Review Article

iMedPub Journals
http://www.imedpub.com/

Journal of Neoplasm
ISSN 2576-3903

2017
Vol.2 No.2: 7

DOI: 10.217672576-3903.100016

Emerging Trends in Ocular Drug Delivery: A Review on Recent Updates

Md. Kabir Imtiazul* and Reedwan Bin Zafar Auniq

Department of Pharmacy, International Islamic University Chittagong, Bangladesh

***Corresponding author:** Md. Kabir Imtiazul, Department of Pharmacy, International Islamic University Chittagong, Bangladesh. Tel: +88-01714489798; E-mail: kabirimtiazul.ik@gmail.com

Received: July 06, 2017; **Accepted:** July 26, 2017; **Published:** August 01, 2017

Citation: Imtiazul K, Auniq RBZ (2017) Emerging Trends in Ocular Drug Delivery: A Review on Recent Updates. J Neoplasm. Vol.2 No.2:7.

Abstract

The distance from cornea to retina (1.7 cm) appears to be the difficult path for most of the small molecule therapeutics. Ocular drug delivery is extreme difficult task owing to complexity and intricate barriers of the eye. However, there is an urgency and need to overcome these barriers for the treatment of sight threatening ocular complications. Delivery of drugs through topical application is compromised by physiological, static, dynamic and metabolic barriers. Currently, intravitreal therapy is a gold standard for targeting therapeutic entities to the posterior segment of the eye. Various viable platforms using topical non-invasive to invasive techniques are currently under development and may progress into efficient delivery platforms. In this review, recent advances/developments in ocular delivery were discussed.

Keywords: Ocular compounds; Formulations; Non-invasive; Drug delivery

Introduction

Many numbers of drug delivery systems and formulations techniques are available for effective drug delivery and significant research is being conducted in the field. Conventional drug delivery forms include eye drops, ointments, chemical modified drug forms, polymer embedded drug delivery and more. The objective behind the idea of effective drug delivery is reaching optimum drug concentration at target [1-3]. Especially, drug delivery to various parts of the eye is challenging due to complex anatomical structure of the eye such as corneal epithelium, blood-aqueous barrier, and blood-retinal barrier. Different routes of administrations including systemic topical, periocular and intravitreal drug delivery are already developed to significant levels [4].

Anatomically eye can be largely divided into anterior and posterior chambers. Anterior chamber consists of 1/3rd and posterior chamber consists of 2/3rd of the eye. In case of anterior segment eye associated disease, currently, topical eye drops are most widely used for the intervention/treatment [5]. Biocompatible responsive formulations and also biodegradable polymer containing formulations are successfully used for local delivery via corneal and non-corneal routes. However, there exists a complex capillary bed while the drug is passing through conjunctiva and sclera which results in drug clearance into systemic circulations. Blood-aqueous barrier in anterior segment of the eye, and blood vessels in iris body have tight junctions which prevent free distribution of molecules in between anterior and posterior chambers. Because of these and other complex structure limitations, drug molecules cannot pass to the posterior chamber from anterior chambers [6]. However, the formulation/compound will not be completely or significantly absorbed into the intraocular tissues due to the rapid pre-corneal mechanisms. Only a small fraction (1-3%) is absorbed into the intraocular tissues upon delivery of the same into eye in the form of drops. It is difficult to provide and maintain high drug concentrations in the pre-corneal area [7]. Numerous ophthalmic platforms such as viscosified solutions, suspensions, emulsions, ointments, gels, and polymeric inserts, colloidal systems have been investigated for topical application to the eye [8]. To overcome the limitations, systemic and peri-ocular administration is the next line of choice after intravitreal injection for the treatment of posterior ocular diseases. Developing ocular drug formulation with optimized and accurate drug delivery profile is challenging in pharmaceutical research due to complexity of the eye anatomy. Most of the used formulations for ocular diseases are ointments, drops or solutions. After a proposed formulation is developed, it needs to pass through the bioavailability challenges by surpassing anatomical barriers of eye [9]. Several sustained drug release formulations, nano formulation are developed for various types of diseases or physiological conditions [10-13]. However, using the same methodology of formulation in eye diseases may not work. Various advanced delivery platforms targeting the intraocular tissues are discussed hereunder.

Literature Review

Novel drug delivery systems

Lipid nanoparticles functionalized with ligands such as chitosan and poly (ethylene) glycol and polymeric melt extruded films were developed and targeted for posterior segment ocular tissues using various model drugs [14,15]. Novasorb® is a patented drug delivery platform. The cationic

emulsion which is based on electrostatic attraction with negatively charged ocular surface improving absorption of lipophilic drugs. Novasorb takes advantage of the negatively charged mucin layer and enables the drug to retain at the site for longer periods of time [16]. Cationorm®, a drug-free and preservative free cationic emulsion developed by Novagali using oleylamine (cationic emulsifier) is indicated for mild dry eye syndrome launched in Europe. Refresh dry eye therapy®, Soothe® XP emollient and Lipimix™ are placebo emulsions used for the treatment of dry eye syndrome. Cyclosporine A and latanoprost cationic emulsions are currently in phase III clinical trials. Tear Again® is a liposomal spray for dry eye syndrome [17]. Durasite® DDS polycarbophil based aqueous solution with innate ability for hydrogen-bonding with the mucus, corneal and conjunctival epitheliums, to provide the sustained effect [18,19]. Durasite consists of polymeric matrix as drug carrier and so used as a vehicle for delivery of small molecules to the target efficiently. Visudyne® is an intravenous liposomal formulation containing photosensitizer, verteporfin, in photodynamic therapy for predominantly classic subfoveal choroidal neovascularization due to AMD, pathologic myopia or presumed ocular histoplasmosis [20].

Punctual plugs are being developed by Mati therapeutics using model drugs latanoprost and olopatadine for glaucoma and allergy relief. Phase 2 clinical studies demonstrated the efficacy and safety in subjects with open angle glaucoma and ocular hypertension [21]. Intracanalicular inserts loaded with travoprost is being developed by ocular therapeutix for the treatment of glaucoma and ocular hypertension. The insert could deliver drug onto the ocular surface for 3 months. If approved, insert may become first non-invasive sustained release product for glaucoma [22]. LX201 is a silicone matrix episcleral implant designed to deliver cyclosporine A to the ocular surface for one year. Each implant is 0.08 inches wide and 0.04 inches high [23]. An episcleral implant developed by 3T Ophthalmics can be re-filled with drugs in any form, such as a solution, gel or matrix [24,25]. In pre-clinical studies with model drug (sodium fluorescein), the episcleral implant delivered high levels in the retina and posterior vitreous [25].

Sustained release drug delivery

Evaluation of the eye targeting drugs' pharmacokinetic profile in human subjects is not practically possible. Because frequent samplings of drug from eye chambers is very dangerous and usually not recommended. Especially, the aqueous and vitreous humor are not good places to collect samples from [6]. Hence, most of the studies are conducted in small animals and correlated to humans. Large experimental groups of animals are needed considering the sample volume and number of samples need to be taken for estimation of peak concentration in tissue and time to achieve maximum concentration in tissue. As patient acceptance is less regarding multiple drug dosages, sustained release formulations are being developed [26]. Several studies are already available where sustained release dosage forms are developed [13]. But these formulations need further techniques to study continuous drug release profile.

As sustained release dosage forms are promising in other fields, the same were being developed in ocular diseases [27,28]. Subconjunctival erodible sustained release implant (Durasert™) is being developed by psivida corp which is under safety and efficacy testing (phase I/II clinical trial) in patients with elevated intraocular pressure [29]. A microelectromechanical systems (MEMS) drug delivery device is investigated for the treatment of chronic and refractory ocular diseases with nanoliter sized doses until refilled [30]. The Replenish, Inc ophthalmic micro pump system is comprised of four sub systems namely Anterior microPump™ (glaucoma), Posterior MicroPump™ (retinal complications), Eye link™ and drug refill system™ [31]. Cortiject® developed by Novagali Pharma is emulsion encapsulating corticosteroid prodrug with activated tissue targeting mechanism. Dexamethasone (DEX) palmitate prodrug released is de-esterified by esterase enzyme in the retinal tissue and activated to DEX. Sustained release effect can be provided from 6-9 months following single injection into vitreous body. Cortiject is under the phase I/II development [32,33]. Carotuximab, (DE-122) an anti-endoglin antibody is being developed by Santen pharmaceuticals as an intravitreal injection for the treatment of age related macular degeneration [34]. Novel refillable intraocular drug delivery device is manufactured by hot melt extrusion of Bionate II® (DSM), a polycarbonate urethane. *In vitro* results indicated biocompatibility with ocular tissues. *In vivo* histology studies demonstrated that drug levels can be maintained in the retina greater than 3 months without any signs of inflammation [35,36]. Neurotech Pharmaceuticals, Inc has been developing "Encapsulated Cell Technology", which provides extracellular delivery of CNTF through long-term and stable intraocular release at constant doses through a device implanted in the vitreous [37]. Icon Bioscience, Inc. is developing IBI-10090 (Dexycu) containing dexamethasone using Verisome™ sustained drug delivery platform technology following injection into anterior chamber. Dexycu has undergone Phase III clinical trials [38].

For the better advancement of ocular drug delivery, bioavailability of the therapeutic compounds need to be evaluated critically. The bioavailability and bioequivalence issues will impede the drug development and can be a huge burden to drug market [39-41]. Selection of appropriate compartmental model needs to be developed for eye targeting drug formulations. Because there are limitations with obtaining precise data to study local drug distribution in various chambers of the eye. At the same time, drug elimination from different parts of the eye effect drug concentration at target.

Conclusion

Drug delivery to the posterior segment ocular tissues of eye presents significant confrontations to drugs/drug candidates. Topical application is not yet promising and needs to be addressed with novel drug delivery platforms developed with integration of multi-disciplinary technologies encompassing biomedical engineering and nanotechnology. Until then, ocular

invasive methodologies caters need for treatment of sight threatening posterior ocular complications. Further research is required in the field to optimize the drug formulation to target a specific ocular region which can enhance drug delivery and minimize any unwanted adverse effects.

References

1. http://www.google.co.in/patents/US20090011038.
2. Allen L, Popovich NG, Ansel HC (2013) Ansel's pharmaceutical dosage forms and drug delivery systems. Lippincott Williams & Wilkins Philadelphia, Pennsylvania, USA.
3. Ananthula S, Parajuli P, Behery FA, Alayoubi AY, Sayed KA, et al. (2013) Abstract P3-03-11: Oxazine derivatives of g- and D-tocotrienols display potent anticancer effects in vivo. Cancer Res 73.
4. Vadlapudi A (2015) Ocular drug delivery. Drug Delivery. Jones Bartlett Learning, USA. pp. 219-263.
5. Patel A, Cholkar K, Agrahari V, Mitra AK (2013) Ocular drug delivery systems: An overview. World J Pharmacol 2: 47-64.
6. Barar J, Aghanejad A, Fathi M, Omidi Y (2016) Advanced drug delivery and targeting technologies for the ocular diseases. Bioimpacts 6: 49-67.
7. Gaudana R, Ananthula HK, Parenky A, Mitra AK (2010) Ocular drug delivery. AAPS J. 12: 348-360.
8. Lee SS, Hughes PM, Robinson MR (2009) Recent advances in drug delivery systems for treating ocular complications of systemic diseases. Curr Opin Ophthalmol 20: 511-519.
9. Prausnitz MR, Noonan JS (1998) Permeability of cornea, sclera, and conjunctiva: a literature analysis for drug delivery to the eye. J Pharm Sci 87: 1479-1488.
10. Ananthula S, Parajuli P, Behery FA, Alayoubi AY, Sayed KA, et al. (2013) Oxazine derivatives of g-and D-tocotrienols display potent anticancer effects in vivo. Anticancer Res 34: 2715-2726.
11. https://www.google.com/patents/WO2015028637A1?cl=en12.
12. Lin Z, Gao W, Hu H, Ma K, He B, et al. (2014) Novel thermo-sensitive hydrogel system with paclitaxel nanocrystals: High drug-loading, sustained drug release and extended local retention guaranteeing better efficacy and lower toxicity. J Control Release 174: 161-170.
13. Ananthula S, Parajuli P, Behery FA, Alayoubi AY, Nazzal S, et al. (2004) Delta-tocotrienol oxazine derivative antagonizes mammary tumor cell compensatory response to COCl2-induced hypoxia. Biomed Res Int. 2014: 285752.
14. Balguri SP, Adelli GR, Janga KY, 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. Int J Pharm 529: 32-43.
15. Balguri SP, Adelli GR, Majumdar S (2016) Topical ophthalmic lipid nanoparticle formulations (SLN, NLC) of indomethacin for delivery to the posterior segment ocular tissues. Eur J Pharm Biopharm 109: 224-235.
16. Daull P, Amrane M, Garrigue J (2017) Novasorb® Cationic Nanoemulsion and Latanoprost: The ideal combination for glaucoma management. Glauc Open Access. 2017. 2: 107.
17. Gan L, Wang J, Jiang M, Bartlett H, Ouyang D, et al. (2013) Recent advances in topical ophthalmic drug delivery with lipid-based nanocarriers. Drug Discov Today 18: 290-297.
18. Singh MS, Tandle RL (2016) Gastroretentive in situ gel formulation system. Indo Am J Pharm Res 6: 8.
19. Plazonnet B (2002) Ophthalmic drug delivery. Marcel Dekker, CRC Press, NY, USA. p. 289-313.
20. Liu S, Jones L, Gu FX (2012) Nanomaterials for ocular drug delivery. Macromol Biosci 12: 608-620.
21. Chen J, Runyan SA, Robinson MR (2011) Novel ocular antihypertensive compounds in clinical trials. Clin Ophthalmol 5: 667.
22. Gooch N, Molokhia SA, Condie R, Burr RM, Archer B, et al. (2012) Ocular drug delivery for glaucoma management. Pharmaceutics 4: 197-211.
23. Kim H, Csaky KG, Gilger BC, Dunn JP, Lee SS, et al. (2005) Preclinical evaluation of a novel episcleral cyclosporine implant for ocular graft-versus-host disease. Invest Ophthalmol Vis Sci 46: 655-662.
24. Kuno N, Fujii S (2011) Recent advances in ocular drug delivery systems. Polymers 3: 193-221.
25. De Carvalho RAP, Krausse ML, Murphree AL, Schmitt EE, Campochiaro PA, et al. (2006) Delivery from episcleral exoplants. Invest Ophthalmol Vis Sci. 47: 4532-4539.
26. Ananthula S, Sinha A, El-Gassim M, Batth S, Marshall GD Jr, et al. (2016) Geminin overexpression-dependent recruitment and crosstalk with mesenchymal stem cells enhance aggressiveness in triple negative breast cancers. Oncotarget 7: 20869-20889.
27. Islam MT, Maniruzzaman M, Halsey SA, Chowdhry BZ, Douroumis D (2014) Development of sustained-release formulations processed by hot-melt extrusion by using a quality-by-design approach. Drug Deliv Transl Res 4: 377-387.
28. Ananthula S, Janagam DR, Jamalapuram S, Johnson JR, Mandrell TD, et al. (2015) Development and validation of sensitive LC/MS/MS method for quantitative bioanalysis of levonorgestrel in rat plasma and application to pharmacokinetics study. J Chromatogr B Analyt Technol Biomed Life Sci 1003: 47-53.
29. Novack GD (2017) Generally regarded as safe. The Ocular Surface 15: 152-155.
30. Lo R, Li PY, Saati S, Agrawal RN, Humayun MS, et al. (2009) A passive MEMS drug delivery pump for treatment of ocular diseases. Biomed Microdevices 11: 959-970.
31. Flanigan J (2009) Biotech tries to shrug off setbacks. The New York Times. New York. USA.
32. Pipis A, Scholl S, Augustin AJ (2008) Emerging drugs for diabetic retinopathy. Expert Opin Emerg Drugs 13: 669-681.
33. Sarao V, Veritti D, Boscia F, Lanzetta P (2014) Intravitreal steroids for the treatment of retinal diseases. Scientific World Journal 2014: 989501.
34. Adelli GR, Balguri SP, Bhagav P, Raman V, Majumdar S (2017) Diclofenac sodium ion exchange resin complex loaded melt cast films for sustained release ocular delivery. Drug Deliv 24: 370-379.
35. Adelli GR, Hingorani T, Punyamurthula N, Balguri SP, Majumdar S (2015) Evaluation of topical hesperetin matrix film for back-of-the-eye delivery. Eur J Pharm Biopharm 92: 74-82.

36. Gooch N, Burr M, Gale B, Ambati B (2012) Biocompatibility of a novel ocular drug delivery system. Invest Ophthalmol Vis Sci 53: 435-435.

37. Kuno N, Fujii S (2010) Biodegradable intraocular therapies for retinal disorders. Drugs & Aging 27: 117.

38. Chen H (2015) Recent developments in ocular drug delivery. J Drug Target 23: 597-604.

39. Ananthula S (2014) Bioavailability and bioequivalence issues associated with oral anticancer drugs and effect on drug market. J Bioequiv Bioavailab 6.

40. Oehlke K, Adamiuk M, Behsnilian D, Gräf V, Mayer-Miebach E, et al. (2014) Potential bioavailability enhancement of bioactive compounds using food-grade engineered nanomaterials: A review of the existing evidence. Food Funct 5: 1341-1359.

41. Sylvester PW, Akl MR, Malaviya A, Parajuli P, Ananthula S, et al. (2014) Potential role of tocotrienols in the treatment and prevention of breast cancer. Biofactors 40: 49-58.