et al., 2005). The term used to describe these single-dose solid units as *in situ* gelling inserts/films denotes rapid wetting and transformation into mucoadhesive gel-based films, when in contact with mucus membranes (nasal mucosa, buccal cavity and conjunctival membranes) under physiological conditions (Bertram et al., 2010; Bertram and Bodmeier, 2006).

In situ gelling films for ocular drug delivery are a rather contemporary concept with few reports published about their potential for treatment of ophthalmic diseases. Recently, the film casting method was adopted to prepare ocular film formulations loaded with riboflavin for treatment of keratoconus (Khutoryanskaya et al., 2014). These film formulations were composed of a mixture of polyacrylic acid and methylcellulose and showed good mucoadhesive and minimal irritation when tested using the slug irritation assay (Khutoryanskaya et al., 2014). Glycero-gelatin films were also prepared by the solvent casting method; loaded with aceclofenac for treatment of inflammatory ocular conditions. The prepared films showed prolonged ocular retention, better *in vivo* efficacy and minimal irritation, compared with conventional eye drops (Mathurm and Gilhotra, 2011).

Naltrexone is an opioid growth factor receptor antagonist that can enhance corneal epithelialisation, restore corneal sensitivity, treat severe dry eye and enhance corneal wound healing without scar formation (McLaughlin et al., 2010; Zagon et al., 2009). The chemical stability of naltrexone has been studied in solution and in niosomes in an attempt to formulate eye drops (Abdelkader et al., 2011a,b, 2012a,b). Naltrexone is prone to rapid autoxidation in these liquid dosage forms which undermines its utility as shelf-stable ophthalmic pharmaceuticals (Abdelkader et al., 2011a,b). Ocular *in situ* gelling inserts/films could be a potential alternative to enhance the stability of naltrexone, prolong its pre-corneal residence time and enhance ocular bioavailability. Furthermore, these prospective formulations are suitable for patients with compromised wound corneal healing after undergoing refractive eye surgery. The ability to leave the eye patch undisturbed after surgery and to avoid patient manipulation of the eye post-surgery, that may occur when the patient is instilling eye drops, could be potential advantages for this formulation, especially during the post-operative period.

This work aimed to characterise and evaluate single-dose solid units of naltrexone hydrochloride, in a variety of polymer films that have acceptable shelf-life, stability, sustained drug delivery and good ocular tolerability, in order to determine which film provides the optimum treatment. Specific objectives and criteria of formulation, optimisation and selection include:

- mechanical properties suitable for withstanding patient manipulation during insertion,
- ultra-violet (UV) sterilisability while maintaining inherent mechanical and physicochemical properties,
- mucoadhesive properties to allow retention in the cul-de-sac, withstand blinking, tear flow, and
- long-term stability under accelerated storage conditions.

2. Materials and methods

2.1. Materials

Naltrexone hydrochloride (NTX) was kindly donated by Mallinckrodt Inc., St. Louis, MO, USA. Polyvinyl alcohol high molecular weight (PVA), methyl cellulose, Methocel 90HG, (MC), sodium alginate (ALG), carboxymethylcellulose sodium (CMC), triethyl citrate 99% (TEC), glycerol (GLY) and polyethylene glycol 400 (PEG) were purchased from Alfa Aesar, Heysham, England. Cellulose membranes of molecular weight-cut off 12,000–14,000 were purchased from Sigma–Aldrich, USA. All other chemicals and solvents were of analytical grade and were used as received.

2.2. Drug-polymer interaction studies

2.2.1. Differential scanning calorimetry (DSC)

Physical mixtures of the drug and the polymers used were prepared by uniformly mixing equal amounts of the drug and polymer using a spatula for 2–3 min. An amount of between 2–4 mg of NTX powder depending on the polymer with which the NTX was to be mixed, and the same amounts of each polymer prepared as standards (*i.e.* without mixing with NTX) were weighed separately in an aluminium pan, covered with an aluminium lid and hermitically sealed using a pan press (Thermal Science, USA). The temperature of the pan was gradually increased from 25 to 300 °C at a rate of 10 °C/min using a differential scanning calorimeter (Mettler Toledo DSC 822e0, Switzerland) pre-calibrated with indium. The purging gas was nitrogen at a flow rate of 45 ml/min. Data were collected online using Mettler STARe software version 8.10, Switzerland.

2.2.2. Fourier transform infrared spectroscopy (FTIR)

The FT-IR spectra for NTX, polymers and their physical mixtures were recorded using an FT-IR spectrometer (Thermo Scientific Nicolet is5, Thermo fisher, Madison, USA). A clean diamond window was used to measure the background spectrum. A sufficient amount (approx. 2–4 mg) of the sample was placed to form a thin film covering the diamond window. The data were acquired and analysed using Omnic software (Omnic version 8.2, USA). The FT-IR spectra were recorded at spectral resolution of 2 cm^{-1} with an average of 120 scans.

2.3. Preparation of NTX ocular films

2.3.1. Preparation of the starting gels

With the exception of MC gel, all other gels were prepared by dispersing specified amounts of PVA, CMC and ALG in water at approximately 80 °C to produce final concentrations of 2%, 2% and 5% w/w, respectively. Preparation of the MC gel required dissolution in cold water to produce a final concentration of 2% w/w. All gels were allowed to cool down to room temperature and the pH was measured using an Orion 3 Star pH meter (Thermo Scientific, Singapore); the final gels were stored in a fridge (4 °C) till further use.

2.3.2. Solvent casting method used to fabricate the in situ gelling ocular films

In situ gelling ocular films were prepared by the solvent casting method. Specified weights of the polymer solutions (as described above), plasticisers (GLY, TEC or PEG) and NTX (in accordance with the compositions shown in Table 1) were mixed and dissolved together in a 50 ml beaker over a stirring plate (VWR International Ltd., Poole, England). The concentrations of NTX and plasticiser in all film formulations were kept constant at 8% w/w and 30% w/w, based on solid polymer weights in solutions, respectively. The final solution was poured into a Petri dish of 120 mm diameter and allowed to dry for 48 h in ambient conditions. The films were cut using a cork borer into circular discs of 6 mm diameter each, to fit into the lower conjunctival sac (see graphical abstract); the final film formulations were transferred to glass vials and stored in a cool and dry place until further use.