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Recent Overview of Ocular Patents

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Abstract

Ocular drug therapy has always been considered as a major challenge in the field of drug delivery. The presence of blood ocular barriers and efflux pumps has imposed a great concern as well. Various vision threatening disorders require a long term therapy of drug molecules, especially for the diseases that affect the posterior segment. Pharmaceutical companies and other research institutes have adopted a multidisciplinary approach to meet the current challenges which is evidenced by the trends seen in the published and filed U.S. patents. Various strategies have been employed to achieve long term sustained and targeted delivery for both the anterior and the posterior segments of the ocular diseases. These strategies include formulating drugs into implant, micro or nanoparticulate systems and hydrogel-based systems. Transporter targeted approach has also allowed scientists to deliver drugs to both the segments of the eye. Recent developments such as delivery of drugs utilizing ultrasound, iontophoresis and microneedle based devices have been promising. Gene-based therapeutics has opened a new avenue for vision threatening disorders. In all, the current developments in the entire field have been very exciting for finding out new strategies to treat vision threatening disorders.

Keywords

Drug delivery; nanotechnology; patents; prodrug; transporter targeting

Introduction

Eye is a unique organ and drug delivery to treat various ocular diseases is a challenging task. Various routes of administration have been investigated to treat ocular ailments. These modes of administration include topical, oral, intravenous, intravitreal, and periocular routes of administration. However, no single route has gained wide acceptance to treat diseases occurring both in anterior and posterior segments of the eye. Topical mode of drug delivery is mainly applicable to deliver drugs to cornea, conjunctiva, sclera and anterior Uvea.

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Penetration of drug molecule to the deeper ocular tissue is negligible due to various precorneal factors (solution drainage, blinking, tear film, tear turn over, and induced lacrimation) and anatomical factors (lipoidal nature of corneal epithelium, hydrated nature of corneal stroma, and presence of tight junctions etc.) [1]. Hence this route may not be used to treat diseases of retina. Systemic administration has also failed to deliver drugs to the targeted ocular tissues in anterior and posterior segments of the eye due to presence of ocular barriers. These barriers are known as blood-aqueous barrier and blood-retinal barrier, respectively. Blood-aqueous barrier is composed of the endothelium of the iris/ciliary blood vessels and the non-pigmented ciliary epithelium, while blood-retinal barrier is made up of retinal capillary endothelial cells and retinal pigment epithelium cells (RPE). Due to above mentioned barriers; a therapeutic concentration of drug is not achieved in desired ocular tissues even after administration of a higher dose. Hence, this route has also not gained momentum in treating ocular diseases. After oral administration, drug has to go through first pass metabolism before systemic exposure. Hence, this route has not been considered as a potential route to treat various anterior and posterior segment diseases. Intravitreal and periocular routes of administration have gained momentum in last decade to deliver drugs to the targeted ocular tissues especially to the retina. Intravitreal administration of drug leads to rapid achievement of higher concentration in retinal tissue to treat posterior segment diseases. However, the administration process is very painful and hence this route suffers from poor patience compliance. Various approaches have been adopted to deliver drug to the retinal tissue after transscleral/subconjunctival mode of administration. However, different dynamic barriers (conjunctival blood and lymphatic circulation) rapidly clear drug molecule after transscleral administration [1]. Hence designing drug therapy for ocular diseases has always been considered as a major challenge for scientists in the field. A detailed description of anatomy, physiology and barriers is beyond the scope of this manuscript. A reader is encouraged to refer to our previously published literature to get more insight into above topics. The description of barriers has been explained in previously published literature in detail [2-4, 5]. Pharmaceutical companies have actively pursued various strategies which have been adapted to deliver drug effectively to targeted tissues especially for the posterior segment diseases. Current literature in the field such as published papers, published and filed patents reinforce the same idea of adaptation of novel approaches in the field of ocular drug delivery.

A lot of research was focused on the synthesis and development of new drug molecules which can be effective in various ocular ailments. Pharmaceutical companies have also exploited new therapeutic indications for the available drug molecules. This was largely accomplished to avoid higher cost of new drug development and expedite regulatory approval. The transporter targeted drug delivery system has gathered a lot of attention because of its non-invasive nature, ability to transport a wide variety of substrates and ability to overcome inherent problems with drug molecules such as solubility, stability, permeability etc. In this concept, promoiety (nutrient) has been attached to a parent drug molecule so that it can be recognized by the transporters present on various ocular tissues. Recent trends in the development of prodrug strategies of therapeutic molecules have been very promising [6]. This approach has been shown to overcome efflux-related problems of many drugs.

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In the last decade, a wide variety of formulations and devices have been employed for treatment, diagnosis and delivery purposes. Achieving sustained and controlled release of drug molecules at the particular desired site is a long-term objective for many ocular ailments. Rapid development of sustained release implants and hydrogel-based formulations occurred mainly because of their potential to deliver drug for a longer period of time. Various other dosage forms such as microparticles, nanoparticles and liposomes have also been developed to obtain sustained drug delivery and to target drug moiety [7]. Several novel ocular dosage forms have also been developed to enhance the penetration of drug into ocular tissues. Recently, various non-invasive methods of drug delivery were also designed such as ultrasound, iontophoresis and microneedle-based delivery of therapeutics.

A trend was also seen in the development of gene-based therapeutics, which can effectively treat diseases especially in posterior segment disorders. Delivery of these therapeutics has also been challenged by the intrinsic nature of these molecules. Wide ranges of techniques were also employed to deliver the therapeutic agents. Improvement in safety, efficacy and targeting desired cells were among the basic requirements of this therapy [8].

In the present chapter, we have attempted to cover both the published and filed U.S. patents that accompany all the above-mentioned developments happened in the last decade. We have briefly focused on the developments of new drug molecules, their application, drug delivery devices/systems and gene-based therapeutics.

Development of New Drug Molecules

A wide variety of new molecules have been developed and tested against disease conditions of both the segments. A clear trend and momentum were seen in the development of molecules for the treatment of posterior segment ailments particularly for the vision-threatening disorders. In Table 1, we have summarized the development of new molecules occurred in the last decade for the treatment of various posterior segment ailments such as wet age related macular degeneration (AMD), proliferative vitreo-retinopathy (PVR), uveitis etc. and anterior segment ailments (glaucoma, cataract, dry eye etc.). We have also briefly summarized some important developments in the following write-up.

The U.S. patent application no 20080103211 filed by Robert Collier mentions the use of levo-betaxolol, a betaadrenoceptor antagonist for the treatment of ocular pathologies of the outer retina. The inventors have developed levobetaxolol and studied its *in vivo* performance as well. Levobetaxolol was found to inhibit photo-oxidative induced retinopathy in male Sprague Dawley rats. They also claimed to study preservation of vision and up-regulation of retinal endogenous neurotrophic factors [9].

In another patent, the inventors have disclosed the use of novel water-soluble tryptophanyl-tRNAsynthetase-derived polypeptide for the inhibition of neovascularization. *In vivo* efficacy of these molecules was also claimed in the disclosure [10].

In a patent disclosed by Alcon (Robert Collier *et al*), the use of compounds with 5-HT1A agonist activity for the treatment of the outer retina was disclosed. The inventors have successfully studied the retinal-protective effect of these compounds in photo-oxidative-

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induced retinopathy paradigms. These molecules have shown functional and structural protective effect in photo-oxidative-induced retinopathy in the rat model at the dose of 1mg/ml [11].

A patent disclosed by Stephen Donovan from Allergan Inc. mentioned the use of botulinum toxin for the treatment of various ocular disorders in the form of an implant. The botulinum neurotoxin was administered via the intravitreal route and concentration in the vitreous humor was observed 10 times higher than aqueous humor. Intravitreal-sustained release dosage forms were developed by encapsulating the toxin into the PLGA polymers. The inventors have claimed to formulate a pulsatile release dosage form, water-in-oil emulsion and controlled-release microsphere-based formulation to achieve the extended release of the neurotoxin [12].

Recently, the delivery system of a sirtuin-activating agent, resveratrol, was developed and patented by Allergan Inc. The inventors claimed to use this formulation for the treatment of posterior segment disorders like AMD and macular edema. The inventors have shown prolonged retinal ganglion cell survival and neuroprotection by administration of resveratrol embedded in biodegradable polymer like PLGA [13].

In an interesting patent filed by Alcon Inc., the inventors have claimed the effect of a vitamin supplement which acts as an antioxidant to treat AMD along with anecortave acetate. These vitamins include vitamin C, vitamin E, betacarotene and zinc oxide. This supplement has been proven to improve vision significantly in the human [14].

In another patent, anti-prostaglandins have been shown to treat neovascularization in various parts of the eye. The inventors have delivered flurbiprofen at neutral pH and claimed to inhibit neovascularization in different parts of the eye. The same inventors have also claimed to treat neovascularization using heparin and tetracycline derivatives. In another attempt to treat autoimmune ocular inflammatory diseases in the human subject, compounds which inhibit the interleukin-23 (IL-23)/interleukin-17 (IL-17) were developed. The inventors have also performed *in vivo* studies to demonstrate inhibition of interleukin-23 (IL-23)/interleukin-17 (IL-17) following administration of their antagonist compounds [15].

Inosine monophosphate dehydrogenase (IMPDH) was found to play a crucial role in cell proliferation. Utilizing this concept, the inventors at Johns Hopkins University have hypothesized the use of IMPDH inhibitors in the treatment of angiogenesis. These molecules have shown anti-proliferative activities both *in vitro* (inhibition of HUVEC proliferation) and *in vivo* (in a rat model) [16].

Transporter Targeted Prodrug Approach

Transporter targeted drug delivery has been considered as a viable alternative to deliver drugs to various ocular tissues. This approach includes targeting nutrient transporters present on various ocular tissues. In this approach, a parent drug moiety is being modified in such a way that it becomes a substrate of influx transporter. For this purpose, amino acid/peptide/monocarboxylate transporter/vitamins and other nutrients have been conjugated with parent drug moieties. Following administration into the eye, due to presence of the promoiety, this

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prodrug will be trans-located by the influxtransporter resulting in high permeability [17]. Evasion of efflux pumps such as Pgp, MRP and BCRP can also be achieved by utilizing this approach Fig. (1).

In a recent patent from our laboratory, prodrugs of quinidine hydrochloride were synthesized. Quinidine has been shown as a substrate of efflux transporters that results in significant reduction in the cell permeation following administration. We have developed (valine conjugated) prodrugs of the quinidine (val-quinidine and val-val-quinidine) which have shown higher affinity for the peptide transporters and less affinity for the efflux transporters Fig. (2). Transport of the quinidine prodrug was mediated by a carrier-mediated process resulting in higher permeation as compared to the parent drug (1.5 and 3 times higher permeability of val- quinidine and val-val- quinidine compared to parent drug), which was a substrate of the efflux transporter [18].

This approach has further been exploited by Patrick Hughes from Allergan Inc. They claimed to make the prodrug of a wide variety of drug molecules which can be recognized by influx transporter and bypass efflux transporters. These investigators proposed to make glycyl and tryptophyl ester prodrug of bimatoprost (targeting amino acid transporters); glycylsarcosine ester of bimatoprost(targeting peptide transporters); succinate ester of bimatoprost (targeting monocarboxylic acid transporter); uridine di-ester of bimatoprost (targeting nucleoside transporters); and D-glucopyranosyl ester of dexamethasone (targeting glucose transporter) [19].

In a novel way to enhance drug delivery utilizing the transporter targeted approach, guanidino and amidino moieties were covalently conjugated to the parent drug molecules. Inventors have also used the linker whenever required in between parent moiety and transporter. The inventors have also used D-arginine to conjugate with the parent drug. D-arginine was preferred over L-arginine because conjugates containing D-arginine were found to be more stable than the conjugates of L-arginine [20].

In a recent development to treat glaucoma, parent moiety was conjugated with the acetylcholine or the psuedoacetylcholine group. These conjugates will have the ability to bind to the acetylcholine or psuedoacetylcholine receptors present on the cell surface. This selective binding to receptors will improve the internalization of the parent drug. The prodrug would convert back to the parent drug in the cell cytoplasm where the drug would later chelate to calcium ions to produce its therapeutic activity [21].

In a totally different approach to deliver drug to posterior segment diseases following oral administration, the therapeutically active drug was covalently bound to xanthophyll,a carotenoid. This concept exploits the fact that retina and macula have natural tendencies to concentrate xanthophylls. Hence, the inventors have hypothesized to make a prodrug by covalently linking drug molecules to these xanthophylls. Selective uptake of the prodrug would be facilitated due to the presence of the carotenoid. The inventors disclosed the synthetic method to form the prodrug by attaching zeaxanthine to various drug molecules used in ocular ailments such as ciprofloxacin, fluocinolone, etoposide etc. This sort of

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prodrug-based delivery approach would allow non-invasive targeting of drug molecules following oral administration [22].

In an interesting development, Rabinovich-Guilatt Laura has developed the prodrug of dexamethasone by attaching palmitic acid to it. The inventors have aimed to decrease the adverse effect of the parent drug on other tissues such as glaucoma. They hypothesized a higher uptake of lipophilic ester prodrug of dexamethasone palmitate in inflammatory cells compared to normal cells resulting in improved site specific targeting. Slow hydrolysis of the prodrug would give sustained release at the targeted retinal site and fewer side-effects in other ocular tissues. Two months following the intravitreal injection of same dose of drug and prodrug, undetectable amount of drug was observed in aqueous humor generated from the prodrug. This *in vivo* experiment suggests less toxicity of the prodrug compared to the dexamethasone. This study would be very significant, since, by utilizing this approach, vision-threatening adverse effects of dexamethasone can be avoided [23]. In another attempt to deliver drugs non-invasively to retina, some inventors have hypothesized the delivery of a prodrug following subconjunctival injection. They have prepared ester prodrug of tazarotene which will convert to the parent drug following the enzymatic breakdown by esterases. This slow regeneration of parent moiety would significantly diminish the side effect on the other part of the eye such as elevation in intraocular pressure etc. [24].

In a recent development, vitamin D was found to inhibit angiogenesis. Utilizing this fact, some inventors have developed a method to deliver calcitriol to inhibit angiogenesis. They have also demonstrated inhibitory effects on migration, capillary morphogenesis and proliferation of retinal cells [25].

Drug Delivery Devices and Implants

Various strategies have been adopted by pharmaceutical scientists to formulate and deliver drug molecule to various targeted ocular sites. It is beyond the scope of this manuscript to cover in detail all developments in the field of drug formulation, delivery and designing devices for various purposes. So, we have attempted to summarize recent updates in the field of development of various devices, implants and formulations in Table 2 and 3 respectively. We have also attempted to deal briefly with the most widely investigated avenues in ocular drug delivery in the following discussion.

Technological revolution in ophthalmic drug delivery has resulted in the development of microchip arrays. The inventors in a recent patent have described the sophisticated design of a microarray chip device which enables them to modulate the delivery of drug molecules in the ophthalmic region. Microchip array consists of device elements and each element is composed of reservoirs. The drug molecule is placed in a reservoir either in a pure form or in a matrix that releases drug in the desired fashion. The device can conform to curved shape and hence accessible to curved or rounded tissue in the eye. The communication to the device can be made by a laser source that initiates the reservoir to release the drug. The release from each reservoir can be made different by using different release system for the reservoir and hence the kinetics can be varied. This research has a breakthrough in the delivery system since many drugs can be incorporated in the same device. The categories of

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drugs such as antibiotics, antiviral, immunomodulators etc. can be delivered by this technique. The inventors have claimed to use an implant for the treatment of ocular diseases such as wet AMD, macular degeneration, choroidal neovascularization and anterior segment disorder as well [26].

In a different approach, delivery of biologically active molecules without activating the immune system was developed. A micronized device was invented which could control the release of various growth factors, cells or metabolic factors. The release of these factors could be controlled using various biodegradable and biocompatible polymers. This encapsulated cell technology device can be implanted to various sites of the eye depending upon the nature of the diseases. The investigators have successfully delivered ciliary neurotrophic factor (CNTF) and/or interleukin-10 (IL-10). The rate of release of these factors could be modulated by using different polymers and thus release profile from 2 weeks to several months (18 months in case of CNTF) could be achieved. The device was found to be viable for studied time and was non-irritating as well. The inventors have also claimed to deliver IL-10 for the treatment of autoimmune uveo retinitis. They have also studied the safety, efficacy and pharmacokinetic behavior of this device following implantation in the vitreous humor [27].

In a patent disclosure by Allergan, the inventors have modified chitosan and used this biomaterial for various purposes. They claimed to use modified chitosan as tissue adhesive, filler and also for local targeted delivery application. Safety and efficacy of this biomaterial was also demonstrated. This biomaterial did not show any cytotoxicity or immune reaction. This biomaterial has shown a comparable release profile for prednisolone acetate and ketorolac tromethamine with their marketed formulations. Inventors have also conjugated this biomaterial with bimatoprost and this complex was found to convert to parent drug only in the presence of the enzymes such as esterase and lysozyme. Investigators have claimed to use this concept of covalent linking to the biomaterial to target various drug molecules in the eye [28].

In a recent patent filing, the inventors have designed polyethyleneglycol (PEG)-polyacetal (PA) copolymer and polyethyleneglycol (PEG)-polyacetal (PA)-polyorthoester (POE) copolymer for the drug delivery purpose. Polyacetal will be more susceptible to break under acidic conditions. This kind of graft polymers is liquid at room temperature. This solution form will convert to gel form at body temperature. Inventors have claimed to use this polymer in the preparation of micellar formulation containing anticancer drugs for targeting purpose [29].

A patent filed by Paul Ashton and Hong Guo elaborates a novel device for sustained release of adrenergic agents in the field of ocular drug delivery which can overcome disadvantages of topical and systemic routes of administration. This patent outlines the invention of a sustained release drug delivery device that can be instilled to provide the controlled release of adrenergic agents within the ciliary body. The inner core of the device consists of one or more adrenergic agents and the outer layer is made of biocompatible polymers which would allow the diffusion of drug through pores. Among the many possible modifications to optimize desired delivery, one is the formulation of *in situ* gelling system that can release

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the drug for a longer duration. The gelling system consists of the drug, PEG and biocompatible/erodible polymers [30].

Drug Delivery Systems

In a patent application from our lab, we have attempted non-invasive transscleral delivery by utilizing ultrasonic waves. In a typical experimental setting, an entire assembly that includes an ultrasound device and coupling media which hold drug formulation in coupling well was developed. It also consists of a functional generator connected to an amplifier, a matching network and a transducer. This was placed at particular distance from the sclera. Ultrasonic waves generated by the system would aid in enhancing the porosity of the tissue resulting in higher permeation of the drug across tissue [31].

In another patent to sustain the drug release following ocular administration, the inventors have suspended emulsion comprising hydrophobic agent (cyclosporine A) into hydrophilic gel. They claimed to get a sustained release of a therapeutic agent utilizing carbopol-based bioadhesive gelling system. They have also formulated a molecular dispersion based gel and successfully sustained the release of the cyclosporine A [32].

In an attempt to sustain the release of Pegaptanib, a VEGF inhibiting antibody, researchers from Eyetech Inc. have prepared microparticle-based formulation. This formulation has provided a sustained release profile as compared to the Pegaptanib solution. Pegaptanib, being a protein molecule, has been studied for effect of the formulation variable on biological effect. Researchers observed no change in the biological activity following formulation of microparticle-based system utilizing polymers such as poly (lactic acid) (PLA), poly (glycolic acid) (PGA), and copolymers. They obtained sustained release up to one month without significant burst release of the encapsulated protein drug molecule [33].

In another attempt to sustain the drug release following intravitreal injection, some researchers have developed nanosphere-based formulations. They have administered whole antibody, Fab, and Fab-nanosphere in the rat vitreous and studied kinetics of all of them. They observed faster elimination of a whole antibody and Fab within 1 day while Fab-nanospheres were found to retain in the vitreous humor for more than 10 days. They have also observed biological activity of Fab after 28 days of administration. This study shows that the controlled release could be obtained following intravitreal injection of Fab-nanospheres [34].

A novel bioadhesive liposomal formulation was designed for topical delivery to enhance the retention time of the applied drug molecule. Cationic lipid was used to formulate liposomal structure. Inventors have evaluated the residence time and drug absorption by putting diclofenac sodium into a liposomal formulation. Conventional phosphatidylcholine-based liposomes could not provide bioadhesion and thus it was hypothesized that drug permeation would be less as compared to bioadhesive liposomal formulation. The inventors have compared concentration of diclofenac following topical administration in different tissues. The concentration of the drug in aqueous humor was significantly higher from bioadhesive liposomal formulation than the drug solution alone.

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The similar pattern was observed for tissues like the irisciliary body and the cornea where 2 and 3.2 times higher concentration was observed, respectively. The inventors have even observed diclofenac in the retina which suggests higher permeation of diclofenac from the liposomal formulation [35].

In a recent attempt to deliver macromolecules in posterior segment ocular diseases such as AMD, researchers have developed a technique to conjugate hydrophilic moiety such as polyethelene glycol (PEG) to a specific functional group of an aptamer. They claimed that this conjugate would interact better with the VEGF than the unmodified aptamer [36].

A recent patent elaborates the inventor's work on deducing the role of emulsion for delivery of drugs to intraocular and periocular regions. O/W type of emulsion with and without drugs was formulated and characterized. The emulsion with Cyclosporin A (CsA) as an active ingredient, oleylamine as cationic lipid, alpha-tocopherol as antioxidant along with blank emulsion without drug was administered intravitreally to animal models. The emulsion with CsA significantly reduced the scores of inflamed eyes as compared to blank emulsion, demonstrating the effectiveness of the formulation [37].

In another attempt to deliver drug for posterior segment ailments, inventors have designed a method to overcome the disadvantages associated with the traditional iontophoretic method. The current problem associated with the iontophoresis is very short half-life of water soluble compounds following administration which requires frequent administration of these compound. Due to this, cost of the treatment increases dramatically and at the same time patient compliance decreases. Investigators of this patent have attempted to address these issues by delivering a depot forming agent along with active agent through iontophoresis. They delivered the active agent and depot forming agent separately. Following administration in the subject, the depot forming agent will make an ionic complex with the active agent resulting in the decreased solubility of active agent. This complex formation would release the active drug slowly and thus sustained release into ocular tissues would be achieved. As per this invention, the depot forming agent should have an opposite charge than the drug molecule. Multiple opposite charges on the depot forming agent would be the preferred one. The inventors have claimed to use various ions such as Ca^{+2}, Sn^{+2}, $Fe^{+2,}$ $Fe^{+3,}$ Mn^{+2}, Mg^{+2}, Zn^{+2}, NH^{+4}, organic anion, chelating agent and other excipients etc. The inventors have also floated the idea of concurrent administration of a vasoconstrictive agent which can actually decrease the clearance of this complex from the desired site resulting in a higher sustained delivery. They have claimed to deliver triamcinolone acetonide and dexamethasone phosphate using this approach [38].

In a recent discovery, the use of cyclodextrin in the topical ophthalmic solution for the delivery of a drug to the posterior segment of the eye has been emphasized. The topical administration has the disadvantages of drainage, lachrymation and presence of corneal barriers that limits the corneal absorption of the drug. Cyclodextrins have been found to provide promising results when formulated with drugs in the form of aqueous suspension. In the current patent, the delivery of a lipophilic corticosteroid was attempted by formulating an aqueous suspension. In one of the experiments, the aqueous isotonic suspension of dexamethasone with β-cyclodextrin was tested for its bioavailability after the topical

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administration. About half of the drug administered reaches vitreous (54%) and retina (59%) which demonstrates the efficacy of the formulation in enhancing the bioavailability of the drug [39].

Recent studies have also focused on potential toxicity of nanocarriers on ocular tissues. Various kinds of materials have been investigated to formulate nanoparticles such as chitosan, PLGA, iron oxide, poly-acrylate copolymer (eudragit) and lipids [40]. Toxicity of above mentioned materials after short and long term administration needs to be studied along with various excipients used to formulate nanocarriers. A residual organic solvent used in preparation of nanoparticles may cause severe toxicity to the ocular tissues. Since nanoparticles have a tendency to accumulate following ocular administration, one also needs to understand safety and efficacy following their long term application. Several studies have documented an effort to study acute and chronic toxicity of nanoparticles in animal models using rabbit, mice and rat. A recently published review article summarizes the toxicity studies carried out using above mentioned materials [40].

Gene Therapy

Viral vectors have gained immense popularity as a vehicle to deliver genetic material to particular targeted cells. But this delivery has always suffered from the potential of toxicity associated with it. Later on, with the development of avirulent virus, it was possible to target particular type of the tissue. RR deficient herpes simplex virus-1 (HSV) is among those viruses which has tremendous potential to target genetic material to a specific cell. The desired gene can be expressed in the vector which will later be delivered to a particular cell. In a U.S. patent application, inventors have attempted to incorporate a bovine bFGF gene in RR deficient HSV. This was successfully evaluated in animals. Investigators have claimed to use this concept to deliver growth factors, neurotrophins and cytokines as well [41].

Pigment epithelium-derived factor (PEDF) has been shown to have protective effect against choroidal neovascularization. In an attempt to deliver nucleic acid which encodes PEDF, recombinant adeno-associated viral (rAAV) vector was employed. This vector was hypothesized to enhance pigment epithelium-derived factor expression resulting in decreased CNV. The inventors have also mentioned the process of making this viral vector which includes the selection of promoter, enhancers and other inactive ingredients. The optimized formulation was studied *in vivo* in a mouse model. It was observed that there was a significant reduction in sizes of laser-induced CNV lesions following intravitreal as well as sub-retinal injection of this formulation [42].

Short interfering nucleic acid (siNA), which can modulate the gene expression, can be delivered in an efficient manner across the cell membrane. In a recent patent the cationic polymer was synthesized and complexed with siNA. The nucleic acid to cations ratio could be varied depending on the desirable final charge (neutral, positive and negative nucleic acid-to-cations ratio). In one of the experiments conducted, the siNA molecules were designed as anti-angiogenic agents to target the genes responsible for angiogenesis (VEGFR1, VEGFR2 and VEGFR3). *In vitro* studies have shown 20% decreased level of gene expression following the delivery of the siNA molecules [43].

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Connective tissue growth factor (CTGF) is a secreted cytokine, the over-accumulation of which can result in condition like glaucoma that can increase the intraocular pressure. The extracellular matrix production in trabecular meshwork cells is governed by CTGF. A patent filed by Fleenor *et al*. described that the antagonist of endothelial differentiation gene subfamily 3 receptor (EDG-3) results in less production of CTGF, thereby can be used to treat conditions like glaucoma, macular degeneration etc. Cultured human trabecular meshwork cells were treated with or without CAY10444 (antagonist for EDG-3 receptor). Enzymed linked Immunosorbent Assay (ELISA) was used to estimate the level of secreted PAI-1 protein (Plasminogen activator inhibitor), an extracellular matrix related protein. The result of the experiment has demonstrated successful inhibition of the agonist activity of substrates by CAY1044 [44].

One of the approaches to the nucleic acid delivery to the ocular tissue has been described in the patent filed by Chalberg *et al*. This patent discloses the electron avalanche mediated transfection of nucleic acid in which the permeation into the cell is achieved by the mechanical stress and the electric field. The nucleic acid that enters the cell may encode therapeutic proteins. The application of this technique can be useful in treatment of AMD, CNV and glaucoma. The conjunctival tissues were transfected with the luciferase marker gene with and without the electron avalanche technique. The bioluminescence indicates that the emission from the tissue transfected using the electron avalanche method was 2 folds higher than without using this technique [45].

The targeted and efficient gene delivery to ocular tissue has been described in a recent patent. The use of defective recombinant virus encapsulating the gene of interest can be used to treat ocular genetic pathologies like retinitis pigmentosa and retinal degeneration etc. Moreover, the expression of gene last for more than 50 days and hence proved to be stable. One of the merits in this technique is that it does not produce any cytopathological effects. The patent further describes an experiment based on the delivery of a defective recombinant adenovirus AdRSV Gal. The virus when administered to the anterior chamber resulted in the expression of β-galactosidase activity by endothelial cells. Furthermore, the intravitreal and retrobulbar injections based delivery was also successfully evaluated by the investigators [46]. A brief overview of other gene therapy related developments is shown in Table 4.

A lot of research is currently focused on studying the potential toxicity of viral vectors following ocular administration. Viral vectors may cause undesired adverse and sometimes fatal reaction to various organs of the body. Hence even after exhibiting a great success in animal models, the use of these vectors in human subject requires a careful and critical evaluation.

Current & Future Developments

Current trends in published as well as filed patents show the immense development ongoing in the different fields related to ocular drug delivery. Adaption of multidisciplinary approach which emerged as a very powerful tool has generated a great momentum in the development of new molecules, delivery systems and devices. Considering the immense cost of development for a new drug molecule, it would be more desirable for pharmaceutical

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industry to focus on minimizing adverse effects of the existing drug molecules and improving their delivery aspects. Sustained and controlled drug delivery systems have been developed and evaluated especially for the posterior segment diseases. Industry-academic collaboration would also serve as a major boost for the development of novel technologies. Delivery of protein and gene based molecules consists of various challenges including safety and efficacy related issues. Currently, very limited literature information is available in this area. By considering the future market potential, we anticipate a steep increase in development in this area. Development of novel polymers, delivery systems and devices would also continue and an immense focus will be given to improve patient compliance and reduce cost of the therapy. Transporter targeted drug delivery has shown promising result for the delivery of many therapeutics. We anticipate involvement of more research groups in the area of identification of various transporters and evaluate their role in studying drug disposition. Various non-invasive drug delivery systems for the treatment of posterior segment ailments following periocular administration have been patented. For this purpose, iontophoresis, microneedle and ultrasound based devices have been investigated. We foresee a lot of development and activities in this field to deliver small and large molecules. However, getting approval from regulatory agencies like FDA for this sort of delivery systems would be a challenge. Many research groups have also claimed to deliver drug to the posterior segment tissues such as retina following topical drug administration. This sort of approach would minimize/eliminate the use of intravitreal and periocular route. However, a lot of research would be required to prove the concept of retinal delivery following topical administration. A nanomicelle based delivery system possesses a great promise in this area. Overall, the current developments happening in the field hold a great future for ocular drug therapy.

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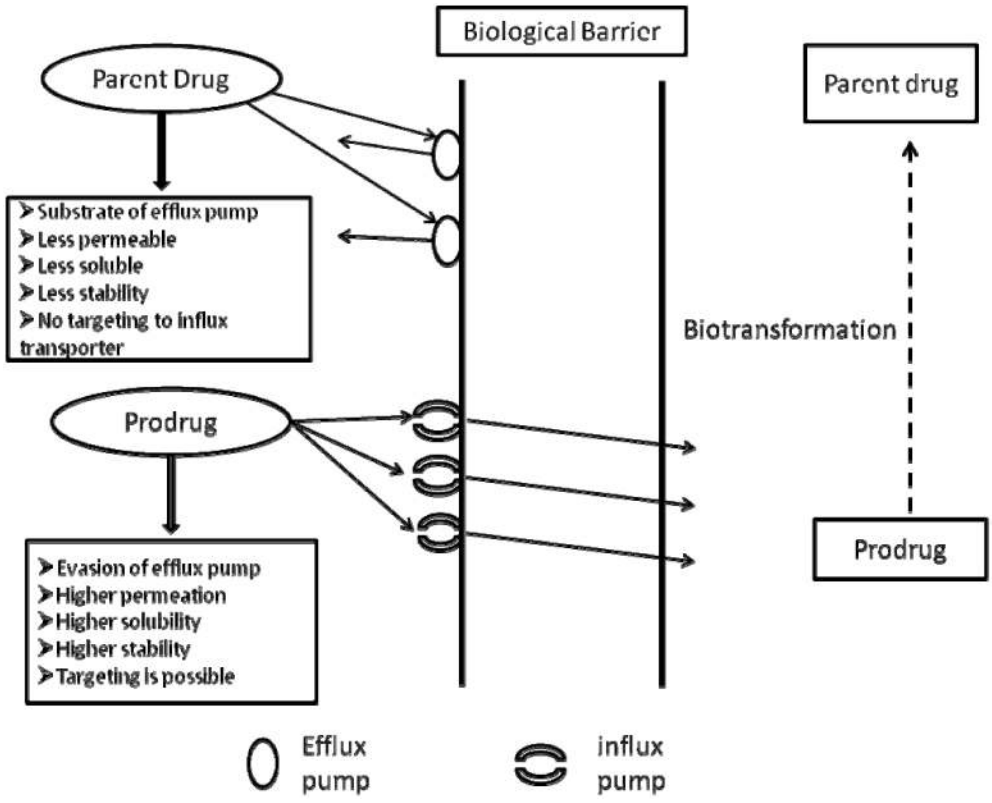

Fig. (1).
Representation of transporter targeted prodrug approach.

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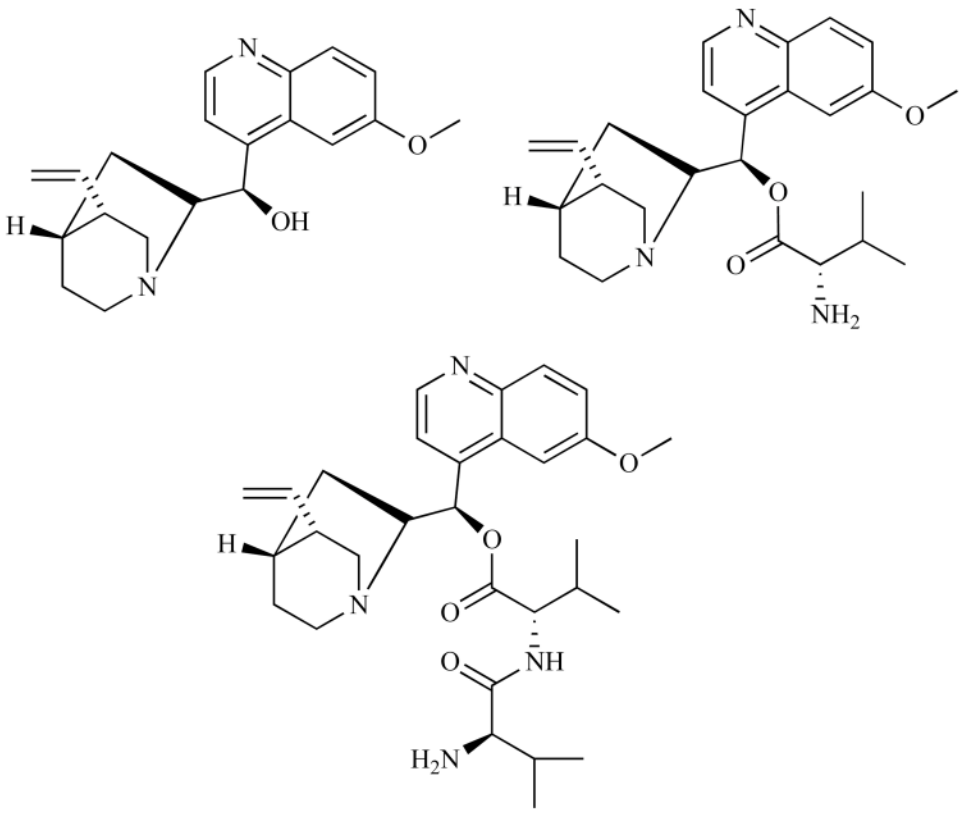

Fig. (2).
Structure of (**a**) Quinidine, (**b**) Val-quinidine and (**c**) Val- Val- quinidine.

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Table 1
Development of new molecules and their therapeutic implications

Specification of New Molecule	Usefulness in Diseases Condition	Ref
Synthesis of hydroxyeicosatetraenoic acid and Omega chain modified 15-hydroxyeicosatetraenoic acid derivatives	Dry eye	[47,48]
Novel isolated polypeptides were designed	AntiVEGF activity and inhibition of HUVEC cell proliferation	[49]
A series of peptides were developed which can bind to pro-gly-pro sequence of polymorphonuclear leukocyte chemoattractants.	Alkali-injured eyes and other types of ocular diseases.	[50]
A series of Piperidinyl prostaglandin E analogs were developed	Glaucoma	[51]
EP 4 agonist	Glaucoma	[52]
Topical administration of amide derivatives of flurbiprofen and ketorolac	Ocular inflammation and angiogenesis	[53]
Concentrated enzymatic solution of trypsin	To remove nuclear,cortical and subcapsular regions of the cataractous lens	[54]
Clostridial toxin	Ocular inflammation or Uveitis	[55]
Lipopolysaccharides which enhances the level of polypeptide.beta.-defensin-2 (hBD-2)	Corneal infections and wounds	[56]
Calcium blockers were found to inhibit migration of glutamate and RPE proliferation	Proliferative vitreoretinopathy.	[57]
Prostaglandins analogues	Glaucoma	[58]
Dithiolane derivatives were designedto inhibit peroxisome proliferator-activated receptor-alpha and gamma	Posterior segment ailments	[59]
Indazole derivatives, which act as inhibitor of tyrosine kinase	Posterior segment ailments	[60]

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Table 2
Recent advancement in designing ocular devices and implants

Novelty Claimed in Designing Devices and Implants	Ref
A counter pressure device was designed to prevent reflux and facilitate placement of drug to the site of administration	[61]
A device was developed to facilitate removal of subretinal fluid and to perform fluid exchange in vitreoretinal surgery	[62]
A device comprising an insert stabilizer, an interlock opening and a replaceable implant was developed to deliver drug by trans-scleral route.	[63]
An implantable device which provides single and dual mode drug release following administration into periocular and intravitreal route has been fabricated.	[64]
An implant was developed to sustain and control the release of a hydrophobic and hydrophilic drug molecule (Dexamethasone and Ciprofloxacin HCL respectively) where the hydrophilic drug molecule could act as release modulator for hydrophobic drug moiety.	[65]
A biodegradable implant was developed to control the release of dexamethasone at 0.05 and 0.03 mu.g/ml for 2 days and 3 weeks respectively following intravitreal administration for the treatment of ocular inflammation.	[66]
A bioerodible implant encapsulated dexamethasone in PLGA was developed to reduce transplant rejection	[67]
Intraocular implant, lenses, corneal inlays were formulated which were made up of crystalline or semi-crystalline polymeric materials for the treatment of various ocular ailments	[68]
A control release biocompatible device was fabricated containing drug such as dexamethasone and ganciclovir which were encapsulated in impermeable polymer	[69]
A tonometer system was developed to measure applanation and hemodynamics of the eye such as ocular blood flow and pressure in the ocular blood vessels.	[70]
A novel carrageenan based transitional viscoelastics was disclosed which will not enhance IOP in the eye following surgery	[71]
A novel bioadhesive drug delivery system was developed to deliver timolol maleate by using NOCC as adherent in the treatment of glaucoma	[72]
A device containing drug in the impermeable holder (made up of silicon) was designed for intraocular administration.	[73]
An implantable device containing, a pump and a reservoir with soft and smooth surface to minimize stress was developed to deliver drug to the retina.	[74]

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Table 3
Novel ocular formulations and drug delivery systems

Characteristic of the Formulation	Usefulness in Diseases	Ref
Neurotransmitters and neuropeptides were designed to deliver by topical route	dry eye diseases	[75]
Polysialic acid-neural cell adhesion molecule (PSA-NCAM) modulators (INF, EGF, NGF) were topically delivered	dry eye diseases	[76]
BOL-303213-X, was delivered by putting into various dosage form such as solution, suspension, insitu gel etc	Anti-angiogenic, anti-inflammatory	[77]
Lidocaine HCL based aqueous gel was developed	Local anesthesia	[78]
Stable liquid and lyophilized formulation of anti-VEGF was developed for intravitreal injection	Treatment of posterior segment diseases	[79]
A hollow microneedle was designed to deliver drug to sclera and corneal stroma. Delivery of micro/nanoparticle was also mentioned	both the segments	[80]
Suprachoroidal delivery of small and macromolecule encapsulated in particulate delivery	posterior segment diseases	[81]
An eye drop based dosage form containing the metal chelator (EDTA) and the transport enhancer (methylsulfonylmethane) was developed.	Diabetic condition	[82]
A self-emulsifying formulation containing rapamycin was developed	posterior segment diseases	[83]
Microparticulatre based formulation having an aptamer (EYE001) was designed	Wet AMD	[84]
Topical eye drop and ointment was developed to deliver tacrolimus	immune-related diseases of the anterior segment	[85]
Oral dosage form containing nutrients such as omega-3 and omega-6 essential fatty acids was invented	Dry eye diseases	[86]
Nutreint dosage form containing vitamins, minerals, phytonutrients and amino acids was developed	both the segments	[87]
Topical formulations of ketotifen fumarate was invented	antiallergenic agents	[88]
Gelling based formulation of pilocarpine HCL was obtained by combining of Carbopol and Pluronic polymers	Glaucoma	[89]

INF (Insulin-like growth factor), EGF (Epidermal growth factor), NGF (Nerve growth factor), VEGF (Vascular endothelial growth factor)

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Table 4
Recent development in gene based therapeutics

Characteristics of the Patent	Ref
Multiple genes which cause AMD and destruction of RPE were identified and method to detect them was developed. Animal models were also developed to screen the effectiveness of the compound against these genes	[90]
Application of lentiviral vectors to transduce both mitotically active and inactive cells was exploited for the treatment of proliferative ocular disease	[91]
New vectors to deliver gene such as recombinant fiv vectors and method to use this vector for the treatment of retinal diseases associated with lysosomal storage disorders was developed.	[92]
Recombinant adeno-associated viral vector was designed which can deliver anti-angiogenic factor to targeted cell for the treatment of posterior segment ailments	[93]
A mammalian gene CACNA 1 F, encoding an (alpha).sub.1 f-subunit of a retinal calcium channel was identified. Mutation of which causes congenital stationary night blindness	[94]
A diagnostic method to find out the susceptibility of a human to develop cataract or anterior segment mesenchymaldysgenesis was designed by identifying aberrant pitx3 polypeptides.	[95]
A novel drug molecule to inhibit RTP801 gene was identified to treat microvascular disorder of the eye	[96]
Gfr.alpha.3 agonist such as neublastin was formulated to treat retinal disorders	[97]
A method to inhibit RTP801 L gene was designed to treat microvascular disorder of the eye	[98]
A method to modulate gene expression was developed using narrow band multichromatic electromagnetic radiation having a wavelength of from about 300 nm to about 1600 nm.	[99]
A composition containing 15-lipoxygenase-1 gene was developed to replace ocular surface epithelium in the treatment of dry eye of postmenopausal women	[100]
A method to identify mutation in freac3 gene was developed to understand susceptibility of a human subject to glaucoma and anterior segment dysgenesis	[101]
Novel dihydrazide derivatized hyaluronic acid/nucleic acid bioconjugates were formulated to treat dry eye syndrome	[102]
Delivery of glial cell-derived neurotrophic factor using a recombinant viral vector was developed	[103]
Novel electroporation device method was developed to deliver DNA to specific site in the eye	[104]