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Research paper

Electrically atomised formulations of timolol maleate for direct and on-demand ocular lens coatings

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ABSTRACT

Advances in nanotechnology have enabled solutions for challenging drug delivery targets. While the eye presents numerous emerging opportunities for delivery, analysis and sensing; issues persist for conventional applications. This includes liquid phase formulation localisation on the ocular surface once administered as formulated eye-drops; with the vast majority of dosage (>90%) escaping from the administered site due to tear production and various drainage mechanisms. The work presented here demonstrates a single needle electrohydrodynamic (EHD) engineering process to nano-coat (as an on demand and controllable fiber depositing method) the surface of multiple contact lenses rendering formulations to be stationary on the lens and at the bio-interface. The coating process was operational based on ejected droplet charge and glaucoma drug timolol maleate (TM) was used to demonstrate surface coating optimisation, bio-surface permeation properties (flux, using a bovine model) and various kinetic models thereafter. Polymers PVP, PNIPAM and PVP:PNIPAM (50:50%w/w) were used to encapsulate the active. Nanofibrous and particulate samples were characterised using SEM, FTIR, DSC and TGA to confirm structural and thermal stability of surface coated formulations. More than 52% of nano-structured coatings (for all formulations) were <200 nm in diameter. *In vitro* studies show coatings to exhibit biphasic release profiles; an initial burst release followed by sustained release; with TM-loaded PNIPAM coating releasing most drug after 24 h (89.8%). Kinetic modelling (Higuchi, Korsmeyer-Peppas) was indicative of quasi-Fickian diffusion whilst biological evaluation demonstrates adequate ocular tolerability. Results from permeation studies indicate coated lenses are ideal to reduce dosing regimen, which in turn will reduce systemic drug absorption. Florescent microscopy demonstrated probe and probe embedded coating behaviour from lens surface *in vitro*. The multiple lens surface coating method demonstrates sustained drug release yielding promising results; suggesting both novel device and method to enhance drug activity at the eyes surface which will reduce formulation drainage.

1. Introduction

Glaucoma is the 2nd leading cause of blindness in the world; affecting 2% of the worlds' population over 40 years of age [1]. It is a progressive multifactorial optic neuropathy, often resulting in vision loss due to heightened elevation in ocular pressure (OP). The increase in OP is a result of insufficient drainage of the aqueous humour (AH); (a transparent gel produced by the ciliary body in the eye which occupies the space between the cornea and lens). The reduction in removal of AH is due to anatomical changes in the trabecular meshwork. Here, the tubes which remove AH from the eye to the bloodstream are damaged which consequently lead to impairment of retinal nerves and the optic nerve [2]. At present, there is no cure for glaucoma and there is an urgent need to enhance the quality of life for patients and those currently on life-long treatment. Many of these regimens often require multiple dosing of active throughout the day.

Treatment of glaucoma is usually in the form of eye drops, a dosage form that makes up approximately 90% of all ocular formulations [3]. They are classed into those that reduce AH production (beta blockers, alpha agonists, carbonic anhydrase inhibitors) and those that improve the drainage of AH (prostaglandin analogues, cholinergics). Timolol (a beta adrenergic blocking agent) blocks

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the action of the sympathetic nervous system by competing with adrenergic neurotransmitters [4]. For the treatment of glaucoma, beta blockers like Timolol work by blocking the receptors in the ciliary body; reducing AH production [2]. However, Timolol also has an adverse effect on the cardiac and pulmonary system. If Timolol is present in the blood stream over a specific threshold concentration, it can slow down the heart rate, decrease blood pressure and reduce the function of the lungs, which can cause more inconveniences for the patient [4].

Despite ease of formulation and patient compliance, there are limitations with regards to the use of eye drops including nasolacrimal drainage and inability to control drug release leading to less than 5% of drug permeating through the cornea to targeting tissue; the ciliary body for glaucoma [5]. The biggest limitation is poor drug bioavailability as a result of short residence time in the eye. Consequently, to reach the therapeutic concentration in the eye, a higher dose of the drug needs to be administered [6]. Addressing these limitations has led to research being directed at the potential of various ocular devices; the most common being soft contact lenses [7]. Contact lenses (CLs) are becoming increasingly common; replacing glasses for vision correction. However, recent developments have extended the use of CLs for cosmetics and therapeutics. The concept of using CLs as drug delivery devices was first introduced in the 1960's [8] but only in the last 2 decades have CLs been considered as useful ocular devices for delivery of drugs such as antibiotics [9], non-steroidal anti-inflammatory drugs (NSAIDs) [10], and anti-glaucoma actives [11,12]. Timolol (more specifically the maleate salt of Timolol (TM)) has been extensively used to assess the feasibility of CLs as drug delivery devices, with promising conclusions [13–15].

Many concepts, conventional and novel, to alter CLs and exploit the properties (e.g. the hydrophilicity [16]) of common hydrogel (HG) materials have been introduced to achieve sustained ocular drug delivery. Such notions include the simplicity of soaking lenses in a drug solution with consequent drug uptake in post-lens region (soak and release) [17] whilst more complex methods include molecular imprinting on HG matrix [18] or modifying the composition of the HG matrix [12]. Other methods involve embedding colloidal carriers (nanoparticles (NPs) [14], micelles [19]) within the HG matrix in an attempt to retard diffusion.

Electrohydrodynamic atomisation (EHDA) is a one-step deposition and an on demand method to coat biomaterials and is extendable to CLs. The principle revolves around using electrical forces to atomise liquids for the generation of nano and micrometre structures suitable for drug delivery. The fundamentals of this process are based on two vital processing parameters; applied voltage and flow rate. Various physical properties (viscosity, density and surface tension) also influence the resulting size and morphologies of the structures produced. This process is a versatile technique with great potential for enhancing bio-interfaces [20]. A large array of materials including temperature and stress sensitive active pharmaceutical ingredients (APIs)/materials (e.g. proteins and genes [21,22]) have been utilised to demonstrate the application of EHDA. Based on the choice of materials, it is possible to alter the release of drug when needed; in a controlled manner over minutes, hours or even days.

Since ocular formulation (liquid phase eye-drops) administration suffers loss from extensive drainage and tear forming mechanisms, the aim of this study was to develop an on demand nanostructured multiple lens coating process; enabling greater formulation stability on lens surface and at the bio-interface. Polymers polyvinylpyrrolidone (PVP) and poly (N-isopropylacrylamide) (PNIPAM) were selected alongside glaucoma drug Timolol Maleate (TM) to optimise the multi-lens EHDA coating process. Formulation stability in matrix form was assessed using several techniques and the permeation (diffusive flux) across the bio-interface (cornea) was determined. *In vitro* release data was used to determine ideal kinetic models for TM release from various nano-structured systems on the lens coating. Fluorescent microscopy was also used to determine surface behaviour of both probe and probe-embedded lens coating *in vitro*.

2. Materials and methods

2.1. Materials

PVP (4.4×10^4 g/mol) was obtained from Ashland, UK. Methanol, PNIPAM ($2–4 \times 10^4$ g/mol) timolol maleate (TM, ≥98%), acetone, sodium hydroxide and Rhodamine B were supplied by Sigma Aldrich, Dorset, UK. PureVision® (Balafilcon A) silicone hydrogel contact lenses manufactured by Bausch and Lomb (New York, USA) were utilised in this study. All reagents were of the analytical grade.

2.2. Solution preparation

Polymeric solutions (selected polymer, or composite systems, at 5%w/v) containing TM (5% w/w of polymer) were prepared using methanol as the solvent by magnetic stirring for 10 min at ambient temperature (23 °C). Table 1 shows the composition of each formulation used.

2.3. Coating application

A syringe containing 5 mL of solution was attached to a syringe infusion pump (Harvard Apparatus, Pump 11-Elite, USA) which controlled the flow rate of polymer-drug solution. The solution was passed through silicone tubing which was connected to a stainless steel coaxial needle device (only single needle was utilised here, inner diameter 1.6 mm) at various flow rates (5, 10 and 15 μL/min). The device was attached to a high power voltage supply (Glassman High Voltage Supply, UK). The electrically driven spraying process was carried out at ambient temperature (23 °C). Jetting mode-maps were constructed by varying the flow rate to optimise the processing parameters of the atomising system (Fig. 1a).

Atomised coatings were deposited on microscope slides for preliminary analysis and subsequently onto commercial contact lenses. Pure Vision lenses were used in this study. For controlled deposition *via* atomised coatings, a lens holder device (accommodating up to 4 lenses) was built (Fig. 1b and c), hosting ground electrodes, which enabled deposition onto peripheral regions of lenses whilst keeping the central regions un-coated (for sight). The lenses were weighted before and after to ascertain the mass of each coating. An illustration of the process mechanism is provided in Fig. 1d. Exploratory experiments were performed to determine the spraying distance; as this is crucial in ensuring particle or fiber formation for thin film engineering.

Table 1
Formulated sample composition and their loading efficiency. Polymer concentrations were 5% w/v and timolol maleate concentration 5% w/w of the polymer. [PVP: polyvinylpyrrolidone, PNIPAM: poly (N-isopropylacrylamide), TM: timolol maleate].

Formulation	Composition	Loading efficiency (%)
F1	PVP, TM	64.63
F2	PNIPAM, TM	79.8
F3	PVP, PNIPAM, TM	99.7