

Advances, Challenges, and Future Directions of Ocular Drug Delivery Systems

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ABSTRACT: Ocular drug delivery systems (ODDS) play a significant role in the management of eye diseases that have the potential to result in vision loss; however, the successful delivery of therapeutics to target tissues is limited due to several anatomic and physiologic barriers.

ODDS primarily consist of topical eye drops or ointments, which represent the majority of products on the market but have extremely limited ocular bioavailability (typically < 5%), due to the rapid elimination of drug from the precorneal area (predominantly due to nasolacrimal drainage), as well as the eye's other protective mechanisms; thus, patients must frequently dose to achieve therapeutic effect.

Recent advancements in ODDS have introduced many different forms of systems, including nanocarriers, in situ gels, ocular inserts, liposomes, niosomes, microneedles, and mucoadhesive devices. The most critical features of these types of systems are their ability to increase the length of time that drug remains in contact with the anterior segment of the eye and increase the delivery of drug into the anterior and posterior segment over an extended time period.

In this review, we discuss the anatomic and physiologic barriers to drug delivery, the different types of systems available, the route(s) of absorption and the pharmacokinetics of both conventional and advanced types of systems, the recent developments in innovation, including the use of biomimetic and "stimuli responsive" systems, and some of the most important current hurdles to the successful delivery of drugs to the eye, including the challenges associated with sterility, toxicity, scaling-up, and obtaining regulatory approval of these systems. The future of ODDS will be characterized by the development of "smart" biomaterials that utilize artificial intelligence (AI) to optimize the formulation of ODDS, long-acting biodegradable implants, and the development of combination strategies that integrate multiple technologies to overcome barriers that impede the development of precision and personalized ocular therapeutics.

KEYWORDS: Ocular drug delivery, Corneal permeability, Nanocarriers, In-situ gels, Mucoadhesive systems, Ocular inserts Posterior segment delivery, Bioavailability, Nanotechnology

I. INTRODUCTION

Ocular drug delivery systems are classified as conventional and newer, or non-conventional, systems. These systems play an important role in preventing and treating diseases that may result in loss of vision.(1) (example: Eye drops and ointments are considered to be the most commonly used form of ocular drug delivery, however, they make up approximately 70% of all marketed dosage forms in ophthalmic drugs; their effectiveness is severely limited by the rapid turnover of tears, nasolacrimal drainage of the eye, and other natural defense mechanisms of the eye that remove

medications from the ocular surface almost immediately after application.)ka Therefore, the low bioavailability associated with the medications derived from topical applications (i.e. eye drops) is too low for effective outcomes, it can be less than 5% of active drug.(2) The low bioavailability associated with topical medications means that patients will require more frequent doses of medications, which results in both inconvenience to the patient and sub-optimal therapeutic outcomes. To counteract the limitations associated with low bioavailability, over the last several decades, there have been a number of advances in ophthalmic formulations aimed at providing sustained and controlled delivery of medications to the ocular surface and into the intraocular (within the eye) tissues, to increase the amount of drug that is delivered and sustained in the eye. There are several primary goals of these newer therapies: to provide for continuous, controlled, and prolonged release of drugs from a dosage form, to increase the amount of drug delivered from a dosage form (improved precision of dosing), and to minimize the adverse effects associated with the pulsed dosing mechanism.(3) The current review consolidates all of the information provided to evaluate and illustrate the anatomical and physiological barriers and limitations of the eye, evaluate the advantages and disadvantages of the conventional and advanced ocular drug delivery systems, provide the basic scientific and mechanistic principles of sustained/controlled release systems, and discuss and address future needs, opportunities, and challenges needed to transition as discussed above into standard medical and industrial use. (4)

II. LITERATURE SEARCH STRATEGY

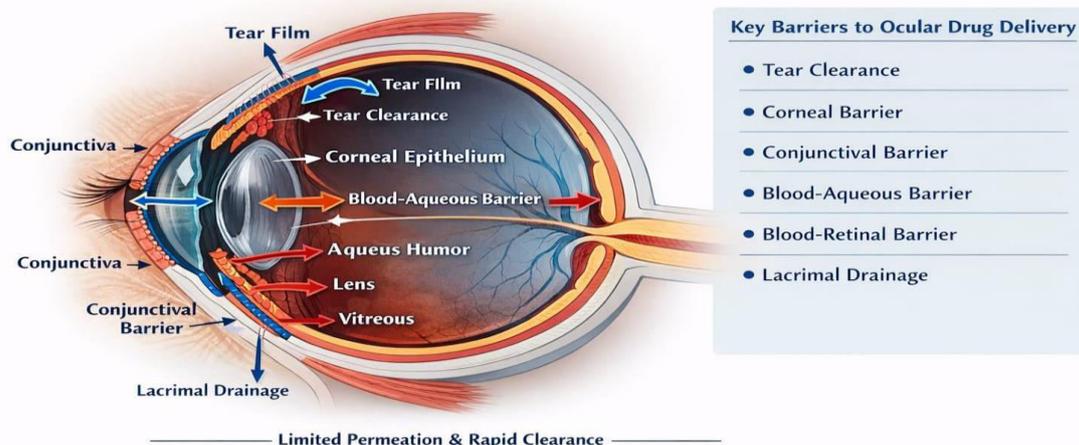
The literature search strategy for the proposed Scopus-oriented format indicates that a dedicated literature search strategy is essential to the document. This strategy includes establishing databases, search terms and the inclusion/exclusion criteria, as well as a time frame. The PRISMA-style flow describes how the review is positioned conceptually; it employs several major scientific databases to conduct the review, with the primary focus being the period of review for ocular drug delivery systems from 2010-2025 as per Scopus guidelines. As such, it follows a structured approach to identifying structured searches on ocular drug delivery systems, nanocarrier-based systems and gel-based formats, as well as posterior segment delivery systems through the implementation of Boolean-based search methodologies. A PRISMA-style flow will also illustrate the flow of records from their initial identification to final inclusion for review.(5)

Anatomy and Physiological Barriers in Ocular Delivery

The Eye's Physiology and Anatomical Barriers during Drug Delivery

There are many anatomy and physiology-related barriers to ocular drug delivery, which severely limit the ability of drugs to frequently enter through the tears or anterior chambers of the eyes.(6) As soon as drug solutions enter the eye after instillation into the conjunctival sac or posterior segment, they are rapidly removed by the lacrimal fluid, which has a turnover rate of approximately 1 μ l/min. The remainder is drained through the nasolacrimal duct, thereby resulting in massive losses from the total ocular bioavailability of a drug before it passes through the corneal tissue.(7) Significant losses occur also via systemic absorption from the capillaries of the conjunctiva and from the backflow of the drug into the nasal cavity, thereby contributing to extremely low local concentrations and, consequently, very low levels of overall effectiveness. The corneal epithelium is one of the most significant barriers to drug delivery in the anterior segment, in part, due to tight junctions found in the apical surface cells of the cornea which prevent the paracellular route of passage. Therefore, the cornea presents a rate-controlling site for drug delivery. (7)

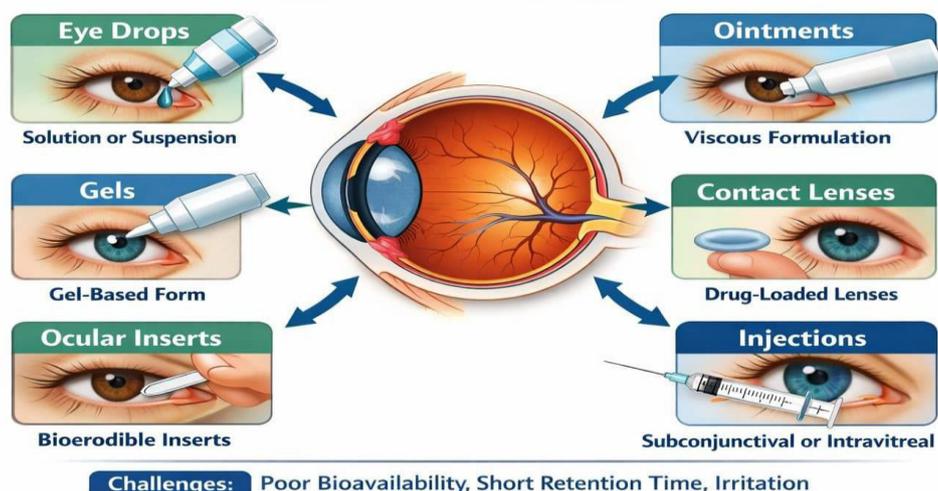
Anatomy and Physiological Barriers in Ocular Drug Delivery



III. CONVENTIONAL OCULAR DRUG DELIVERY SYSTEMS

Ocular Delivery Systems are typically used to treat illnesses of the eye and are formulated as liquid solutions (eye drops), as well as suspensions, ointments, and traditional gels with similar topically applied modes of administration.(8) These products are advantageous because they are simple to use and patients are generally accustomed to using them; however, they generally suffer from rapid clearance from the precorneal region, poor adhesion and retention of the drug to the surface of the eye, and drainage of the drug through the nasolacrimal duct and sinuses.(1) Therefore, the quantity of administered drug that reaches the intraocular tissues is significantly reduced from the amount initially dosed due to these barriers and rates. The bioavailability of drugs from standard topical administrations is frequently less than 5%.(9) Frequent dosing with low amounts of the drug in the eye caused by poor (10)retention of drugs and limited penetration into the eye by conventional methods makes it difficult for patients to maintain consistent therapeutic drug concentrations, leading to increased risk of systemic exposure and fluctuating drug levels. In addition, these drawbacks have led to an increased focus on creating other types of delivery systems that can help improve patient drug retention, control the rate of release, penetrate the eye more effectively, and allow for ease of use, all while enhancing comfort levels and ease of administration. (9)

Conventional Ocular Drug Delivery Systems



IV. ADVANCED OCULAR DRUG DELIVERY SYSTEMS

Systems for the advanced delivery of drugs directly to the eye are designed to address the limitations of conventional ocular drug formulations by providing longer durations of drug action at the site of intended therapeutic use; better penetration into the eye via both the cornea and other tissues (non-corneal routes); and targeted delivery of drugs through controlled or targeted release.(3)

Ocular inserts provide a solid dosage solution that ensures adequate drug levels can be delivered to the intended part of the eye for a longer period of time than with regular drops.(1) These types of systems act as prolonged-release (sustained-released) systems, providing either an undissolvable (insoluble) method of drug delivery, such as Ocusert® pilocarpine, or a dissolving (erodible) method of delivery, with products like collagen shields.(1) Lacrisert® is a type of hydroxypropyl cellulose (HPC) pellet used to treat the condition known as dry eye syndrome There have been significant developments in both biodegradable or non-biodegradable types of ocular inserts that can now reduce the frequency of administering drugs when compared to typical drops while providing a more consistent therapeutic level and dose sustained over time. (3)

In-situ gel formulations are injected as low-viscosity liquids and then turn into rigid gel-like structures because of certain external stimuli acting upon them when injected into a conjunctiva. These external triggers can be changes in the conjunctival cul-de-sac's temperature, the chemical make-up of the body fluids surrounding the conjunctival cul-de-sac, pH level etc.(8) Formulations of in-situ gels include hybrids of solubilized and gelforming materials that take advantage of a combination of improved absorption through the ocular mucosal membrane with a longer duration of effective absorption for the administered drug. Examples include niosomes or other vesicles incorporated into an in situ gel matrix.(11) Increasing the number of individual carriers allows for greater surface area/volume for dispersion. Nanocarriers include nanoparticles, nanocapsules, nanosuspensions. Compared to simple eye drop formulations, the use of nanocarriers significantly increases the rate of ocular drug absorption. A particle size of 200 nanometers or less is typically considered a favorable range for penetration into ocular tissue through the conjunctival and/or scleral membranes.(12) The size range of nanomicelles (5 to 100 nanometers) allows for the encapsulation of lipophilic drugs in their hydrophobic cores while being able to maintain their dispersible nature in aqueous formulations. Ocular targeted nanoparticles can be coated with mucoadhesive agents (to enhance adhesion to the ocular surface) and/or coated with a permeability enhancer (to slow the rate of elimination), both of which will improve the probability of ocular delivery through the transepithelial or transepithelial route.(13)

Liposomes are small vesicles with a phospholipid bilayer that encapsulates an aqueous core. Because they are classified as lyotropic liquid crystals, they can take on many different shapes and sizes.(14) Their structure provides an excellent means of encapsulating both hydrophilic (water soluble) drugs within their aqueous interior and lipophilic (fat soluble) drugs inside their lipid bilayers and/or at their lipid-aqueous interface. Because of their versatility as drug-delivery vehicles, they are commonly used for the delivery of both hydrophilic and lipophilic drugs.(15)

Typically, commercial liposome formulations include approximately 30 mol% of cholesterol, which can alter the rigidity of the liposomal membrane and make it more stable in serum.(14) Biologically with respect to their native lipid compositions, liposomes exhibit a relatively low intrinsic toxicity, biodegradability, and weak immunogenicity compared to their synthetic counterparts.(16)

The physicochemical properties of liposomes have a significant impact on liposome stability and biological properties (in vivo). The fluid characterization of the lipid bilayer is defined by a phase transition temperature; the Lipid bilayer can form a gel-like structure (gel phase) below this transition temperature and form a continuous (fluid) structure above The Phase Transition Temperature.(17) The Chain Length and saturation of the fatty acids determine the phase transition temperature. In addition to their size, the clearance and distribution of unilamellar vesicles are influenced directly by the vesicle size; hence the most commonly used size range for systemic delivery is from 50 nm to 100 nm, as exemplified by the AmBisome liposome, which has been formulated to be between 45 nm and 80 nm in diameter to minimize the amount of drug taken up by the reticuloendothelial system.(9)

Modulation of surface charge can thus affect the biological activity of liposomes. For example, neutral liposomes have a relatively low level of clearance from the reticuloendothelial system but can form aggregates.(11) In contrast, negatively charged liposomes have higher levels of non-specific uptake but also offer greater suspension stability than

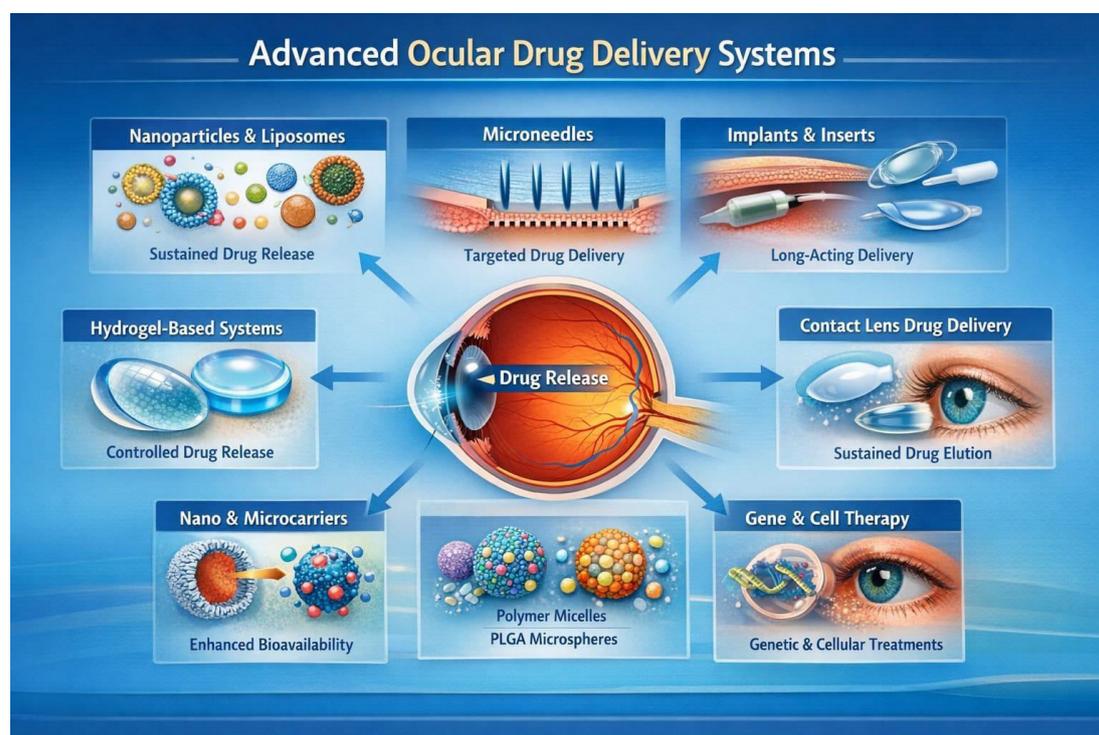
neutral liposomes. In addition, cationic (positively charged) liposomes exhibit significant interactions with serum proteins. (18) Cationic liposomes are continuously taken up by clearance organs, such as the liver, spleen, and lung, at very high levels. For ocular delivery of drugs, cationic liposomes may potentially improve drug retention time and local drug concentrations due to their ability to adhere to the negatively charged corneal surface. However, stability will be a significant concern when developing cationic liposomes for ocular delivery.

The use of surface modified materials by using hydrophilic polymers such as poly(ethyleneglycol)'s (PEG) have been shown to produce 'stealth liposomes' that are sterically stabilised and thus produce a reduced recognition by phagocytic cells. (18) PEGylated liposomes have a long circulation time due to high content of the PEG, which generally ranges between 5 and 10 mol%. (19) Liposomes have an upper size limit of approximately 150–200 nm and thus are suitable for delivery to areas of the body that contain deteriorated blood vessels and for systemic and potentially ocular applications.

Niosomes (like liposomes) are vesicular systems that consist of cholesterol and surfactants that are mostly non-ionic and not made from phospholipids. Their use increased after their introduction onto the cosmetics market and they quickly became recognized as viable vehicles for delivering pharmaceutical products, due to increased chemical stability and durability when compared to liposomes, more economical to manufacture, longer shelf-life and good compatibility with living organisms because they use nonionic materials. (20) The typical components of niosomes include surfactants from the Tween group, Span group, and cholesterol for rigidity and membrane shape, and optionally charge inducers for stabilisation of the niosomes and drugs encapsulated within them (e.g. dicetyl phosphate, chitosan). Niosomes have bilayer structures which allow both hydrophilic and lipophilic drugs to be encapsulated in their structure, which also supports stabilising agents being created and enabling controlled and sustained release of the agent. (17) Proniosomes are a type of niosome formed after hydration of proniosome gels and represent an improved formulation in terms of handling, topical performance, stability and potential use in ocular or transdermal products.

Systems that utilize mucoadhesion and other types of delivery mechanisms Mucoadhesive formulations for ocular use typically utilize polymers, including macromolecular hydrocolloids, to extend the amount of time that a drug remains at a site of action and to increase the availability of the drug to be absorbed into the body by binding non-covalently with mucin and increase the amount of time. In addition to macromolecular hydrocolloids, many researchers have tested the use of polyacrylic acid (PAA) as an ocular formulation vehicle because of its resistance to the natural drainage mechanisms and lacrimation that are present in the human eye while providing comfort to the patient. (2) Ocular iontophoresis is a non-invasive technique that utilizes a direct current applied to the dosage form during its application in order to drive the anionic drug molecules through the ocular tissues for more rapid therapeutic response time, i.e. painless, site-specific delivery of the correct type of drug molecule. Microneedle systems create micro-channels (usually in the sclera) through which drugs can be delivered directly to the site of action and minimally invasively (13). These systems are capable of delivering drug solutions, microparticles, or nano-sized particles, and directly address one of the greatest issues in treating patients with ocular drugs - getting the drug to the site of action efficiently and with sustained release for a prolonged period of time. (11)

Solid ocular inserts utilize different physicochemical mechanisms to provide sustained (controlled) release of drugs to the ocular tissues and the tear film. Examples of diffusion-based systems include those that provide continuous release of drugs by diffusing through a porous material such as a membrane or matrix. (20) The non-erodible devices allow the diffusion of drug through the porous area and the soluble devices provide for drug release that is controlled by the swelling and relaxation of the polymer, with the drug subsequently diffusing out of the device. Osmotic systems are composed of two chambers separated by an impermeable elastic membrane. (21) Upon an increase in water influx into the solute-containing compartment, the elastic membrane stretches and compresses the drug reservoir while forcing the drug through a small opening in the membrane. Bioerodible inserts consist of a biodegradable material matrix in which the drug is uniformly dispersed throughout. The release of the drug is sustained as the matrix material undergoes surface erosion or hydrolytic degradation. Bioerodible inserts provide sustained release approximating zero-order kinetics by maintaining the drug at nearly constant concentrations within the ocular tissues and the tear film throughout the duration of therapy. (22)

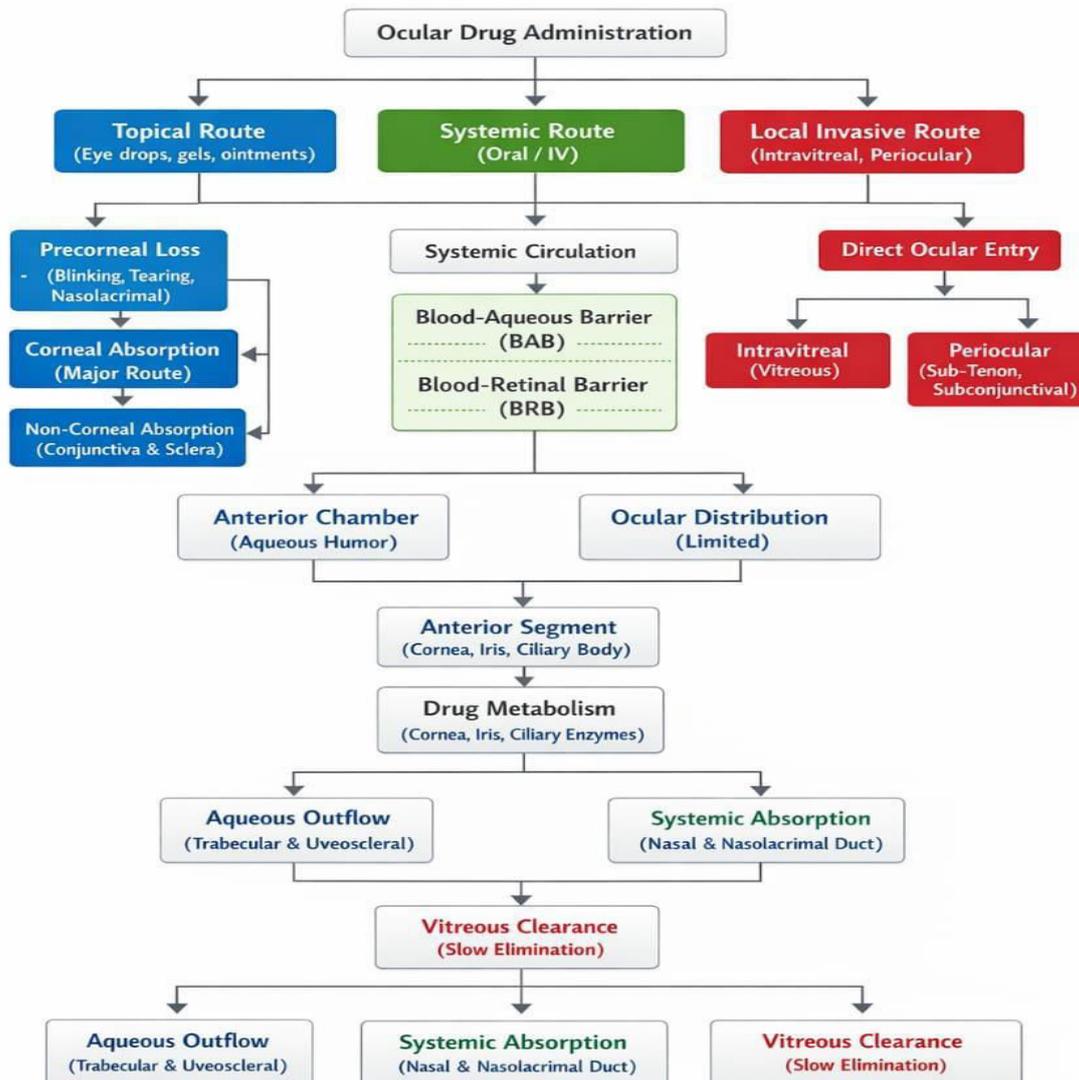


V. ROUTES OF OCULAR DRUG ABSORPTION & PHARMACOKINETICS

The Most Important Routes of Ocular Delivery Routes Choose Ocular Delivery Routes According to the Target site of the Ocular Drug and the Physicochemical Properties of the Ocular Drug.(2) Transcorneal Delivery Route will primarily target anterior chambers, as well as, iris/ciliary bodies and highly favors small lipophilic molecules with high lipophilicity(most common molecules used in topical eye drops will be <1000 daltons and peak concentrations of ocular eye drops delivery occur approximately) 20-30 minutes after installation of topical eye drop. (8)

Methods of delivering therapeutic agents to ocular sites via non-corneal routes through the conjunctiva or sclera are effective in delivering therapeutic agents to anterior segments (anterior uvea) and posterior segments (posterior segment structures) of the eye, and are particularly useful for large, hydrophilic molecules (e.g., peptide and protein substances).(7) Studies suggest that scleral routes may be 10 times more permeable to drugs than corneal routes, and that even large molecular weight compounds may be absorbed through the sclera, although topical drug delivery using these routes is limited by systemic loss of drug; intravitreal (IVT) injections access the vitreous body and retina directly by bypassing any potential barriers, but due to the complexity of subsequent distribution of drug to the choroid through the retinal pigment epithelium barrier and eventual elimination from the retina, the IVT injection route has its own limitations with respect to drug delivery to the choroidal structures, i.e., anterior and posterior pathways of elimination.(6) Subconjunctival (SCJ) administration also allows for high concentrations of drug in the anterior uvea and posterior segment tissues through penetration through the sclera and use of the scleral transport system, which do not rely on lipophilic properties and can transport large molecules, but this method serves to facilitate drug delivery to an intermediate degree between topical and IVT routes.(6)

Routes of Ocular Drug Absorption & Pharmacokinetics



Recent Advances (Last 5-7 Years)

New Developments: The outline for new developments in the field of ocular drug delivery highlights a number of innovative technologies under investigation, including biomimetic nanocarriers, stimuli-responsive formulations (for example, responsive to changes in pH, temperature, ions or enzymes), dendrimers, AI/ML optimization, smart contact lenses, hybrid (i.e., combination) systems.(18) The use of biomimetic nanocarrier and stimuli-responsiveness (for example, being responsive to pH, temperature, ions or enzymes) is discussed as an approach to match physiological conditions to enhance site specific delivery of therapeutic agents. An example of a hybrid delivery system is niosomal in-situ gel, where vesicular systems (i.e., niosomes) are combined with stimuli-sensitive gelling agents, thus combining the benefits (for example, loading capacity, controlled release, retention, and accuracy of targeting) of both delivery technologies.(21) Smart contact lenses and three-dimensional (3D) ocular inserts are identified as additional innovative platforms that combine drug reservoirs with optical or structural components to create sustained therapeutic benefit while allowing visual functionality and comfort.(2)

Examples of the clinical use of vesicular systems are provided in detail by this document, with many examples related to the systemic use of liposomal formulations indicating the applications of these systems in an ocular context. Vesicular systems demonstrate their potential for clinical use by providing clinically approved liposomal drugs (Doxil (pegylated liposomal doxorubicin) and DaunoXome (liposomal daunorubicin) used in the treatment of Kaposi sarcoma and some cancers); Adverse drug reactions with certain antifungal drugs (AmBisome, Abelcet, and Amphotec are all amphotericin B formulations with improved safety profiles compared to standard amphotericin B).(23) An alternative liposomal formulation used as a non-viral gene delivery system (the cationic liposome) could prove beneficial as it combines the cationic lipid and the neutral phospholipid (dioleoylphosphatidylethanolamine to create a complex with DNA via electrostatic interaction). An example of a liposome-based vaccine is the hepatitis A vaccine Epaxal, which demonstrates the ability of vesicular carriers to deliver antigens to macrophage-rich tissues, thereby increasing antigen presentation and immune responses.(18) This principle could be applied to the development of controlled and targeted immunotherapies for ocular conditions. By providing improved stability, a more cost-effective and versatile composition (provided that the niosomal vesicle is formed from non-ionic surfactants) than liposomes, niosomes are also a viable vesicular platform for drug delivery. Niosomes can encapsulate both hydrophilic and lipophilic drugs, enhance penetration (including that of drugs delivered through the skin), and sustain controlled release; therefore, they are well-suited to meet the requirements for the effective delivery of ocular drugs.

Ocular Inflammation Induced by Medication and Treatment for Ocular Inflammation with Medication Approximate The connection between the systemic exposure to medication and the local exposure to medication as a cause of ocular inflammation are inherent in ophthalmic therapeutics.(24) Many medications have been implicated in causing ocular inflammation, such as uveitis and orbital inflammation, with some of the medicines that can cause inflammation being systemic medications including cidofovir, sulfonamides, rifabutin, bisphosphonates and Intraocular medications including vascular endothelial growth factor (VEGF) inhibitors as well as cidofovir. Medications prescribed topically to decrease intraocular pressure, including brimonidine, metipranolol and prostaglandin equivalents, are also implicated in causing ocular inflammation. Patients that develop anterior uveitis while using brimonidine typically present with various periods of onset ranging from one week to five years.(6) Anterior uveitis is typically associated with diffuse stellate keratic precipitates in the eye and is sometimes accompanied by mild anterior chamber inflammation or elevations in intraocular pressure in the affected eye. These features of anterior uveitis can frequently lead to misdiagnosis as herpetic uveitis or Fuchs uveitis. Discontinuing the use of brimonidine will usually resolve the anterior uveitis within a few days to a few weeks which will help clinicians to appropriately assess for any other potential causes of ocular inflammation by taking a detailed medication history in order to make appropriate diagnosis.(3)

The onset of bisphosphonate-related inflammation following intravenous administration of zoledronate occurs in the orbital area with extraocular muscle involvement or at the orbit's apex; however, there are also cases of bilateral uveitis, which can occur with pamidronate. Immune checkpoint inhibitors (especially ipilimumab and anti-PD-1) have been implicated in ocular and orbital inflammatory processes including uveitis and peripheral ulcerative keratitis, which are part of the immunologic side effects associated with this class of drugs. (3)There are important implications for systemic therapy on ocular health given the association with ocular and orbital inflammation. Topical corticosteroids are standard therapies for ophthalmic inflammatory conditions due to allergies, infections, uveitis, trauma, or surgical intervention. However, conventional topical corticosteroids have substantial risks associated with their use including increased intraocular pressure, steroid glaucoma, cataracts, and other complications. (22)Soft corticosteroids (e.g., loteprednol etabonate and etiprednol dicloacetate) have been developed by retrometabolic strategies to maintain their potency and efficacy while undergoing rapid metabolic breakdown to non-active forms of themselves to decrease systemic exposure and minimize adverse consequences related to prolonged elevation of intraocular pressure.

VI. CHALLENGES AND LIMITATIONS

The ultimate goal of a successful ocular drug delivery system is to provide sustained therapeutic levels of drug at the target tissues, while minimizing drug exposure throughout the entire body and providing as much patient acceptability.(16) To date, many of the challenges and limitations that impede the development of these systems are as follows: Difficulty in getting medication into the posterior segment of the eye; stability problems with the particulate drug delivery systems (i.e., Nano-particles, Liposomes) and; technological limitations that preclude the ability to manufacture sustained-release formulations simply and at a reasonable cost. Manufacturing difficulties (i.e., process complexity as well as reproducibility) can be a significant barrier to the production and commercialisation of promising sustained-release ocular products. (16)Developing sustained-release formulations using particulate delivery systems

presents unique technical challenges and will be subject to the most stringent sterility and stability requirements imposed by regulatory agencies. Additional barriers to the development and successful translation of innovative technologies for the delivery of ocular drugs include concerns of toxicity from polymers used in the delivery systems, along with surfactants and excipients, as well as excess uncertainty surrounding the regulatory status of those products due to the limited number of large-scale clinical trials.(3)

VII. FUTURE DIRECTIONS

Combining complementary technologies such as liposomes/ nanoparticles in combination with bioadhesive polymers or droppable in situ gelling systems is a rational way to address individual technology limitations to achieve synergistic benefits such as enhanced stability, prolonged residence time, and localized release.

The emerging areas of ocular drug delivery research highlighted in this report are: 1) The development of smart, responsive biomaterials that can dynamically react to a patient's eye microenvironment; 2) development of precision ocular therapeutics, which takes into account each patient's individual needs; and, 3) The use of Artificial Intelligence (AI) tools to help predict permeability and release profiles for ocular therapeutic formulations to help guide the formulation process.(15)

Some key areas of focus for future research and development in ocular drug delivery include long-acting biodegradable implants, gene/ peptide delivery systems, and new methods for crossing the barrier to the posterior segment of the eye.

Roadmaps for ocular drug delivery solutions that are accessible to patients include personalized therapies, commercialization channels that consider the issues associated with manufacturing, cost, and regulatory compliance.(21) Hybrid platforms such as niosomal in situ gelling systems and smart contact lenses will form the basis of a comprehensive ocular drug delivery solution.”(13)

VIII. CONCLUSION

Advanced drug delivery methods face many difficulties due to the eye's natural defensive systems and rapid cleaning processes that limit the use of traditional topically applied drugs for prolonged timeframes between doses and low levels of drug in the eyepiece. Many new advanced drug delivery methods consist of nanocarriers, liposomes, niosomes, in-situ gels, ocular inserts and microneedle delivery systems which permit extended residence time, controlled-release and targeted delivery to both anterior and posterior segments, but translate poorly due to stability issues, toxicity, complicated user/manufacture instructions, and the uncertainty surrounding the approval of any of the delivery methods.(17) Future knowledge will result in the combination of information and innovation in developing long-lasting ocular therapeutics that meet the unmet needs specified in this document by integrating hybrid technologies and incorporating new developments in nanotechnology into the current and future markets.

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