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Insights to Using Contact Lenses for Drug Delivery

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Abstract

There has been considerable interest in the potential application of contact lenses for ocular drug delivery. This short communication provides an overview of the challenges faced by delivering drugs using contact lenses, highlights the solutions to limitations that have already been achieved, and describes the barriers that remain before commercial application can be realized.

Introduction

In the last few decades, potential applications of Contact Lenses (CL) beyond their use to correct refractive error have been investigated, including extensive research towards their use for ocular drug delivery. At present, topical eye drops remain the most common method for treating ocular disease, accounting for 90% of all ophthalmic formulations [1-4] and they are readily accepted by patients due to their convenience and cost effectiveness [1]. However, the ocular anatomy presents several barriers that prevent the effective and efficient delivery of medication from eye drops, including continuous tear dilution [5-7], dispersion and drainage during blinking and tear flow [5,7,8], non-specific absorption [1,5,7], and variable drug penetration [4]. This results in only 1-7% of the medication within an eye drop reaching the target tissue and exerting a therapeutic effect [8], with the remainder being either spilled onto the external ocular surface or absorbed systemically [9]. High turnover and poor absorption leads to the need for multiple dosing over extended periods to achieve therapeutic drug concentrations, leading to problems relating to patient compliance [10,11], as well as the potential for drug overdosing [12]. These limitations suggest that there is considerable room for improvement if efficient and effective treatment of anterior segment diseases is to occur.

Contact lenses are often used in cases of ocular trauma or post-surgery as so-called 'bandage lenses', as a means to manage pain and promote re-epithelialization [13]. Several commercially available CLs, including Pure Vision (balafilcon A, Bausch+Lomb), Acuvue 2 (etafilcon A, Vistakon Inc.), Acuvue Oasys (senofilcon A, Vistakon Inc.), and Air Optix Night & Day (lotrafilcon A, Alcon) are FDA approved for use as bandage lenses [13-19]. In most cases, antibiotics and anti-inflammatory drugs are administered in conjunction with the CLs by adding the medication topically over the lens *in situ* [13,20]. This practice, although simple, is cumbersome and may not provide the desired effectiveness, with the uptake and release of the drug during such a process being unknown and uncontrolled. A survey of ophthalmic practitioners across the United States and Canada revealed that there is a strong interest in a CL that is specifically developed for use as a drug delivering therapeutic CL and that such a product would be well received by practitioners [13].

Advantages of using Contact Lenses

The use of CLs for ocular drug delivery overcomes several of the barriers that limit the effective use of eye drops. The placement of a CL on the cornea separates the tear film into pre-lens (exposed to the external environment) and post-lens (between the lens and cornea) compartments, with the post-lens compartment being of particular interest due to limited tear mixing and exchange [21,22]. As a result, drugs released from the CL into this compartment potentially have a prolonged contact time with the cornea, leading to improved bioavailability [23]. Over 50% of the drugs released from a CL can diffuse into the cornea, which is at least 35 times more efficient than eye drops [24]. This increase in efficiency permits substantially reduced concentrations to be used, decreasing the potential for side effects as less drug is absorbed systemically.

Another advantage to using a CL as a drug delivery platform is the ability to deliver drugs over extended time periods, which eliminates the need for multiple dosing. For ocular infections such as microbial keratitis, eye drop applications can be as frequent as applications every hour [25]. This can be very difficult for patients, especially during sleep, and severe infections often lead to hospitalization, purely to ensure appropriate drug administration [10,11]. Contact lenses effectively serve as a drug reservoir and release the drug over a set time period. In an ideal situation, the target drug forms an interaction with the CL polymer, and dissociates from the lens network in a time-dependent manner into the post-lens tear film, for eventual absorption by the ocular tissues.

Past Barriers - Contact Lenses Coming of Age

It is somewhat surprising that although the potential application of CLs for ocular drug delivery was suggested in the 1960s [26,27], there continues to be no commercial products available. The initial problem with this concept was that early Conventional Hydrogel (CH) CLs did not provide adequate oxygen transmission to the cornea, resulting in hypoxia-related complications during overnight wear, limiting their long term therapeutic potential [28,29]. This issue was eventually overcome in the late 1990s, when highly oxygen permeable Silicone Hydrogel (SH) CLs were introduced. These lenses permitted near-normal corneal physiology during extended periods of wear [30,31], and the idea of CLs for drug delivery became all the more promising, with this significant hypoxic hurdle seemingly solved.

Aside from oxygen delivery issues, the use of CLs for drug delivery also has another major obstacle. Simple drug loading methods, such as soaking a commercial CL in pharmaceutical preparations inevitably leads to rapid release kinetics [32]. While different CL material and drug combinations provide different release durations, the overall

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time frame for drug release is in the order of minutes and is thus not clinically useful [20,33,34]. This is not surprising as commercial CLs are intended solely for refractive error correction, but they are not designed for release of pharmaceuticals. As a result, extensive research has been conducted in the past decade to develop CL materials capable of extended drug delivery, and the *in vitro* results so far have been very promising. Strategies such as molecular imprinting [35], vitamin E coatings [33] and nanoparticles [36,37] have been investigated and tested. These materials are designed to form interactions with the target drug molecule in a manner that promotes drug retention and slow release over time. Molecular imprinting creates specific drug recognition sites within the polymer through the use of molecular templates [35]. Vitamin E coatings form diffusion barriers within the lens, which forces the target drug to take long complex paths to diffuse from the lens [33]. Nanoparticles encapsulated with the target drug can be loaded and released from the CL, and the extended release is controlled by the degradation of the nanoparticles [36,37]. CL materials developed using these technologies are capable of releasing ophthalmic drugs for up to several days and even weeks, in some cases [33,35,37].

Future Barriers - Fine Tuning Drug Release Characteristics

Although the issue of extended drug release has been partially solved with the development of novel CL materials, the kinetics are far from optimal. Currently, drug release from these materials has been primarily diffusion controlled and first-order kinetics are typically observed [33,35,36]. Thus, the rate of drug release is not constant over time, with the majority of the drug within the lens being delivered in the initial stages rather than at the end of the treatment period. It can, therefore, be very difficult to design therapies when the drug dose cannot be controlled for a specific time point. One potential solution to this problem is to use the CLs only for the duration in which the release kinetics are zero-order and thus a linear, predictable drug release rate. However, this is not an optimal solution, as it would require frequent lens replacement at time periods which may be inconvenient for the patient, and so development of CL materials capable of zero-order release kinetics at all time periods is still preferred.

Aside from the development of the 'ideal' drug delivery device, other issues are also worthy of mention. Antibiotic resistance among ocular pathogens, due to misuse and overuse of topical antibiotics in the eye, improper dosing regimen, and extended duration of therapy, is becoming increasingly prevalent [38-40]. As such, continuous release of antimicrobials from a CL raises concerns in regards to microbial resistance. The continuous presence of the antibiotic at potentially sub-therapeutic concentrations can lead to selection pressures favoring resistant organisms [41]. One of the key considerations is the ability for some microbes (such as fungi) to develop resistant spores. Upon exposure to an antimicrobial agent, the vulnerable microbes are killed but the spores can continue to remain dormant and unaffected [42]. When the agent is removed, the spores become active and resume normal growth [42]. The current approach to drug delivery using CLs in which drugs are continuously released, may lead to the development of resistant spores. Pulse drug delivery systems, although still in their infancy, have addressed some of the problems in regards to microbial resistance. By delivering the drug in multiple-timed doses, this method offers greater efficacy in killing microbes at doses almost half that of conventional therapies [42]. This concept has not yet been adapted to CLs for drug delivery, and is worth considering for future development. Continuous drug release also raises concerns regarding ocular toxicity. Unlike conventional eye drops, drugs released from CLs become trapped beneath the post-lens tear film, and are not rapidly removed [23]. It could be argued that because CLs are more efficient than eye drops at delivering topical drugs, the amount of drug required to be released from CLs will be substantially less than eye drops. Based on this assumption, ocular toxicity should not be greater, and may even be lower when using CLs. However, it is important to keep in mind that the post-lens tear film formed when a CL is placed on the eye is only 4 microns thick [43]. Thus, even small concentrations of drug released into this micro-environment over extended periods could lead to unforeseen ocular toxicity, as concentrations may be reached that are many times what is currently available through the use of topical pharmaceutical agents.

A major limitation in this field currently is a shortage of *in vivo* studies to validate the effectiveness of a CL-delivery platform. To our knowledge, there have only been two published animal studies using CLs to treat an ocular condition [37,38], both of which revealed that CLs provide better bioavailability and reduced systemic drug uptake compared to conventional eye drop treatment [44,45]. Further *in vivo* research is needed to help facilitate this technology into the clinical trial phase, and lead to the development of a viable commercial product.

Acceptance - Can it Reach Clinicians and Affect Clinical Practice?

From a scientific and clinical standpoint, drug delivering CLs could revolutionize the way ocular diseases are treated. Still, there is an underlying concern whether this treatment platform will be readily accepted by patients and clinicians alike. Considering that CL dropout is already a pressing problem for the CL industry [46-48], it may be difficult to convince a non-CL wearer to wear CLs, let alone wear it for extended periods. However, the CL market is anything but small, with approximately 140 million current CL wearers worldwide that could benefit from using this technology, should the need arise for therapeutic intervention [49,50]. In addition, many spectacle wearers who undergo refractive surgery are able to wear a bandage lens for a short period of time [14,17,18,51], demonstrating the potential short-term success of a therapeutic lens to treat disease. The higher cost of using a drug-delivering CL compared to eye drops may also be a barrier, thus putting the onus on the prescribing practitioner to be an advocate of the technology such that the virtues of the treatment strategy can be appropriately communicated. Of final concern is that the patient population for this technology may not be the most appropriate for certain diseases (for example glaucoma and chronic inflammatory diseases), as they are often elderly, for whom the prevalence of CL wear is already poor due to lens intolerance and issues with CL insertion and removal, providing another potential barrier.

Conclusion

There has been considerable progress in the past decade in developing a viable CL-drug delivery platform and future work must focus on demonstrating *in vivo* effectiveness using these technologies. Furthermore, using this system to deliver other therapeutic agents (such as wetting and comfort agents to enhance the CL wearing experience) is an area rife with potential discoveries. The successful development of a CL platform that can deliver therapeutically relevant amounts of topical ocular drugs over extended periods will change the way ocular diseases are treated. Though the cost of such a system will likely be higher initially than conventional eye drops, the effectiveness of the treatment and the reduction in the frequency of application will make this system commercially attractive to clinicians.

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