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Analysis of release kinetics of ocular therapeutics from drug releasing contact lenses: Best methods and practices to advance the field

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ABSTRACT

Several methods have been proposed to achieve an extended and controlled release of ocular therapeutics *via* contact lenses; however, the experimental conditions used to study the drug release vary greatly and significantly influence the release kinetics. In this paper, we examine variations in the release conditions and their effect on the release of both hydrophilic and hydrophobic drugs (ketotifen fumarate, diclofenac sodium, timolol maleate and dexamethasone) from conventional hydrogel and silicone hydrogel lenses. Drug release was studied under different conditions, varying volume, mixing rates, and temperature. Volume had the biggest effect on the release profile, which ironically is the least consistent variable throughout the literature. When a small volume (2–30 mL) was used with no forced mixing and solvent exchange every 24 h, equilibrium was reached promptly much earlier than solvent exchange, significantly damping the drug release rate and artificially extending the release duration, leading to false conclusions. Using a large volume (200–400 mL) with a 30 rpm mixing rate and no solvent exchange, the release rate and total mass released was significantly increased. In general, the release performed in small volumes with no force mixing exhibited cumulative mass release amounts of 3–12 times less than the cumulative release amounts in large volumes with mixing. Increases in mixing rate and temperature resulted in relatively small increases of 1.4 and 1.2 times, respectively in fractional mass released. These results strongly demonstrate the necessity of proper and thorough analysis of release data to assure that equilibrium is not affecting release kinetics. This is paramount for comparison of various controlled drug release methods of therapeutic contact lenses, validation of the potential of lenses as an efficient and effective means of drug delivery, as well as increasing the likelihood of only the most promising methods reaching *in vivo* studies.

1. Introduction

Topical eye drops in the forms of suspensions and solutions are the most widely used platform for delivering ocular therapeutics. Together with ointments, they account over 90% of currently administered ocular drugs [1–3]. However, less than 7% of drug delivered through eye drop formulations is absorbed, resulting in very low drug bioavailability [4,5]. To overcome low bioavailability, topical formulations have remained effective by the administration of high concentrations of drug multiple times on a daily basis. Variability in the effectiveness of topically applied drugs is introduced primarily through patient non-compliance when patients fail to follow the dosage regimen, which can lead to poor prognosis and ocular side effects [6].

An interesting alternative to overcome low drug bioavailability and patient non-compliance is the use of soft contact lenses as drug delivery devices. In the US, current contact lens wearers are estimated at nearly 50 million, with more than 170 million people needing corrective lenses (contact lenses or eyeglasses). Contact lenses (corrective and cosmetic) generated approximately $7.3 billion in revenues worldwide in 2012, and the market is expected to increase to nearly $7.9 billion by 2017 [7]. In the last 50 years, several methods have been proposed to achieve an extended and controlled release of ocular therapeutics from soft contact lenses; however, the experimental conditions used to study the release kinetics vary greatly, making the comparison of methods difficult.

Since the mention of soft contact lenses as a potential drug delivery device [8], drug soaking has remained the prevalent method to achieve drug delivery [9]. However, a sufficient reservoir of drug for

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a therapeutically relevant effect is hard to attain, and in the overwhelming majority of these cases, the drug is released very quickly with no control over the release profile and only slight improvements over topical eye drops have been demonstrated [10–13]. The most telling fact of their non-superiority to topical therapy is that after 48 years, no contact lens product, that loads or releases drug this way has made it to market.

Other approaches have been investigated to enhance the drug loading capability and to control the release rate of therapeutics from contact lenses. These include the incorporation of chemistry [14–16] or cyclodextrins [17,18] able to interact with the drug, long chain molecule eluting lenses [19], molecules used as a diffusion barrier [20], supercritical solvent impregnation [21,22], nanospheres [23], and (poly[lactic-*co*-glycolic acid]) coatings [24]. Another approach is molecular imprinting, which has been shown to considerably extend and control release and improve loading [25–27]. We direct the reader to the following reviews for the advantages and disadvantages of various methods [9,28–30].

Developing an effective method that allows for controlled and extended drug release *via* contact lenses may revolutionize the ocular therapeutics field as well as have a huge impact on the market. Unfortunately, there is an issue hindering the field. Various researchers do not use consistent release conditions (*e.g.*, release volumes, temperature, and mixing rate). Using different conditions for the study of drug release kinetics has created an environment that allows for no true basis of comparison, and therefore leads to issues assessing which techniques are more effective than others. At this stage in the field, proper comparisons among different release mechanisms are vital toward the understanding and comparison of release mechanisms and the translation of promising technologies to the clinic.

Currently, *in vitro* release studies in the field can be generalized into three separate categories: small volume, large volume, and microfluidic flow devices. Some researchers use the term release sink, which refers to the volume of solvent in which the lenses are placed during release studies. A small sink is typically an aqueous volume approximately between 2 and 30 mL with no forced mixing and with or without a timed interval of water exchange. For release studies conducted in small sinks, solvent exchange is required to re-establish the driving force for mass diffusion. A large sink is typically a solvent volume of 200 mL or more that is mixed, where, at times, can be classified as an infinite sink where the majority of drug release is achieved without the necessity for solvent exchange. The infinite sink is defined as an environment where the accumulation of drug in the solution surrounding the lens is considered to be negligible, attaining the greatest driving force possible and corresponding to the fastest possible release. It allows for the quickest comparison between formulations of a certain method or various methods to control release. The microfluidic device consists of a small chamber where the contact lens sits, and it is designed to mimic the continuous, volumetric flow rate of tear fluid [31]. While these provide better mimics to release kinetics under ocular flow, the experiments take much longer periods of time to complete and include more variables to consider to adequately match release conditions. Thus, the field is better suited for initial testing between systems to involve larger volume experiments.

Most drug-eluting lens systems described in the literature to date have used small volumes (*i.e.*, 2–10 mL), which are not well mixed (Fig. 1) [9]. We hypothesize that this stems from characteristics pertaining to the fluid flowrate of the eye. The tear turnover rate within the eye is 0.5–2.2 μL/min [5,32]. This flowrate, although not constant *in vivo*, can be used to calculate the total amount of tear fluid that comes into contact with the eye during a 24 h period – an average of 2 mL, making the assumption that a small sink is a good setting for drug release kinetic studies. Moreover, the turnover rate during contact lens wear can be 2.82 ± 1.45 μL/min [32], meaning

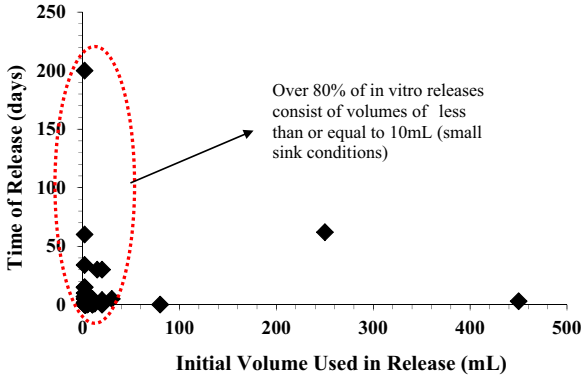

Fig. 1. Typical volumes used in release studies of contact lenses. The area enclosed by the red circle indicates that the majority (over 80%) of *in vitro* drug release studies are conducted in small volumes.

that the eye surface can be flushed with an average of 4.1 mL of tear fluid a day. A common, incorrect assumption made with small volumes, is to proclaim them as perfect sinks or infinite sinks. In some cases the Higuchi equation [33,34] is misused to calculate the release kinetics parameters such as the diffusion coefficient.

The focus of this paper is to explore the effect of release conditions on the release rate as well as the reasons why so many promising *in vitro* studies have failed to show extended release during *in vivo* studies. We hypothesize that a stagnant, small sink is neither a suitable environment for testing extended release nor a reliable representation of the ocular environment. The continuous tear turnover rate of the actual eye is expected to lead to very different diffusion kinetics than a stagnant volume. Variations in the release conditions (*e.g.*, volumes, temperature, and mixing rate) and their effect on drug release were examined for both hydrophilic and hydrophobic drugs (ketotifen fumarate, diclofenac sodium, timolol maleate and dexamethasone) (Fig. 2) from conventional hydrogel lenses and silicone hydrogel lenses.

2. Materials and methods

2.1. Materials and reagents

Diethylaminoethyl methacrylate (DEAEM), acrylic acid (AA), acrylamide (AM), methacrylic acid (MAA) 2-hydroxyethylmethacrylate (HEMA), N-vinyl-2-pyrrolidone (NVP), ethylene glycol dimethacrylate (EGDMA), azobisisobutyronitrile (AIBN), timolol maleate salt (TMS), ketotifen fumarate (KF), dimethyl acrylamide (DMA), and Darocur 1173 were purchased from Sigma-Aldrich (Milwaukee, WI). Diclofenac sodium salt (DS) was purchased from Sigma–Aldrich (Saint Louis, MO). Tris(hydroxymethyl)aminomethane (TRIS), and 900–1200 MW methacryloxypropyl-terminated polydimethylsiloxane (PDMS) were purchased from Gelest, Inc. (Morrisville, PA). Dexamethasone (DEX), and ethanol (97%) were purchased from VWR International (Radnor, PA). Polyethylene glycol (200) dimethacrylate (PEG200DMA) was purchased from Polysciences, Inc. (Warrington, PA). All chemicals were used in their respective forms as received.

2.2. Synthesis of therapeutic hydrogels films

Therapeutic hydrogel films that are approximately the size of contact lenses on the market today without curvature were synthesized using molecular imprinting techniques, where macromolecular framework or memory for the drug is produced during polymer synthesis. Imprinted networks have been shown to improve loading and considerably extend and control release. Excellent review articles give background of the field [22–24] with