DOI: 10.21276/sjmps

Saudi Journal of Medical and Pharmaceutical Sciences
Scholars Middle East Publishers
Dubai, United Arab Emirates
Website: http://scholarsmepub.com/

ISSN 2413-4929 (Print)
ISSN 2413-4910 (Online)

Review Article

Current Perspective on microneedles for ocular drug delivery

Zheng Chao, Chen Dong, Huan Fang
School of Pharmacy, Jiangsu University, Jiangsu Sheng, China

***Corresponding Author:**
Dr. Huan Fang
Email: huanfang001@gmail.com

Abstract: Many ocular inflammatory and proliferative diseases require long-term pharmacological intervention/treatment. However, delivery of drugs in therapeutic levels to the back of the eye is challenging using conventional topical application, due to the poor efficacy. Systemic injections of drugs pose severe adverse effects. Direct injection into the eye may need surgical intervention. In the recent years, small size microneedles are fabricated to insert into various ocular tissues depending upon the complexity and state of disease to be treated. Microneedles are capable of delivering drugs through cornea or sclera in a minimally invasive way. There are few reports that large molecules, proteins, vaccines could be delivered into eye using microneedles. Drug delivery to the posterior segment of the eye is a significantly challenging task due to the various ocular barriers and precorneal factors. In this review, the targeted drug delivery to the ocular tissues via minimally invasive approach is discussed.
Keywords: Invasive techniques, ocular delivery, vitreous humor, retina, ocular bioavailability

INTRODUCTION

Topical delivery of drugs to treat posterior ocular complications is the most sought task for the pharmaceutical scientists. The approaches enhancing transcorneal permeability and improving mucoadhesion are being reported in the literature for targeting retina and vitreous humor tissues. Various advanced and conventional formulation platforms are being explored for the delivery of therapeutic agents in to the anterior and posterior segments of the eye since the past four decades [1, 2]. Till now, topical delivery is not promising due to various factors and challenges with respect to sensitivity and complexity of the ocular tissues. Different mode of administrations such as intravitreal injections, periocular injections, and systemic administration can be used for delivery of drugs into ocular posterior segment. Presence of blood ocular and retinal barriers in the eye makes intravenous application an impractical approach. Intravitreal injection is used to inject drugs directly into the vitreous body to deliver the drugs at the targeted sites such as retina and vitreous humor tissues. Each intravitreal injection requires surgical intervention and it is associated with several side effects such as endophthalmitis, hemorrhage, retinal detachment and poor patient tolerance. In the recent decades, transscleral delivery of drugs with periocular administration route offered an attractive approach to target the ocular tissues. To improve ocular bioavailability by overcoming the ocular drug delivery barriers, various conventional and novel drug delivery systems such as emulsion, ointments, suspensions, aqueous gels, nanomicelles, nanoparticles, liposomes, dendrimers, implants, contact lenses, nanosuspensions, microneedles, and *in situ* thermosensitive gels are developed. Literature reports suggest that topically instilled drug could only deliver 5-10% of the total dose into the ocular tissues. Most of the drug concentrations is lost due to non-productive conjunctival absorption or systemic drainage. Higher drug doses ae required to overcome the blood retinal and aqueous barriers, for systemically administered drugs which results ocular toxicity [3-5]. Orally administered drugs have solubility and permeability issues and have the minimum feasibility to reach the site of action and perform at levels where minimum inhibitory concentrations could not be reached. Microneedles are designed such that they could penetrate only hundreds of microns into sclera, layers which could avoid damage to the deeper/inner ocular tissues. Deposition of drug/ drug embedded carrier into sclera or into the narrow space between sclera and choroid called “suprachoroidal space” (SCS) could be possible with the use of microneedles. Puncturing of sclera and depositing drug solution or carrier systems in sclera or SCS may facilitate diffusion of drug into deeper ocular tissues, such as choroid, neural retina and vitreous humor. Minimally invasive techniques like microneedles are currently being explored by various research groups to determine the potential possibilities of delivering drugs across various routes like eye, skin etc. [6]. Latest developments and recent trends in these minimally invasive microneedle techniques are mentioned and discussed below.

Microneedles

Microneedles are developed for various routes and applications since decades. Effective therapeutic agents are limited by their inability to reach the retina/vitreous humor, due to the excellent barrier properties of biological membranes, mainly superficial tissues such as sclera/cornea of the eye. In the recent years, minimally invasive microneedles (500 to 750 µm length) have been employed through transscleral route to target therapeutic agents for delivery into the posterior ocular tissues. Prausnitz and co-workers were first to demonstrate the application of coated microneedles to the eye. In this study, individual stainless steel microneedles measuring 500-750 µm in length and 200 x 50 µm in width, and 55° in tip angle were tested for anterior and posterior drug delivery via either intrascleral or intracorneal routes, respectively. Microneedles were coated with model drug sodium fluorescein (approx. 280 ng) and inserted halfway into the cornea of a rabbit eye and left in place for 2 mins and then retrieved back. After 1 min following microneedle insertion, a sharp increase of intraocular fluorescein concentration and then gradually further increase peaked at 3 hrs and then gradually decreased to background within 24 hrs [7]. Chiang *et al.* 2016 recently have investigated the circumferential distribution of particles in the SCS of rabbit and human cadaver eyes. A 200 nm diameter red-fluorescent microspheres with injection volumes ranging from 50 - 200 µL were performed in the SCS. In rabbit eyes, particles when injected in the superior or inferior hemispheres did not significantly cross into the other hemisphere, due to a barrier formed by the long posterior ciliary artery [8]. Drugs either free or encapsulated could be delivered via the sclera in a controlled process. A similar technique was used to deliver sodium fluorescein and pilocarpine. Intrascleral hollow microneedles are also developed for the targeted delivery of the drugs. These microneedles are able to deliver drugs through suprachoroidal, subconjunctival, transcleral routes into the posterior segment of the eye. This delivery system has the capability of delivering nanoparticles, microparticles and drugs in a solution in minimally invasive manner. To deliver microparticles, it is necessary that they are to be accompanied with spreading enzymes such as hyaluronidase and collagenase which help in rapidly hydrolyzing the collagenous and extracellular matrix structure of the sclera so as to make the delivery of microparticles feasible [9]. Jiang *et al.* attempted to deliver micro and nanoparticles across the human cadaver eye using microneedles where insertion–retraction protocol was used to deliver the soluble molecule and nanoparticles. Hyaluronidase enzyme is required for microparticles to disrupt the scleral structure and obtain similar tissue distribution profile. Infusion of particles into the sclera for modified drug release over time could prolong the drug release into the back-of the-eye. The study demonstrated that an individual needle was capable of delivering 10–35 mL of a fluid, forming a scleral drug depot, which facilitates the subsequent release of the drug into target area. However, further preclinical studies are to be conducted to investigate the efficacy and safety of microneedles to deliver drugs into the posterior segment of the eye. Jason jiang *et al.*, studied the delivery of solutions containing soluble molecules, poly Lactic acid nanospheres and microparticles using hollow microneedles into the sclera. Infusion volumes of 10-35 µL are delivered into the scleral region. Nanoparticles and soluble molecules were diffused into the sclera but the diffusion of microparticles may be hindered by the collagen fibrils and glycosaminoglucan network and may require the addition of spreading enzymes like hyalouronidase or collagenase to disrupt scleral tissue microstructure. However, the effect of hyaluronidase on the corneal integrity and vitreous body needs to be investigated. Moreover, the factors such as scleral thickness and infusion pressure did not exert any effect on the transscleral drug delivery. Hollow microneedles deliver drugs through the scleral membrane in minimally invasive manner, when compared to the intravitreal injections administered by the hypodermic needles associated with severe complications like retinal detachment, cataract and infections. Thus microneedles serve as potential and feasible posterior ocular delivery framework in the niche of sustained and controlled release platforms [10, 11]. Samir kumar *et al.* studied the suprachoroidal delivery of drug molecules using microneedles to target back-of-the eye. The experiments are carried out using human, cadaver rabbit and pig eyes (*ex vivo*). Microneedles are able to deliver the sulfo-rhodamine nanoparticle and microparticle suspensions to back-of-the eye with infusion volume upto 35uL and the factors like needle length, retraction pressure and particle size play a crucial role in successful delivery through suprachoroidal space. Suprachoroidal infusion through microneedles would be the minimally invasive strategic drug delivery when compared to periocular and intravitreal injections [12, 13]. Geetha mahadevan, *et al.* formulated the drug delivery device using poly (dimethylsiloxane) substrate with embedded hollow microneedles for the delivery to back-of-the eye. In the study microneedles penetrated the bovine sclera (*ex vivo*) without losing the integrity of the PDMS matrix and was able to deliver 0.02 mg of 6-aminoquinolone into vitreous body and uveal face of sclera without clogging internal needle microchannel. PDMS integrated microneedles facilitate integrated drug targeting and controlled release of drugs by minimally invasive manner compared to conventional needles [14, 15]. Patel SR et,al studied the delivery of fluorescein and fluorescently tagged dextrans, bevacizumab, and polymeric particles (20 nm to 10 µm in diameter) using hollow microneedles in newzealand white albino rabbits. The intensity was monitored and measured

using ocular fluorophotometer to investigate the distribution of infused material in the eye compared with fluorescein intravitreal injection. Integrated drug targeting to the suprachoroidal space delivered drug concentration 10-folds higher in the posterior segment of the eye when compared to ocular anterior chamber. But the intravitreal injection primarily targets the vitreous humor apart from posterior and anterior tissues. In contrast polymeric particles (20nm to 10 µm) remained in the suprachoroidal space and choroid for about a month without the drug clearance and adverse effects [16]. Song *et al.* designed microneedle based pen type device to allow easy insertion into a small target region of ocular tissue. A solid SU-8 resin based miconeedle was fabricated and attached to a macroscale applicator to create the microneedle pen. The resulting device had the base area of 200 × 200 µm 2 with the height of 140 µm. Rhodamine B, evans blue or sunitinib malate was used, along with polymer carrier, as a model drugs to dip coat. It was shown that the miconeedle pen enabled precise localization of drug within the stromal membrane of cornea, which is otherwise difficult to achieve when given topically due to corneal epithelium [17]. Tyagi, *et al.* studied the drug delivery and distribution in the suprachoroidal space and compared with subconjunctival and intravitreal routes using noninvasive fluorophotometry. In the present study sodium fluorescein (NaF) was infused into suprachoroidal space of Sprague Dawley rats using 34G needle and NaF levels are monitored and compared with posterior subconjunctival or intravitreal injections. However, results indicated that promising drug levels were in the order of suprachoroidal>intravitreal>posterior subconjunctival routes. NaF concentration (C_{max}) in choroid-retinal was 36-fold and 25-fold higher after suprachoroidal (2744±1111 ng/mL) injection when compared to posterior subconjunctival (76±6 ng/mL) and intravitreal (108±39 ng/mL) injections, respectively. These results suggest that delivery through suprachoroidal route achieves promising drug levels in the posterior segment of the eye particularly in choroid-retinal tissues [18, 19]. Matthaei *et al.* to improve reproducibility of injection method using handheld syringes compared different type of hollow micrnoeedles and syringes and quantified the intrastromal distribution of Indian ink in mouse cornea by injections of different volumes (1 and 2 µL). Needles types and syringes tested were namely 33 G (attached to a 2.5 µL syringe), 35 G needles (attached to a 10 µL syringe) and glass microneedles beveled to 25° and an inner tip diameter of approximately 50 µm (attached to a 2.5 µL syringe), respectively. Injections of 1 µL and 2 µL resulted in an overall mean of 49% and 73% respectively of total corneal area involved. The use of 33 G metal needles provided the most reliable and effective outcomes, whereas the glass microneedle tips broke within the stroma in 25% of cases which is undesirable and create potential safety concerns. Irrespective of needle type, a small amount of leakage was noted in all cases. Palakurthi *et al.* investigated microneedles that were fabricated into an array of 3x3 biodegradable methotrexate loaded microneedles with 2 mm in length, 2 mm in width, and 2.3 mm in height. The microneedles were surgically placed in the deep lamellar scleral pocket in rabbit eye, in vivo, were found to be safe. The fundamental advantage of using microneedles is its ability for painless or minimally invasive nature due to its micron-sized dimensions. However, in this study the term microneedle perhaps needs reconsideration, as the microneedles were surgically implanted and were much higher in dimensions than those employed in both ocular and transdermal application [20]. Abbot F.Clark *et al.* patented the delivery of 4,9 (11)-Pregnadien-17α,21-diol-3,20-dione and 4,9 (11) -Pregnadien-17α,21-diol-3,20-dione-21-acetate using cannula through sub-tenon route. The delivery of pharmaceutical active agents through sub-tenon route using cannulae render promising results in the treatment of posterior segment diseases. The cannula developed was successful in localized delivery of the drugs on the sclera and however had the significant potential in the safety aspects when compared to other cannulae used for injection into posterior segments. This cannula has straight proximal end and the distal portion with radius of curvature substantially equal to radius of curvature of globe of human eye. Cannula is inserted below the Tenon's capsule and above the sclera of the human eye at point posterior to a limbus of the eye [18]. Drug is injected through the cannula to form a drug depot on an outer surface of the sclera and then diffuse into targeted posterior tissues of the eye [21]. Gilger *et al.* attempted to deliver triamcinolone acetonide (TA) into suprachoroidal space (SCS) using microneedles for the treatment of posterior uveitis. Delivery of TA through microneedles to the SCS did not exhibit any signs of adverse effects or toxicity demonstrating safety and effectiveness. SCS injection of low (0.2 mg) and high doses (2 mg) of TA was equally effective in alleviating acute inflammation in the ocular posterior segment when compared to high-dose intravitreal (IVT) injection. The inflammation was not reduced using low-dose IVT TA whereas low-dose SCS TA alleviated the inflammation. The study results indicated that 0.2 mg of SCS TA could arrest the inflammation associated processes as 2.0 mg IVT TA injection in acute posterior segment inflammation model [22]. Kim *et al.* investigated using microneedles measuring 400 µm in length coated with bevacizumab. Results revealed that drug was delivered intrastromally and allowed dramatic dose sparing compared with subconjunctival and topical eye drops – providing just 4.4 µg of the drug needed to produce similar effect as much as 2,500 µg via subconjunctival injection and 52,500 µg when delivered via eye drops [23, 24]. Saffar *et al.* studied the pharmacokinetics and

biodistribution of bevacizumab following SCS injection using hollow microneedle in the rabbit eyes. This minimally invasive approach forms a depot of bevacizumab between the sclera and choroid, which facilitates and targets drug delivery to respective posterior ocular tissues. Bevacizumab (Avastin®, 1250 µg/50 µL) was injected into the SCS of pigmented rabbits using a metal microneedle measuring 700-800 µm in length inserted 5 mm posterior to the limbus and the tissues were separated and analyzed for the drug concentrations respectively. The percent bevacizumab recovered from the eyes at 15 min, 1 day and 2 days was 88.4±0.9%, 4.6±0.5% and 0.2±0.1% respectively. The distribution of bevacizumab in ocular tissues at 15 min after injection was 76%, 13%, 2.9, 1.0, 0.5, 0.9,0.6 and 0.1 in choroid, sclera, retina, vitreous, aqueous humor, anterior chamber, lens and optic nerve, correspondingly. After 24 hrs, the levels of bevacizumab in choroid was 34%, 27% in sclera, 23% in retina, 11% in vitreous, 0.7% in aqueous humor, 1.6% in anterior chamber, 3.8% in lens and 0.3% in optic nerve. After 48 hrs, the distribution of bevacizumab was 0.5% in choroid and retina, 3.0% in sclera and aqueous humor, 55% in vitreous, 36% in anterior chamber, 1.1% in lens and 0.6% in optic nerve. Results from the study suggest that formulation should be optimized to sustain the release of drug in posterior segment of the eye [25]. From the view point of the above discussed studies, microneedles appear to be promising platform, when compared to intravitreal injection in terms of sustained/controlled drug delivery.

CONCLUSION

Tremendous efforts are being put into ocular research toward the development of safe and patient compliant novel drug delivery strategies. Advent of nanotechnology, new techniques, devices and their applications in drug delivery is developing immense interest to ocular scientists. Established technological platforms like microneedles needs to be standardized for optimal penetration characteristics of drug molecules. Nanotechnology is benefiting the patient body by minimizing the drug induced toxicities and vision loss. The current pace of ocular research and efforts being made and put in, it is expected to result in a delivery system which may replace invasive mode of drug administration to back of the eye such as periocular and intravitreal injection.

REFERENCES

1. Adelli, G. R., Balguri, S. P., & Majumdar, S. (2015). Effect of cyclodextrins on morphology and barrier characteristics of isolated rabbit corneas. *AAPS PharmSciTech*, *16*(5), 1220-1226.
2. Patel, A., Cholkar, K., Agrahari, V., & Mitra, A. K. (2013). Ocular drug delivery systems: an overview. *World journal of pharmacology*, *2*(2), 47.
3. Macha, S., & Mitra, A. K. (2002). Ocular disposition of ganciclovir and its monoester prodrugs following intravitreal administration using microdialysis. *Drug metabolism and disposition*, *30*(6), 670-675.
4. Maurice, D. (2001). Practical issues in intravitreal drug delivery. *Journal of Ocular Pharmacology and therapeutics*, *17*(4), 393-401.
5. Adelli, G. R., Balguri, S. P., Bhagav, P., Raman, V., & Majumdar, S. (2017). Diclofenac sodium ion exchange resin complex loaded melt cast films for sustained release ocular delivery. *Drug Delivery*, *24*(1), 370-379.
6. Kang-Mieler, J. J., Dosmar, E., Liu, W., & Mieler, W. F. (2017). Extended ocular drug delivery systems for the anterior and posterior segments: biomaterial options and applications. *Expert opinion on drug delivery*, *14*(5), 611-620.
7. Jiang, J., Gill, H. S., Ghate, D., McCarey, B. E., Patel, S. R., Edelhauser, H. F., & Prausnitz, M. R. (2007). Coated microneedles for drug delivery to the eye. *Investigative ophthalmology & visual science*, *48*(9), 4038-4043.
8. Chiang, B., Kim, Y. C., Edelhauser, H. F., & Prausnitz, M. R. (2016). Circumferential flow of particles in the suprachoroidal space is impeded by the posterior ciliary arteries. *Experimental eye research*, *145*, 424-431.
9. Balguri, S. P., Adelli, G. R., & Majumdar, S. (2016). Topical ophthalmic lipid nanoparticle formulations (SLN, NLC) of indomethacin for delivery to the posterior segment ocular tissues. *European Journal of Pharmaceutics and Biopharmaceutics*, *109*, 224-235.
10. Jiang, J., Moore, J. S., Edelhauser, H. F., & Prausnitz, M. R. (2009). Intrascleral drug delivery to the eye using hollow microneedles. *Pharmaceutical research*, *26*(2), 395-403.
11. Adelli, G. R., Balguri, S. P., Punyamurthula, N., Bhagav, P., & Majumdar, S. (2014). Development and evaluation of prolonged release topical indomethacin formulations for ocular inflammation. *Investigative Ophthalmology & Visual Science*, *55*(13), 463-463.
12. Loria, M. J., White, S. W., Robbins, S. A., Salmeto, A. L., Hymel, K. A., Murthy, S. N., ... & Sufka, K. J. (2013). Brain-derived neurotrophic factor response in vulnerable and resilient genetic lines in the chick anxiety–depression model. *Behavioural brain research*, *245*, 29-33.

13. Patel, S. R., Lin, A. S., Edelhauser, H. F., & Prausnitz, M. R. (2011). Suprachoroidal drug delivery to the back of the eye using hollow microneedles. *Pharmaceutical research*, *28*(1), 166-176.
14. Mahadevan, G., Sheardown, H., & Selvaganapathy, P. (2013). PDMS embedded microneedles as a controlled release system for the eye. *Journal of biomaterials applications*, *28*(1), 20-27.
15. Balguri, S. P., Adelli, G., Bhagav, P., Repka, M. A., & Majumdar, S. (2015). Development of nano structured lipid carriers of ciprofloxacin for ocular delivery: Characterization, in vivo distribution and effect of PEGylation. *Investigative Ophthalmology & Visual Science*, *56*(7), 2269-2269.
16. Patel, S. R., Berezovsky, D. E., McCarey, B. E., Zarnitsyn, V., Edelhauser, H. F., & Prausnitz, M. R. (2012). Targeted administration into the suprachoroidal space using a microneedle for drug delivery to the posterior segment of the EyeMicroneedle use for targeted drug delivery. *Investigative ophthalmology & visual science*, *53*(8), 4433-4441.
17. Song, H. B., Lee, K. J., Seo, I. H., Lee, J. Y., Lee, S. M., Kim, J. H., ... & Ryu, W. (2015). Impact insertion of transfer-molded microneedle for localized and minimally invasive ocular drug delivery. *Journal of Controlled Release*, *209*, 272-279.
18. Tyagi, P., Kadam, R. S., & Kompella, U. B. (2012). Comparison of suprachoroidal drug delivery with subconjunctival and intravitreal routes using noninvasive fluorophotometry. *PloS one*, *7*(10), e48188.
19. Balguri, S. P., Adelli, G. R., Janga, K. Y., Bhagav, P., & Majumdar, S. (2017). Ocular disposition of ciprofloxacin from topical, PEGylated nanostructured lipid carriers: Effect of molecular weight and density of poly (ethylene) glycol. *International Journal of Pharmaceutics*, *529*(1-2), 32-43.
20. Palakurthi, N. K., Correa, Z. M., Augsburger, J. J., & Banerjee, R. K. (2011). Toxicity of a biodegradable microneedle implant loaded with methotrexate as a sustained release device in normal rabbit eye: a pilot study. *Journal of ocular pharmacology and therapeutics*, *27*(2), 151-156.
21. Yaacobi, Y., Clark, A. F., Dahlin, D. C., Struble, C. B., Marsh, D. A., & York, B. M. (2002). *U.S. Patent No. 6,413,245*. Washington, DC: U.S. Patent and Trademark Office.
22. Gilger, B. C., Abarca, E. M., Salmon, J. H., & Patel, S. (2013). Treatment of acute posterior uveitis in a porcine model by injection of triamcinolone acetonide into the suprachoroidal space using microneedlestriamcinolone in the suprachoroidal space. *Investigative ophthalmology & visual science*, *54*(4), 2483-2492.
23. Kim, Y. C., Grossniklaus, H. E., Edelhauser, H. F., & Prausnitz, M. R. (2014). Intrastromal Delivery of Bevacizumab Using Microneedles to Treat Corneal NeovascularizationIntrastromal Delivery of Bevacizumab. *Investigative ophthalmology & visual science*, *55*(11), 7376-7386.
24. Adelli, G. R., Hingorani, T., Punyamurthula, N., Balguri, S. P., & Majumdar, S. (2015). Evaluation of topical hesperetin matrix film for back-of-the-eye delivery. *European Journal of Pharmaceutics and Biopharmaceutics*, *92*, 74-82.
25. Mansoor, S., Patel, S. R., Tas, C., Pacha-Ravi, R., Kompella, U. B., Edelhauser, H. F., & Prausnitz, M. R. (2012). Pharmacokinetics and Biodistribution of Bevacizumab Following Suprachoroidal Injection into the Rabbit Eye Using a Microneedle. *Investigative Ophthalmology & Visual Science*, *53*(14), 498-498.