Contact Lens and Anterior Eye 39 (2016) 97–105

Contents lists available at ScienceDirect

Contact Lens and Anterior Eye

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

Structural design of contact lens-based drug delivery systems; in vitro and in vivo studies of ocular triggering mechanisms

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ARTICLE INFO

Article history:
Received 9 February 2015
Received in revised form 11 July 2015
Accepted 18 July 2015

Keywords:
Ocular drug delivery
Ophthalmic dyes
Trigger release mechanism
Ocular environment

ABSTRACT

This study identifies and investigates the potential use of in-eye trigger mechanisms to supplement the widely available information on release of ophthalmic drugs from contact lenses under passive release conditions. Ophthalmic dyes and surrogates have been successfully employed to investigate how these factors can be drawn together to make a successful system. The storage of a drug-containing lens in a pH lower than that of the ocular environment can be used to establish an equilibrium that favours retention of the drug in the lens prior to ocular insertion. Although release under passive conditions does not result in complete dye elution, the use of mechanical agitation techniques which mimic the eyelid blink action in conjunction with ocular tear chemistry promotes further release. In this way differentiation between passive and triggered in vitro release characteristics can be established. Investigation of the role of individual tear proteins revealed significant differences in their ability to alter the equilibrium between matrix-held and eluate-held dye or drug. These individual experiments were then investigated in vivo using ophthalmic dyes. Complete elution was found to be achievable in-eye; this demonstrated the importance of that fraction of the drug retained under passive conditions and the triggering effect of in-eye conditions on the release process. Understanding both the structure-property relationship between drug and material and in-eye trigger mechanisms, using ophthalmic dyes as a surrogate, provides the basis of knowledge necessary to design ocular drug delivery vehicles for in-eye release in a controllable manner.

1. Introduction

The inefficiency of direct instillation as a delivery method for ophthalmic drugs is well-recognised, as is the potential value of contact lenses for this application [1,2]. Despite this, there are virtually no commercial examples of this area of technology. One reason for this is the perception, gained from in vitro passive diffusion studies, that the use of contact lenses in this way will lead to rapid and uncontrolled release in which much of the active drug will be lost by premature diffusion into the contact lens packaging solution [3–5]. Whilst these conclusions have some basis in fact, they overlook both the difference between in-eye release and passive diffusion under "sink" conditions into saline, and also the potential for specific design and selection of drug–lens combinations in which specific molecular interactions provide a means of extending in vivo delivery times.

The wide range of lens matrix chemistries and the structural variations found in ophthalmic drugs mean that this is a fruitful area for biomaterials research in this specialised field of ophthalmic biomaterials [6,7]. The potential range of drugs coupled with the complexities of the ocular environment mean that such studies must be systematically organised and proceed from a sound knowledge of the materials chemistry and the aspects of the anterior eye that are likely to influence drug elution.

The present contact lens market encompasses many materials for a wide range of replacement (disposable, planned and conventional) and wear schedules (daily, extended and continuous wear) [8,9]. Whereas the primary cosmetic role of contact lenses is vision correction, therapeutic indications for use of bandage lenses include pain relief, corneal protection and enhancement of corneal wound healing [10–12]. Bandage contact lenses play a key role in corneal transplant surgery, and are routinely used in penetrating keratoplasties, pterygia, total superficial keratectomies and corneal ring segment procedures [13,14]. Patients with chronic epithelial defects or recurrent erosions, bullous keratopathy and dry eye typically stay in lenses for several months and in some cases, years. Commercial considerations have meant that a huge

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http://dx.doi.org/10.1016/j.clae.2015.07.007
1367-0484/

amount of research and product development has been directed to the so-called cosmetic lenses which provide an elective method of vision correction. There is very considerable potential for more detailed studies of structure-effect relationships in the under-researched area of therapeutic lenses. Although there is less commercial interest here, it is undoubtedly a field of potential social and economic benefit in patient care.

Appropriate use of bandage contact lenses can speed healing, particularly in uncomplicated postoperative cases. In addition to the promotion of healing, bandage lenses provide symptomatic relief of pain, corneal protection and structural support. Although medication can be distilled onto the eye and absorbed in the presence of the lens this is less effective than the controlled delivery of therapeutic quantities of specific drugs.

The ready availability of drug-loaded contact lenses would be much welcomed by ophthalmologists. Furthermore, common conditions such as contact lens induced dry eye and hay fever which are widely encountered in optometric practice, and can be aggravated by contact lens wear, could ideally be controlled with the use of suitably modified lenses. There are several commonly prescribed ocular drugs that could potentially be released from contact lenses [15–17]. For example, cromolyn sodium, olopatadine and ketotifen fumarate represent a small selection of drugs used to manage ocular allergies that range from seasonal to chronic conditions [18–20]. Given that a small but significant number of allergy sufferers require admission into hospital for eye drop treatment, the administration of the drug using a contact lens is a clear attractive alternative.

Several sophisticated approaches including molecular imprinting and incorporation of discrete nanoparticles have been proposed as strategies for the achievement of zero order release [21–27]. The main disadvantage of these approaches, however, is that purpose-fabricated lenses are necessary to make use of this technology, which has costly manufacturing implications.

Although a number of in vitro studies almost exclusively based on uptake and passive release behaviour of ophthalmic drugs from contact lenses have been carried out [1,28–30], there has been little attempt to mimic the particular features of the ocular environment. This paper uses the understanding of drug–lens interactions, developed from equilibrium passive release studies, and examines the potential influence of in-eye trigger effects on the exploitation of this equilibrium retention in the design of effective in-eye delivery systems. In this respect ophthalmic dyes and dye surrogates enable the use of a simple method to study the quantity retained as the release environment is changed and provide a ready platform for subsequent in vivo studies. This is not readily achieved with conventional ophthalmic drugs for which release monitoring is simple but retained drug extremely difficult to assay accurately. We investigate here the variables that enable maximum retention under passive release conditions from conventional hydrogels and address the effect of the lens material, release media volume and pH, tear proteins and degree of mechanical agitation on the equilibrium of the retained active achieved under passive release conditions.

2. Materials and methods

2.1. Materials and lens loading

Details of the materials used and the procedures followed for incorporating an active into a lens, passive release and analysis of the release media have been previously published [1]. The range of ophthalmic dyes and structurally related compounds used in this study are based on the same core structure (Fig. 1), which is shared by key ophthalmic dyes such as Rose Bengal, Lissamine Green B and sodium fluorescein. The range of substituents, octanol–water partition and distribution coefficients and molecular weights of this family of compounds is shown in Table 1. The shared multi ring core structure is a common feature of many drug systems [1], which have hydrophobicity arising from the aromatic ring systems and hydrophilicity from functional groups. The use of ophthalmic dyes as models indicate the relative influence of the balance of hydrophobicity and hydrophilicity and also relative steric effects which lead to association.

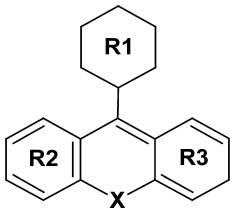

Fig. 1. Ring structure common to the chosen ophthalmic and related dyes.

2.2. Passive release methodology: parallel measurement of release and retained active

The general procedure for treating loaded lenses of each material, dye and loading combination (e.g. Table 2) involved blotting the loaded lens on filter paper to remove excess dye, placing it in a specified volume of fresh phosphate buffered saline (PBS) release medium at pH 7.4 and stirring constantly (on a shaker at 200 rpm). This regime minimised the formation of a stagnant boundary transfer layer, and maintained optimum sink conditions (receiver concentration 25 times greater than donor concentration). At the end of each hour, the lenses were removed and placed in vials containing the same volume of fresh PBS release media and the process repeated until no further dye was released from the lens. This procedure was used for studies involving a series of discrete receiver volumes ranging from 150 μl to 20 ml (Section 3.4).

The optical density (OD) i.e. absorbance of the release media was measured by UV–Vis spectroscopy using a Molecular Devices SpectraMax M2 spectrophotometer at the maximum absorption wavelength of the released active. The absorbencies were then converted to concentrations using standard calibration curves. Release measurements were carried out in triplicate and averaged.

Non-destructive measurement of quantity of active retained was carried out spectroscopically using a Molecular Devices SpectraMax M2 spectrophotometer at the appropriate maximum absorption wavelength of the active (Fig. 4). It is important to note that the extinction coefficients of these actives are stable within the time scales of the spectral assessments [31]. The mass calculations can therefore be reliably linked to absorbencies.

2.3. Mechanical release methodology

2.3.1. Batch triggered release

A healthy human eye has a tear flow rate of circa 1 μl/min, which is conveniently approximated to 100 μl/h [32]. In order to replicate this in-eye extraction volume as closely as possible, an equivalent volume was used. Thus, a contact lens was inserted into a microtube containing 100 μl of phosphate buffered saline (PBS). Furthermore to mimic the mechanical action of the eye-lid blink, on both the lens and the surrounding tear fluid, the microtube was vortexed at 2400 rpm for 10–15 s and placed on a flat bed shaker at 200 rpm for an hour. After an hour the microtube was vortexed again for a further 10–15 s and the release media extracted for analysis. 100 μl of fresh release media was placed into the lens containing microtube and this procedure was repeated for the number of hours desired.