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

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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 a 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 viscousified 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]. Cationnorm™, 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]. Intracanicular implants loaded with travoprost is being developed by oculer 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. 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 erodable sustained release implant (Duraser™) is being developed by psivi da 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 Replenisht, 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]. Cortisject™ 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. Cortisject 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
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