International Journal of Pharmaceutics 532 (2017) 408–420

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Research Paper

Development and characterisation of electrospun timolol maleate-loaded polymeric contact lens coatings containing various permeation enhancers

Prina Mehta[a], Ali A. Al-Kinani[b], Muhammad Sohail Arshad[a], Ming-Wei Chang[c,d], Raid G Alany[b], Zeeshan Ahmad[a,*]

[a] Leicester School of Pharmacy, De Montfort University, Leicester, LE1 9BH, UK
[b] Kingston University London, School of Life Sciences, Pharmacy and Chemistry, Kingston Upon Thames, Surrey, KT1 2EE, UK
[c] College of Biomedical Engineering and Instrument Science, Zhejiang University, Hangzhou 310027, China
[d] Zhejiang Provincial Key Laboratory of Cardio-Cerebral Vascular Detection Technology and Medicinal Effectiveness Appraisal, Zhejiang University, Hangzhou 310027, China

ARTICLE INFO

Keywords:
Electrospinning
Contact lens
Coatings
Fibers
Timolol maleate
Glaucoma
Permeation enhancer

ABSTRACT

Despite exponential growth in research relating to sustained and controlled ocular drug delivery, anatomical and chemical barriers of the eye still pose formulation challenges. Nanotechnology integration into the pharmaceutical industry has aided efforts in potential ocular drug device development. Here, the integration and *in vitro* effect of four different permeation enhancers (PEs) on the release of anti-glaucoma drug timolol maleate (TM) from polymeric nanofiber formulations is explored. Electrohydrodynamic (EHD) engineering, more specifically electrospinning, was used to engineer nanofibers (NFs) which coated the exterior of contact lenses. Parameters used for engineering included flow rates ranging from 8 to 15 µL/min and a novel EHD deposition system was used; capable of hosting four lenses, masked template and a ground electrode to direct charged atomised structures. SEM analysis of the electrospun structures confirmed the presence of smooth nano-fibers; whilst thermal analysis confirmed the stability of all formulations. *In vitro* release studies demonstrated a triphasic release; initial burst release with two subsequent sustained release phases with most of the drug being released after 24 h (86.7%) Biological evaluation studies confirmed the tolerability of all formulations tested with release kinetics modelling results showing drug release was via quasi-Fickian or Fickian diffusion. There were evident differences ($p < 0.05$) in TM release dependant on permeation enhancer.

1. Introduction

Despite being an accessible organ, it is the structure of the eye (more specifically the corneal structure) that poses great challenges with respect to ocular drug delivery (Mehta et al., 2017a; Taskar et al., 2017). The cornea is a transparent tissue located in anterior of the iris; with a primary function of providing protection to the front of the eye and to focus light entering the eye. The corneal tissue is approximately 500 µm thick and 11 mm in diameter. There are three distinct regions to the cornea; endothelium, stroma and epithelium. The endothelium is the inner most layer of the cornea with high porosity allowing the thickness of the cornea to be controlled by hydration. The majority of the cornea is made up of the stroma; a collagen rich layer separated from the endothelium by Descemet's membrane. The Bowmen Layer connects the stroma to the epithelium, the outer most layer of the cornea (Kong and Mi, 2016). The composition of these layers results in various degrees of hydrophilicity across the cornea and as a result of this, drug delivery through the cornea is a challenge. There are 2 mechanisms of drug transport through the cornea; paracellular and transcellular. Paracellular transport is restricted to polar molecules due to the hydrophilic stroma and epithelial whilst larger molecules are often halted by tight junctions between corneal cells. Transcellular drug transport involves partition between hydrophilic (e.g. stroma) and lipophilic (e.g. endothelium) environment.

There are various factors which affect drug permeation through the cornea; all which can be categorised into three groups; physiochemical factors, physiological factors and formulation factors. Physiochemical factors refer to drug properties that interfere with passive diffusion of drug (e.g. partition coefficient of the drug and molecular weight) (Mun et al., 2014). Physiological barriers focus on pre-corneal factors (dilution due to tear production, pre-corneal volume (25–30 µL), corneal tissue components (e.g. proteins)) as well as factors relating to the membrane (porosity, thickness, physiochemical properties (hydrophilicity, lipophilicity)) (Malhotra and Majumdar, 2001).

* Corresponding author.
E-mail address: zahmad@dmu.ac.uk (Z. Ahmad).

http://dx.doi.org/10.1016/j.ijpharm.2017.09.029
Received 3 June 2017; Received in revised form 11 September 2017; Accepted 12 September 2017
Available online 14 September 2017

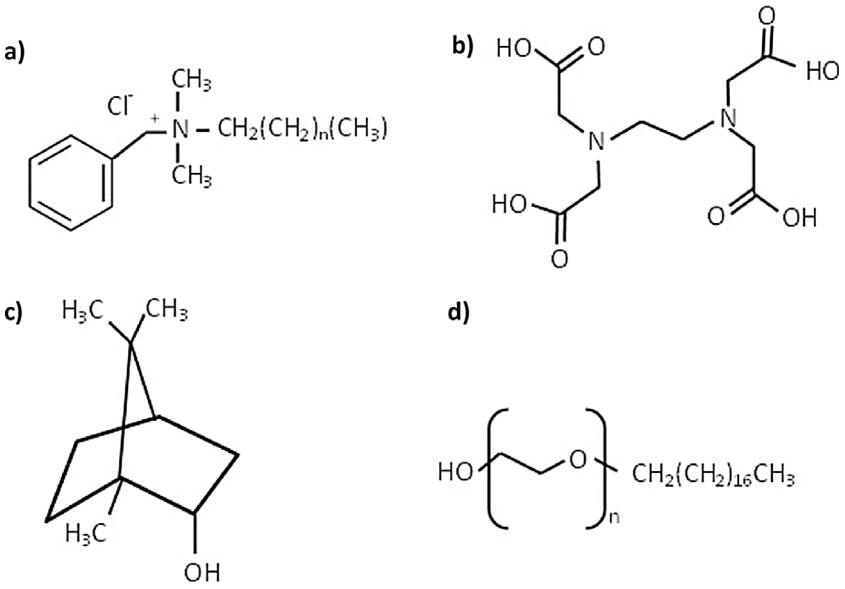

Fig. 1. Structures of permeation enhancers used in this study (a) BAC, (b) EDTA, (c) Borneol and (d) Brij® 78.

From a formulation point of view, the formulation factors are arguably the most critical category to consider due to patient safety. Increasing the concentration of drug in question has found to increase the bioavailability of the active; hence, improving treatment. In addition, increasing particle size or using suspensions (for poorly soluble drugs) has provided sustained drug release. However, there is a maximum particle size which can be utilised (10 μm) before reflex tear production is triggered as a result of "foreign matter" detection (Aldrich et al., 2013). Increased viscosity of formulations prolongs product residence time in the conjunctival sac; providing a more sustained release. However, an increase in viscosity can result in blurred vision; causing inconvenience to the patient (Hiraoka et al., 2012). Other approaches for extended- drug delivery involve altering the pH and the tonicity of ocular formulations, resulting in higher drug bioavailability (Gupta et al., 2010; Reddy and Ahmed, 2013; Suresh and Abhishek, 2016).

One major hurdle met by formulation scientists regarding ocular drug delivery is the poor bioavailability of ophthalmic drugs. As a result of this, permeation enhancers (PEs) have been incorporated into formulations to increase drug absorption and in turn improve ocular bioavailability. There are five main classes of PEs; calcium chelators, preservatives, surfactants, glycosides and fatty acids. Calcium chelators like ethylenediaminetetraacetic acid (EDTA) supposedly work by interfering with the tight junctions between the superficial epithelial cells in the corneal epithelial layer; enhancing paracellular drug movement (Kaur and Smitha, 2002; Morrison and Khutoryanskiy, 2014).

Surfactants, unlike calcium chelators, enhance drug permeation *via* transcellular methods. It has been implied that surfactants interfere with the lipid bilayer of epithelial layers; forming micelles causing the phospholipids to be removed from the membrane. Both non-ionic and cationic surfactants have been used to increase the permeability of various ocular drugs such as prednisolone, dexamethasone, atenolol and timolol. Non-ionic surfactants such as Brij®98 and Brij® 78 have also been exploited as PE showing promising results in ocular drug delivery, highlighting the safety and efficacy of these surface active agents. One of the most common surfactants used in ophthalmic formulations is benzalkonium chloride, a cationic surfactant, usually incorporated in ocular solutions to act as preservative at very low concentrations (de los Angeles Ramos-Cadena and Spaeth, 2016; Fukuda and Sasaki, 2015). The effects of this preservative have proved to be more effective in enhancing corneal permeation that other commonly used preservatives such as chlorobutanol and organomercurials. Borneol is a naturally occurring essential oil of *Cinnamonum camphora*. Although it does not fit into a defined category of PEs, it has shown potential in promoting corneal permeation of ocular drugs timolol maleate (TM) (Wu et al., 2006), dexamethasone (Yang et al., 2009), indomethacin (Yang et al., 2009) and ofloxacin (Yang et al., 2009).

In an attempt to utilise PEs to increase the corneal penetration of TM, electrohydrodynamic atomisation (EHDA) was employed to fabricate drug loaded polymeric fibers containing PEs. EHDA is a versatile technique capable of producing a multitude of micro and nano sized structures for an array of application in the pharmaceutical arena (Mehta et al., 2017b). The one-step, easily modified process has been exploited in recent years with promising results in many remits including anti-cancer therapy (Kaplan et al., 2016; Lee et al., 2016), protein delivery (Hu et al., 2014; Ozcan et al., 2016; Rasekh et al., 2015; Zamani et al., 2014), transdermal delivery (Khan et al., 2014) and ocular drug delivery (Baskakova et al., 2016; Kong and Mi, 2016; Mehta et al., 2015). The fundamental principle revolves around utilising an electrical field to atomise liquids to generate nano sized structures. Modifying the process parameters (applied voltage and flow rate) alongside the physical properties of the liquid being atomised (viscosity, surface tension, electrical conductivity) allows the process to be optimised for specific criteria. Baskakova et al. successfully developed drug-loaded polyvinylpyrrolidone (PVP) or polycaprolactone (PCL) fibers to act as potential intravitreal plants (Baskakova et al., 2016) whilst the electrospinning process has been used to produce fibrous scaffolds for corneal tissue engineering (Kong and Mi, 2016). Mehta et al. successfully utilised the EHD technique to develop double-sided functionalised nano-coatings for contact lenses(Mehta et al., 2015). Rapidly dissolving PVP was used to fabricate nanoparticulate (< 100 nm) and nanofibrous (< 200 nm) coatings demonstrating burst probe release and sufficient antibacterial activity; presenting a multifunctional drug delivery device.

In this study, four conventional PEs (Fig. 1) were selected to develop and characterise fibrous formulations of anti-glaucoma drug TM. TM-loaded PVP, Poly (N-isopropylacrylamide) (PNIPAM) (collectively termed as composite in this study, used at 1:1 ratio) fibers containing various permeation enhancers were synthesized using EHDA technology (electrospinning) and were evaluated using various thermal, spectral and *in vitro* models. In addition model fitting provided an insight into potential TM release mechanism from the various fiber systems. This study is one of the first of its kind; utilising the electrospinning process in conjunction with soft contact lenses to develop a novel drug delivery device for the treatment of glaucoma.