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Composite bi-layered erodible films for potential ocular drug delivery

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ABSTRACT

Bi-layered hydroxypropylmethylcellulose and Eudragit based films were formulated as potential ocular drug delivery systems using chloramphenicol as a model antibiotic. Films were plasticized with polyethylene glycol 400 present in the Eudragit layer or both Eudragit and hydroxypropylmethylcellulose layers, and loaded with chloramphenicol (0.5% w/v in solution) in the hydroxypropylmethylcellulose layer. The weight, thickness and folding endurance of the optimized formulations were measured and further characterised for transparency, tensile, mucoadhesive, swelling and *in vitro* drug dissolution properties. The physical form of chloramphenicol within the films was evaluated using differential scanning calorimetry (DSC), and X-ray diffraction (XRD), complimented with scanning electron microscopy and energy dispersive X-ray spectroscopy. Fourier transform infrared spectroscopy was used to assess the interactions between the drug and the film components and confirm chloramphenicol's presence within the sample. Optimum films showed high transparency (≥80% transmittance), ease of peeling from Petri dish and folding endurance above 250. Average thickness was lower than contact lenses (0.4–1 mm), confirming them as thin ocular films. The tensile properties showed a good balance between toughness and flexibility, and mucoadhesivity showed that they could potentially adhere to the ocular surface for prolonged periods. The drug loaded films showed swelling capacity that was greater than 300% of their original weight. The physical form of chloramphenicol within the films was amorphous (DSC and XRD) whilst *in vitro* drug dissolution showed sustained drug release from the films for four hours, before complete erosion. The chloramphenicol loaded films represent a potential means of treating common eye infections.

1. Introduction

Vision provides 90% of the information within our surrounding environment, with considerable physiological importance including differentiation between light, shape and colour, spatial orientation, equilibrium and cortical tone [1]. Various conditions can affect the eyes and these are classified as periocular and intraocular, according to their location. Periocular conditions occur around the eye and can cause irritation to different parts of the eye. Common periocular diseases include blepharitis, conjunctivitis and chronic conditions caused by bacteria which can even lead to vision impairment [2]. Effective reduction of bacterial load is very important in the treatment of ocular diseases caused by infection.

The development of ocular drug delivery systems is challenging because of the eyes' complex anatomic structure and protective mechanisms which make it difficult to maintain an effective drug concentration over a prolonged period of time [3–8]. The eye is a very sensitive organ to debris, microorganisms and drugs and therefore, ocular drug delivery systems should be simple, non-invasive (to prevent irritation, inflammation, infection), maintain visual clarity, and enable the drug to penetrate the physiological eye barriers to reach the site of action [9].

Ocular drug delivery for treating conditions affecting the front of the eye depends on the corneal barrier and tear film. Apart from the physiological factors, there are also factors affecting formulation development of ophthalmic preparations including osmolality, pH, surface tension and viscosity [10].

Topical eye drops represent the most convenient formulation among patients, especially for conditions affecting the anterior segment of the eye. However, only 5% of the instilled dose can penetrate the ocular pre-corneal, dynamic and static barriers, while constant and prolonged drug release cannot be achieved [11]. Though gels and ointments can remain for relatively longer periods, they are quickly diluted by the tear fluid and leak out, therefore reducing bioavailability [12]. Ocular inserts such as films have been developed, which are expected to maintain the drug on the eye surface for a relatively prolonged period better than drops, gels and ointments. These increase the contact time with the ocular sur-

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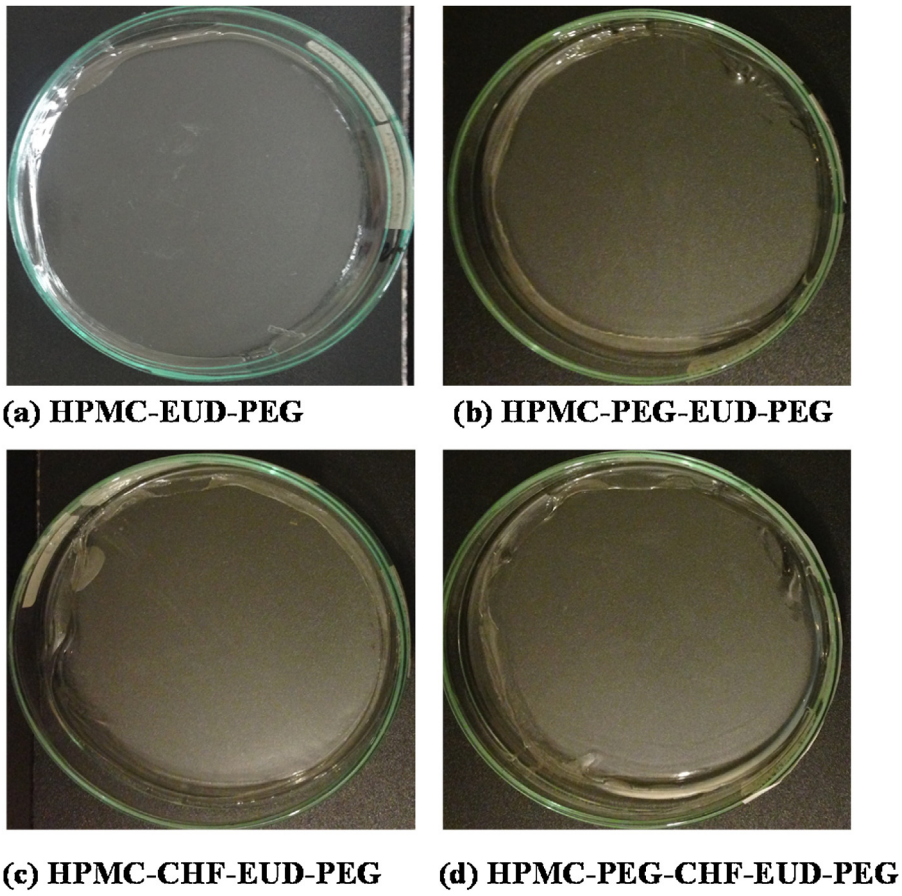

Fig. 1. Digital images of optimum films formulated (a) BLK HPMC-EUD-PEG (b) BLK HPMC-PEG-EUD-PEG (c) DL HPMC-CHF-EUD-PEG (d) DL HPMC-PEG-CHF-EUD-PEG.

face and therefore prolong drug delivery, reduce systemic effects, improve patient compliance and increase bioavailability [12].

Erodible films are made of polymers that can be natural, synthetic or semi-synthetic and that provide support for loaded drug. The polymers used need to be bio-compatible, safe, non reactive, stable and mucoadhesive, and release drug appropriately [13]. The drugs contained within the films are usually in the form of a dispersion within the matrix whilst maintaining film clarity [14]. Acyclovir, phenylepherine, diclofenac sodium, and antibiotics are examples of drugs that can be contained within the ocular inserts. All drugs need an appropriate balance between lipid and water solubility for effective corneal permeation. In addition, films generally need a plasticiser to improve their flexibility and reduce the chances of contact irritation due to britleness.

In the present study, bi-layered erodible ocular films were prepared by solvent casting technique from solutions using hydrophobic Eudragit (EUD) and hydrophilic hydroxypropylmethylcellulose (HPMC). These polymers are safe and biocompatible, stable, mucoadhesive and provide sustained drug release *in vitro*, making them suitable for ocular delivery [15]. Polyethylene glycol 400 was used as a plasticiser in either the EUD or both polymeric layers to increase the flexibility of the films.

Chloramphenicol (CHF) was used as model drug and exhibits broad-spectrum antibacterial activity [16] against Gram-positive bacteria (*Staphylococcus aureus* and, *Streptococcus pyogenes*) and Gram-negative bacteria *Haemophilus influenza* and *Neisseria meningitides*) common in ocular infections such as conjunctivitis [17]. Due to its high lipophilicity, CHF can easily penetrate the ocular barriers, and therefore very effective against ocular infections [17]. However, its high lipid solubility facilitates easy absorption into the systemic circulation and side effects such as aplastic anaemia can occur with prolonged exposure. Therefore, CHF is safely and efficiently used in eye drops at 0.5% w/v (approximately 5000 μg/ml) which was the dose employed in this study [18]. The MIC values of CHF against the above organisms range from 0.25 to 128 μg/ml [19] which is far lower than the dose used in this study. Because the residence time of eye drops on the cornea is poor, the use of the 0.5% CHF dose within a mucoadhesive film which can prolong retention on the cornea and control drug release, is expected to overcome limitation of the former. Further, a more gradual release of CHF which prevents frequent administration, will reduce the incidence of side effects associated with CHF.

2. Experimental

2.1. Materials

Eudragit S100 (EUD) was obtained from Degussa (Germany), hydroxypropylmethylcellulose – HPMC (Methocel™ K100 Premium) was a gift from Colorcon Limited (Dartford, UK). PEG, methanol, absolute ethanol, acetone, isopropyl alcohol, acetonitrile (HPLC grade) and phosphoric acid (HPLC grade) were supplied from Fisher Scientific, (Leicestershire, UK). Chloramphenicol was obtained from Sigma-Aldrich (Gillingham, UK). Sodium chloride, potassium chloride, sodium phosphate dibasic anhydrous (99^{+} % extra pure) and potassium phosphate dibasic anhydrous (99^{+} % extra pure) were all obtained from Acros Organics Ltd (New Jersey, USA).