# Ocular Drug Delivery through thermosensitive strategies

Subjects: Others

Contributor: Simona Sapino

The low bioavailability, due to the presence of physiological barriers, requires repeated ocular administrations. Hence, the development of drug delivery systems that ensure suitable drug concentration for prolonged times in different ocular tissues is certainly of great importance. In situ forming gels, expecially the nanocomposite ones, have the undoubted advantage of being easily injectable and, owing to their sudden thickening at body temperature, have the ability to form an in situ drug reservoir. As a result, the frequency of administration can be reduced, also favoring the patient's adhesion to therapy. Here, some of the most common treatment options for ocular diseases, with a special focus on posterior segment treatments, are summarized highlighting the most recent improvement deriving from thermosensitive drug delivery strategies. Aside from this, an additional section describes the most widespread in vitro models employed to evaluate the functionality of novel ophthalmic drug delivery systems.

ocular drug delivery hydrogels nanocomposites thermosensitive systems in vitro pharmacokinetic models

## 1. Introduction

One of the critical issues of topically administered ophthalmic drugs is that their efficacy is limited by the fast drug clearance due to pre-corneal fluid drainage; consequently, frequent administrations are required. Therefore, various drug delivery systems (DDS) have received increased attention to enhance the efficacy of drugs on the corneal surface.

Aside from this, many limitations make it hard to deliver drugs aimed to treat eye posterior segment diseases, such as diabetic retinopathy and age-related macular degeneration (AMD). In fact, topical ocular medications do not reach the back of the eye; moreover, systemic administration is rarely used because of the small volume of the eye and the presence of the blood retinal barrier (BRB) [1].

A lot of research is currently being done to improve transscleral delivery, which might offer the advantage of removing the need to breach the walls of the eye; many transscleral delivery systems, also associated to iontophoresis, are therefore at different stages of development. However, to date, the majority of treatments of the posterior segment, such as retinal and choroidal disorders, require the intravitreal pathway. Intravitreal injection (IVI) is currently considered the most validated option—although it is invasive and associated with serious side

effects—for the delivery of large molecules such as anti-vascular endothelial growth factors (anti-VEGF antibodies), whose use has reached an exponential growth in recent years due to the progressive expansion of their clinical applications [2]. Nevertheless, the periocular pathway, including the retrobulbar, peribulbar, subtenon and subconjunctival routes, and even topical delivery, continue to be explored.

To overcome the limitations of conventional eye drops in corneal/conjunctival administration, and of invasive injection in intraocular administrations, or of surgery-implanted cannulas in periocular administration, in the last decades, several ophthalmic formulations, such as drug-loaded hydrogels and contact lenses targeted to the anterior segment, or ocular implants and physical devices destined to the back of the eye, have been proposed.

## 2. Hydrogels

Hydrogels are three-dimensional, cross-linked networks of either synthetic or natural water-soluble polymers with great potential in several applications, such as drug delivery, cell encapsulation and tissue engineering [3]. Various advantages make them interesting—their aqueous environment can exert some protection towards cells and labile drugs (such as peptides, proteins, DNA and oligonucleotides) and they have a significant role in transporting nutrients to cells. As a result, they are attractive for various ophthalmic applications, among which are corrective soft contact lenses [4], adhesives for ocular wound repair [5], potential vitreous substitutes [6] and drug vehicles [7]. Regarding the latter application, to our knowledge, most hydrogels on the market are targeted to the anterior segment (such as Pilopine HS, Zirgan and Pilogel), due to their ability to increase viscosity and mucoadhesive properties [8]. Conversely, just few hydrogels have been already approved by the FDA and EMA for intraocular injectable applications; as an example, Akten (Akorn, Buffalo Grove, IIlinois), a 3.5% lidocaine gel, was approved by the FDA for all ophthalmic procedures in October 2008, including intraocular procedures [9,10].

Other hydrogels are currently on the market for ophthalmic application other than drug delivery purposes—as an example, ReSure Sealant is an in situ gel approved to seal clear corneal incisions following cataract surgery [11].

Recently, contact lenses for drug controlled delivery to the anterior chamber have been developed, but several challenges are still arising regarding the limited drug release, the strict regulatory issues and the high cost of clinical studies [12].

On the other hand, the crucial need to reach the eye posterior segment through less invasive strategies other than repeated injections has boosted the development of slow-release implants that can be placed at once at various ocular sites. Currently, intraocular implants that allow sustained drug release in the posterior segment are at different development stages [13]. Most of these consist of non-biodegradable polymers, such as silicone, polyvinyl alcohol and ethylene vinyl acetate, from which long-lasting release of the entrapped drugs occurs [14]. However, they require surgical intervention and need removal or replacement by new implants. On the contrary, biodegradable polymers such as poly(lactic) acid and poly(lactic-*co*-glycolic) acid offer the advantage of releasing the drug at the same time that the polymer degrades in the target site, avoiding the need of surgical removal [15,16].

To date, several ocular implants designed for the treatment of severe indications affecting the posterior segment of the eye, including macular degeneration, are on the market or are undergoing clinical trials. Among them, non-biodegradable Vitrasert, Retisert, Medidur, Iluvien and biodegradable Posurdex, Ozurdex and Surodex must be cited [17,18,19,20]. Most of these implants are loaded with small active compounds, such as fluocinolone acetonide, dexamethasone and ganciclovir; meanwhile no biologics-carrying implants are available in the market, some being, however, in the pipeline [21].

Anti-VEGF therapy, playing a central role in the pathogenesis of choroidal neovascularization, has revolutionized the medical management of diabetic retinopathy and of AMD [22]. Currently, the most common anti-VEGF agents are pegaptanib (Macugen), bevacizumab (Avastin) and ranibizumab (Lucentis) [23,24], followed by other emerging macromolecular drugs already in clinical trials, among these being Fovista (Ophthotech, Princeton, NJ, USA), a platelet-derived growth factor aptamer currently in phase III clinical trials [25], and designed ankyrin repeat proteins [26].

The use of intravitreal administration in anti-VEGF therapy is still presenting some problems—most drugs are rapidly cleared from the vitreous humor, inducing the need of repeated injections that can cause side effects, such as endophthalmitis, retinal detachment, hemorrhage and poor patient tolerance [27]; other drugs induce local toxicity when administered at their effective dose, causing side effects and possible retinal lesions [28]. For these reasons, strategies that can deliver sufficient drug concentrations to this anatomic region in a less invasive manner and with less frequent doses, such as sustained-release DDS, represent an area of active interest in the ophthalmology community. In the last decades, different technologies have been proposed to this aim, including the use of nanomedicine [29,30,31]. Therapies based on nanotechnologies, such as lipid and polymeric nanocarriers, present several advantages, allowing a precisely targeted drug delivery and controllable release of the therapeutics [32]; moreover, the stability and half-life in the vitreous of entrapped drugs might be enhanced, thus reducing the frequency of administration and, consequently, diminishing their toxicity [33]. Therefore, depending on particle charge, surface properties and relative hydrophobicity, nanoparticles (NP) can be designed to be successfully used in sustained ocular therapy [34], both in the anterior and posterior segments [35]. Studies have shown that albumin NP can serve as a very efficient drug delivery system for retinal diseases, such as cytomegalovirus retinitis, as they are biodegradable, non-toxic and have non-antigenic properties [36]. Moreover, NP prepared with natural polymers, such as chitosan, increased the intraocular penetration of loaded drugs, due to their ability to make contact intimately with corneal and conjunctival surfaces [37]. In the past decades, several hydrophilic polymeric particles have been proposed as ocular DDS composed of various biodegradable polymers, such as poly(lactic acid) [38], poly(alkyl cyanoacrylate) (PACA) [39], poly(lactic-*co*-glycolic acid) (PLGA) [40] and poly(ε-caprolactone) (PECL) [41]. However, one of the main barrier-hindering clinical trials of these innovative systems is the requirement to ensure the safety of nano-microsystems and of their biodegradation products in the eye [29,42].

Another appealing approach of drug delivery to the posterior ocular segment consists in vesicular systems such as intravitreal-injectable liposomes (i.e., the ocular liposomal Verteporfin (Visudyne). They provide sustained drug

delivery for weeks or even months, but up until today, most of them are only pre-clinically investigated, with few in clinical use [43].

Recently, preclinical trials have centered around the interesting formulation of nanocomposites, consisting of nanoparticulate systems dispersed into a hydrogel matrix that provide an additional diffusion barrier to drug release, eliminating the burst effect and extending the release profiles of the entrapped drugs [44].

In the literature, various strategies have been proposed to deliver drugs into the eye in a more controlled manner—in the first part of this review, special attention will be given to the thermosensitive approach, considering the different typologies and action mechanisms. The second part deals with the most widespread in vitro models employed to investigate the functionality of novel ophthalmic DDS.

## References


1. Shah, S.S.; Denham, L.V.; Elison, J.R.; Bhattacharjee, P.S.; Huq, T.; Clement, C.; Hill, J.M. Drug delivery to the posterior segment of the eye for pharmacologic therapy. Expert Rev. Ophthalmol. 2010, 5, 75–93.
2. Lee, S.S.; Hughes, P.M.; Robinson, M.R. Recent advances in drug delivery systems for treating ocular complications of systemic diseases. Curr. Opin. Ophthalmol. 2009, 20, 511–519.
3. Hoare, T.R.; Kohane, D.S. Hydrogels in drug delivery: Progress and challenges. Polymer 2008, 49, 1993–2007.
4. Nicolson, P.C.; Vogt, J. Soft contact lens polymers: An evolution. Biomaterials 2001, 22, 3273–3283.
5. Oelker, A.M.; Grinstaff, M.W. Ophthalmic adhesives: A materials chemistry perspective. J. Mater. Chem.2008, 18, 2521–2536.
6. Swindle, K.E.; Ravi, N. Recent advances in polymeric vitreous substitutes. Expert Rev. Ophthalmol. 2007, 2, 255–265.
7. Wang, K.; Han, Z. Injectable hydrogels for ophthalmic applications. J. Control. Release 2017, 268, 212–224.
8. Al-Kinani, A.A.; Zidan, G.; Elsaid, N.; Seyfoddin, A.; Alani, A.W.G.; Alany, R.G. Ophthalmic gels: Past, present and future. Adv. Drug Deliv. Rev. 2018, 126, 113–126.
9. Kozak, I.; Cheng, L.; Freeman, W.R. Lidocaine gel anesthesia for intravitreal drug administration. Retina2005, 25, 994–998.
10. Shah, H.R.; Reichel, E.; Busbee, B.G. A novel lidocaine hydrochloride ophthalmic gel for topical ocular anesthesia. Local Reg. Anesth. 2010, 3, 57–63.

11. Ho, V.Y.; Shah, G.K.; Liu, E.M. Resure sealant for pars plana vitrectomy wound closure. OSLI Retina 2015, 46, 1042–1044.
12. Hsu, K.H.; Gause, S.; Chauhan, A. Review of ophthalmic drug delivery by contact lenses. J. Drug Deliv. Sci. Technol. 2014, 24, 123–135.
13. Haghjou, N.; Soheilian, M.; Abdekhodaie, M.J. Sustained release intraocular drug delivery devices for treatment of uveitis. J. Ophthalmic Vis. Res. 2011, 6, 317–329.
14. Alhalafi, A.M. Applications of polymers in intraocular drug delivery systems. Oman J. Ophthalmol. 2017, 10, 3–8.
15. Herrero-Vanrell, R.; Refojo, M.F. Biodegradable microspheres for vitreoretinal drug delivery. Adv. Drug Deliv. Rev. 2001, 52, 5–16.
16. Saliba, J.B.; Faraco, A.A.G.; Yoshida, M.I.; de Vasconcelos, W.L.; da Silva-Cunha, A.; Mansur, H.S. Development and characterization of an intraocular biodegradable polymer system containing cyclosporine-a for the treatment of posterior uveitis. Mater. Res. 2008, 11, 207–211.
17. Jaffe, G.J.; Martin, D.; Callanan, D.; Pearson, P.A.; Levy, B.; Comstock, T. Fluocinolone acetonide implant (retisert) for noninfectious posterior uveitis. Thirty-four-week results of a multicenter randomized clinical study. Ophthalmology 2006, 113, 1020–1027.
18. Thrimawithana, T.R.; Young, S.; Bunt, C.R.; Green, C.; Alany, R.G. Drug delivery to the posterior segment of the eye. Drug Discov. Today 2011, 16, 270–277.
19. Wang, J.; Jiang, A.; Joshi, M.; Christoforidis, J. Drug delivery implants in the treatment of vitreous inflammation. Mediat. Inflamm. 2013, 2013, 780634.
20. Yasin, M.N.; Svirskis, D.; Seyfoddin, A.; Rupenthal, I.D. Implants for drug delivery to the posterior segment of the eye: A focus on stimuli-responsive and tunable release systems. J. Control. Release 2014, 196, 208–221.
21. Joseph, M.; Trinh, H.M.; Cholkar, K.; Pal, D.; Mitra, A.K. Recent perspectives on the delivery of biologics to back of the eye. Expert Opin. Drug Deliv. 2017, 14, 631–645.
22. Garweg, J.G.; Zirpel, J.J.; Gerhardt, C.; Pfister, I.B. The fate of eyes with wet amd beyond four years of anti-vegf therapy. Graefe Arch. Clin. Exp. Ophthalmol. 2018, 256, 823–831.
23. Syed, B.A.; Evans, J.B.; Bielory, L. Wet amd market. Nat. Rev. Drug Discov. 2012, 11, 827–828.
24. Cundy, O.; Shah, M.; Downes, S.M. Intravitreal aflibercept: Its role in treatment of neovascular age-related macular degeneration. Expert Rev. Ophthalmol. 2018, 13, 75–86.
25. Jo, N.; Mailhos, C.; Ju, M.; Cheung, E.; Bradley, J.; Nishijima, K.; Robinson, G.S.; Adamis, A.P.; Shima, D.T. Inhibition of platelet-derived growth factor b signaling enhances the efficacy of anti-

vascular endothelial growth factor therapy in multiple models of ocular neovascularization. Am. J. Pathol. 2006, 168, 2036–2053.

26. Freund, K.B.; Mrejen, S.; Gallego-Pinazo, R. An update on the pharmacotherapy of neovascular age-related macular degeneration. Expert Opin. Pharmacother. 2013, 14, 1017–1028.
27. Jager, R.D.; Aiello, L.P.; Patel, S.C.; Cunningham, E.T., Jr. Risks of intravitreous injection: A comprehensive review. Retina 2004, 24, 676–698.
28. Patel, A.; Cholkar, K.; Agrahari, V.; Mitra, A.K. Ocular drug delivery systems: An overview. World J. Pharmacol. 2013, 2, 47–64.
29. Hsu, J. Drug delivery methods for posterior segment disease. Curr. Opin. Ophthalmol. 2007, 18, 235–239.
30. Choonara, Y.E.; Pillay, V.; Danckwerts, M.P.; Carmichael, T.R.; Du Toit, L.C. A review of implantable intravitreal drug delivery technologies for the treatment of posterior segment eye diseases. J. Pharm. Sci.2010, 99, 2219–2239.
31. Kompella, U.B.; Amrite, A.C.; Pacha Ravi, R.; Durazo, S.A. Nanomedicines for back of the eye drug delivery, gene delivery, and imaging. Prog. Ret. Eye Res. 2013, 36, 172–198.
32. Moinard-Checot, D.; Chevalier, Y.; Briançon, S.; Fessi, H.; Guinebretière, S. Nanoparticles for drug delivery: Review of the formulation and process difficulties illustrated by the emulsion-diffusion process. J. Nanosci. Nanotechnol. 2006, 6, 2664–2681.
33. Vandervoort, J.; Ludwig, A. Ocular drug delivery: Nanomedicine applications. Nanomedicine 2007, 2, 11–21.
34. Booth, B.A.; Denham, L.V.; Bouhanik, S.; Jacob, J.T.; Hill, J.M. Sustained-release ophthalmic drug delivery systems for treatment of macular disorders: Present and future applications. Drugs Aging 2007, 24, 581–602.
35. Joseph, R.R.; Venkatraman, S.S. Drug delivery to the eye: What benefits do nanocarriers offer? Nanomedicine 2017, 12, 683–702.
36. Irache, J.M.; Merodio, M.; Arnedo, A.; Camapanero, M.A.; Mirshahi, M.; Espuelas, S. Albumin nanoparticles for the intravitreal delivery of anticytomegaloviral drugs. Mini Rev. Med. Chem. 2005, 5, 293–305.
37. Fangueiro, J.F.; Veiga, F.; Silva, A.M.; Souto, E.B. Ocular drug delivery—New strategies for targeting anterior and posterior segments of the eye. Curr. Pharm. Des. 2016, 22, 1135–1146.
38. Giannavola, C.; Bucolo, C.; Maltese, A.; Paolino, D.; Vandelli, M.A.; Puglisi, G.; Lee, V.H.; Fresta, M. Influence of preparation conditions on acyclovir-loaded poly-d,l-lactic acid nanospheres and effect of peg coating on ocular drug bioavailability. Pharm. Res. 2003, 20, 584–590.

39. Das, S.K.; Tucker, I.G.; Hill, D.J.; Ganguly, N. Evaluation of poly(isobutylcyanoacrylate) nanoparticles for mucoadhesive ocular drug delivery. I. Effect of formulation variables on physicochemical characteristics of nanoparticles. Pharm. Res. 1995, 12, 534–540.
40. Vega, E.; Egea, M.A.; Valls, O.; Espina, M.; Garcia, M.L. Flurbiprofen loaded biodegradable nanoparticles for ophtalmic administration. J. Pharm. Sci. 2006, 95, 2393–2405.
41. Calvo, P.; Sánchez, A.; Martínez, J.; López, M.I.; Calonge, M.; Pastor, J.C.; Alonso, M.J. Polyester nanocapsules as new topical ocular delivery systems for cyclosporin a. Pharm. Res. 1996, 13, 311–315.
42. Rawas-Qalaji, M.; Williams, C.A. Advances in ocular drug delivery. Curr. Eye Res. 2012, 37, 345–356.
43. Del Amo, E.M.; Urtti, A. Current and future ophthalmic drug delivery systems. A shift to the posterior segment. Drug Discov. Today 2008, 13, 135–143.
44. Chen, P.C.; Kohane, D.S.; Park, Y.J.; Bartlett, R.H.; Langer, R.; Yang, V.C. Injectable microparticle-gel system for prolonged and localized lidocaine release. Ii. In vivo anesthetic effects. J. Biomed. Mater. Res. A2004, 70, 459–466.