

Mucoadhesive Nanopolymers for Posterior Segment Drug Delivery

Topical formulations show promise as a drug carrier to the back of the eye.

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Topical ocular therapy is often impaired by natural physiologic defense mechanisms to drug application such as blinking and an increase in tear turnover. Additionally, the corneal endothelium can present a barrier to penetration of topical drugs. Conventional topical preparations have significant drawbacks including poor ocular bioavailability—it is approximated that only 5% of applied drop is available at the site of physiologic activity—and toxicities through systemic absorption.^{1,2} Other factors, such as rapid and efficient drainage by the nasolacrimal apparatus, non-corneal absorption, and the relative impermeability of the cornea to both hydrophilic and hydrophobic molecules, also account for poor ocular bioavailability.

Topical therapy has remained elusive for the treatment of posterior segment disease, which accounts for approximately 35% of ocular disorders. Conventional ocular topical therapies fail to reach the target tissues in the posterior segment of eye mainly because of lower intravitreal concentration after topical application. Another hurdle is the blood-retina barrier, which not only blocks pathogens from reaching ocular tissues but also hinders systemic medications from reaching the posterior segment.^{3,4} The blood-retina barrier also reduces convection of molecules because of selective permeability to lipophilic molecules.⁵

There have been reports on effectiveness of certain

conventional topical nonsteroidal antiinflammatory drugs, such as ketorolac 0.5% (Acular, Allergan, Inc.) and nepafenac 0.1% (Nevanac, Alcon Laboratories, Inc.), for retinal conditions such as cystoid macular edema following cataract surgery and for diabetic macular edema.^{6,7} There remains, however, a need for a topical drug carrier that has the following capabilities:

- provides effective penetration of the inner ocular tissues;
- is target specific;
- offers controlled release of a drug in a manner that produces minimal systemic toxicities; and
- is biodegradable and eco-friendly.

If the drug contact time with the corneal and conjunctival surfaces is enhanced, these objectives may be possible. Bioadhesive nanocarriers have demonstrated substantial increase in precorneal resident time and increased aqueous concentration in comparison to conventional drug carriers. Nanoparticles also help to increase drug penetration and to reach target areas.⁸ Our current research in advanced drug delivery is focused on a more tailored, controlled drug delivery system, stabilizing the nanocarriers in different pH and thermal systems of eye, and reducing nanoparticle toxicity to ocular structures.

Figure 1 depicts various routes of drug delivery to and elimination from the posterior segment of the eye.

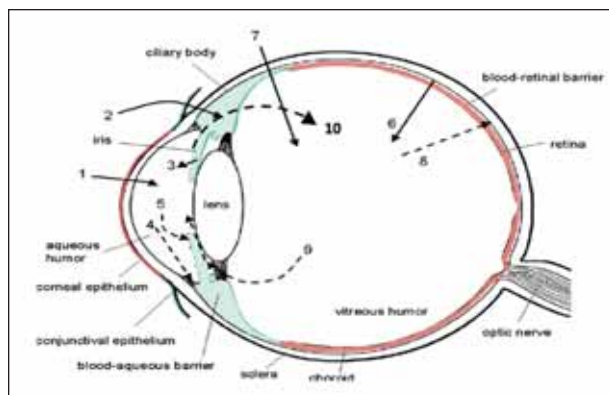


Figure 1. The numbered arrows in this figure represent: 1) transcorneal permeation from the lacrimal fluid into the anterior chamber; 2) noncorneal drug permeation across the conjunctiva and sclera into the anterior uvea; 3) drug distribution from the bloodstream via blood-aqueous barrier into the anterior chamber; 4) elimination of drug from the anterior chamber by aqueous humor turnover to the trabecular meshwork and Schlemm's canal; 5) drug elimination from the aqueous humor into the systemic circulation across the blood-aqueous barrier; 6) drug distribution from the blood into the posterior eye across the blood-retina barrier; 7) intravitreal drug administration; 8) drug elimination from the vitreous via posterior route across the blood-retina barrier; 9) drug elimination from the vitreous via anterior route to the posterior chamber; and 10) drug diffusion into vitreous cavity from aqueous humor.

BIOADHESIVE NANOPOLYMERS AS DRUG CARRIERS

Nanomedicine is defined as the use of nanometer-scale particles or systems to detect and treat diseases at the molecular level. Targeting a particular lesion in a precise manner is the primary goal of a drug delivery system, and our research shows nanocarriers to be effective in this endeavor.

Bioadhesive carriers, such as mucoadhesive nanoparticles, appear to be an effective solution in the challenge of achieving bioavailability with topical drugs. The justification for the development of particulate systems for the delivery of ophthalmic drugs is based on the potential entrapment of particles in the ocular surface mucus layer and the interaction of bioadhesive polymer chains with mucin, which thereby increases the precorneal resident time of the particular drug. Furthermore, it has been envisaged that nanoparticles can induce controlled drug release and enhance absorption, or even endocytosis, thereby improving bioavailability of drug.⁹⁻¹¹ Animal experiments have demonstrated that nanoparticles have the capacity to migrate through the vitreous and neu-

rosensory retinal layers, reaching the retinal pigment epithelium and choroid.⁸ This is particularly promising in the treatment of retinal degenerations that typically require subretinal injections.

NANOPARTICLES FROM CATIONIC POLYMERS

In a study in which flurbiprofen was incorporated in Eudragit R polymer system (Evonik, Essen, Germany), the drug-antagonizing activity against miosis induced by surgical trauma was found to increase the active drug concentration in aqueous humor. This could be due to the increased adhesion of nanoparticles to the ocular surface and a progressive continuous release of the polymer-incorporated drug.¹² Increased aqueous humor concentration may increase drug availability in the vitreous and may prove helpful for treating retinal conditions such as macular edema.

CHITOSAN NANOCOMPOSITES

Chitosan is a natural polymer that has been evaluated for ocular drug delivery. Chitosan is a cationic polysaccharide copolymer of 1,4-(2-amino-2-deoxy-D-glucopyranose) and 1,4-(2-acetamide-2-deoxy-D-glucopyranose). Chitosan nanoparticles labeled with fluorescein isothiocyanate-modified bovine serum albumin have been shown to be well tolerated by ocular surface tissue without compromising cell viability.¹³

It has been demonstrated that indomethacin, when coated with chitosan and polylysine, obtains a positive electrical charge that allows it to interact with the anionic ocular mucin layer of the precorneal tear film. The bioavailability of topically instilled indomethacin has been found to increase substantially,¹⁴ possibly leading to increased vitreous concentration.

De Campos et al¹⁵ compared the effect of a poly(ethylene glycol) vs a chitosan coating on the interaction of poly-caprolactone nanoparticles with ocular mucosa. The *in vivo* study showed that the nanoparticles entered the corneal epithelium by a transcellular pathway and the penetration rate was dependent on the coating composition. Poly(ethylene glycol) coating enhanced the passage of the nanocapsules across the entire epithelium, whereas chitosan coating favored retention in the superficial epithelium, providing a dual benefit of adequate penetration and continuous release of the drug.

LIPOSOMES

Liposomes have been evaluated in an attempt to improve bioavailability of ophthalmic drugs after topical instillation because they are stable, biocompatible, and

biodegradable liquid preparations. There are, however, conflicting reports in the literature.¹⁶⁻¹⁸ For enhancing the adherence to the corneal and conjunctival surface, dispersion of the liposomes in mucoadhesive gels or coating the liposomes with mucoadhesive polymers has been proposed.¹⁸ Similarly, there have been reports of formulations of immunoliposomes of antiviral drugs, such as ganciclovir and iododeoxyuridine, for usage in herpes simplex viral infections.¹⁹ The permeability of conventional ganciclovir solution was compared with a liposomal formulation containing ganciclovir, which showed transcorneal permeability was much higher in the liposomal formulation. And liposomal solutions also had higher ocular tissue distribution including concentration in the vitreous.¹⁹

When encapsulated in liposomes, antisense oligonucleotides, which are traditionally used to treat cytomegalovirus retinitis, have been found to efficiently target the retina.²⁰ Studies by Bochot et al²¹ showed that 37% of antiviral oligonucleotides administered through liposomes were retained in the vitreous humor even fifteen days after administration.²¹

NANOPARTICLES OF HYALURONIC ACID

The concept of producing micro- and nanoparticles of hyaluronic acid is not new.²² Hyaluronic acid alone or in combination with copolymer nanoparticles used to be the most effective soluble polymer. Kyyro Nen et al²³ have studied the release of methyl prednisolone from particles consisting of hyaluronic acid esters both in vitro and in rabbit eyes. They demonstrated that the polymer-bound drug itself increased the penetration to aqueous humor, but when combined with hyaluronic acid the precorneal resident time of methyl prednisolone increased many fold and helped in sustain release of the drug. This would avoid the frequent application of methyl prednisolone. This could also decrease drug toxicities and be considered as an alternative to conventional parenteral steroid therapy for certain retinal disorders.

MUCOADHESIVE POLYMER TAMARIND SEED POLYSACCHARIDE IN OCULAR DRUG DELIVERY

Mucoadhesive polymer tamarind seed polysaccharide (TSP; Farmigee S.p.A., Pisa, Italy; Saettone et al, patent application) has recently become available as a tear fluid substitute because of its activity in preventing alterations of the corneal surface known as keratoconjunctivitis sicca.²⁴ TSP polymer increases the corneal wound healing rate,²⁵ reduces the in vitro toxicity exerted by timolol, methiolate, and fluoroquinolones on human conjunctival

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cells,²⁶ and significantly increases the corneal accumulation and intraocular penetration of gentamicin and ofloxacin when administered topically to healthy rabbits.²⁷ This natural polysaccharide shows promise as drug carrier in topical preparations, but more data regarding its availability in the vitreous cavity are required.

CONCLUSION

Although the current strategies of treating retinal disease via an intravitreal approach have produced good results, there are substantial drawbacks to this approach, particularly in developing nations, including cost and the burden that frequent injections place in terms of clinic setup. Effective topical delivery would provide an alternative that would alleviate this burden. An ideal therapy would maintain effective levels of drug application, obviating the need for frequent patient visits.

Mucoadhesive nanocarriers bear dual advantages as methods of posterior segment drug delivery, increasing precorneal stay of the drug while acting as permeability enhancers.²⁸ Additionally, mucoadhesive polymers can be applied as aqueous solutions, thereby avoiding the ocular irritation usually experienced after application of viscous solutions. Improved formulation techniques, tailoring for controlled release, and measures to prevent nanoparticle toxicities to ocular structures may make mucoadhesive polymers a viable alternative to periocular and intravitreal drug administration. ■

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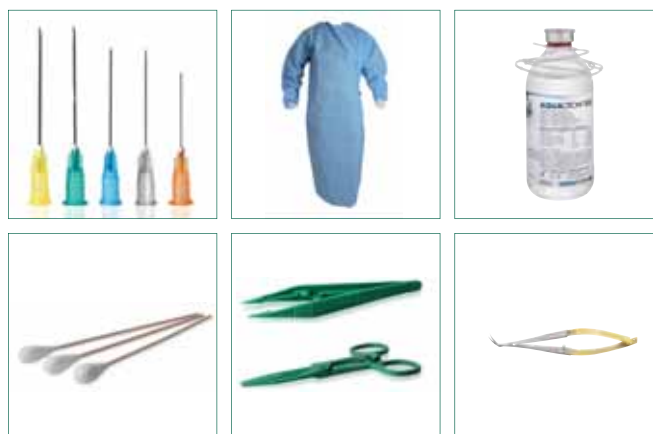
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