Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 8 Issue 6 June 2024

Review Article

Advances and Challenges in Ocular Drug Delivery Systems: A Comprehensive Review

Khushi Verma[1], Rajesh Kumar Nema[1]*, Harish Sharma[2] and Gyanesh Kumar Sahu[1]

[1]*Rungta Institute of Pharmaceutical Sciences, Kohka (C.G), India*

[2]*Rungta Institute of Pharmaceutical Sciences and Research, Kohka (C.G), India*

***Corresponding Author:** Rajesh Kumar Nema, Principal, Rungta Institute of Pharmaceutical Sciences, Kohka (C.G), India.

DOI: 10.31080/ASPS.2024.08.1062

Received: April 08, 2024

Published: May 02, 2024

Abstract

Eye diseases are commonly encountered in day-to-day life, which are cured or prevented through the conventionally used dosage forms like eye drops, ointments. Delivery to the internal parts of the eye still remains troublesome due to the anatomical and protective structure of the eye. The newly developed particulate and vesicular systems like liposomes, pharmacosomes and discomes are useful in delivering the drug for a longer extent and helpful in reaching the systemic circulation. The most recent advancements of the ocular delivery systems provide the delivery of the genes and proteins to the internal structures which were once inaccessible and thus are of great importance in treating the diseases which are caused due to genetic mutation, failure in normal homeostasis, malignancy but also maintaining the physiological function of eye. The review focuses on the developments achieved in this mode of delivery of the drugs along with the pros and cons associated with greater focus on the advanced delivery systems.

Keywords: Advance Ocular Therapy, Control Drug Delivery Systems, Corneal Permeability, Iontophoresis; Eye; Hydrogel

Introduction

The field of ocular drug delivery has undergone a remarkable evolution in response to the intricate challenges posed by the unique anatomy and physiology of the eye. The intricate structure of the eye, comprising multiple barriers and dynamic fluid dynamics, necessitates innovative approaches to ensure the effective and targeted delivery of therapeutic agents. As we delve into the current status and advancements in ocular drug delivery systems, it becomes evident that traditional methods, while widely employed, often encounter limitations such as low bioavailability, short residence times, and patient compliance issues [1].

Current ocular drug delivery relies heavily on conventional formulations, including eye drops, ointments, and injections. While these methods have proven effective for certain conditions, their shortcomings, such as rapid clearance by tears and the need for frequent administration, underscore the need for more sophisticated and tailored approaches. Recognizing these challenges, researchers and pharmaceutical innovators have embarked on a journey to explore cutting-edge technologies and materials, paving the way for advanced strategies that hold the promise of revolutionizing ocular therapeutics [2,3].

In this dynamic landscape, nanotechnology emerges as a beacon of progress, offering nanoparticulate systems designed to enhance drug solubility, stability, and bioavailability. The ability of nanoparticles to facilitate sustained release and improve drug penetration makes them a focal point for overcoming the limitations of traditional formulations. Complementing this, *in situ* gels present a novel solution, undergoing a phase transition upon ocular contact to form a gel that adheres to ocular tissues, thereby extending drug release and addressing the challenge of short retention times [4].

Beyond these innovations, the integration of drug-releasing materials into contact lenses and ocular inserts provides a tangible shift towards patient-centric drug delivery. These technologies

promise prolonged drug release, mitigating the need for frequent administration and improving overall patient compliance. Furthermore, the exploration of iontophoresis and electroporation introduces methods leveraging electrical currents to enhance drug penetration, offering an avenue to overcome barriers that hinder effective drug delivery to ocular tissues [5,6].

The advent of cell-penetrating peptides and gene therapy introduces a paradigm shift towards precision medicine in ocular therapeutics. These approaches aim to enhance cellular uptake of drugs and target the underlying genetic causes of ocular diseases, representing a frontier where innovation meets the intricacies of ocular biology [7].

In this comprehensive exploration of current status and advanced approaches in ocular drug delivery systems, it becomes evident that the convergence of diverse technologies holds immense potential to transform the treatment landscape for a myriad of ocular conditions. As we navigate this frontier, the synthesis of innovative materials, personalized medicine strategies, and smart drug delivery systems with monitoring capabilities emerge as pivotal elements in reshaping the future of ocular therapeutics. The following discourse delves into the intricate details of these advanced approaches, offering insights into their mechanisms, benefits, and the transformative impact they bring to the forefront of ocular drug delivery research and development [8].

The rapid progress of the biosciences opens new possibilities to meet the needs of the posterior segment treatments. The examples include the antisense and aptamer drugs for the treatment of cytomegalovirus (CMV) retinitis and age-related macular degeneration, respectively, and the monoclonal antibodies for the treatment of the age-related macular degeneration. Other new approaches for the treatment of macular degeneration include intravitreal small interfering RNA (siRNA) and inherited retinal degenerations involve gene therapy[9]. This review article briefly covers general outline with examples of various conventional and recent past time formulations for ophthalmic drug delivery. it also provides the limitations of conventional delivery with a view to find modern approaches like vesicular systems, nano technology, stem cell therapy as well as gene therapy, oligonucleotide and aptamer therapy, protein and peptide delivery, ribozyme therapy for treatment of various ocular diseases. Different drug delivery system for ocular therapy is shown in figure 1 [10].

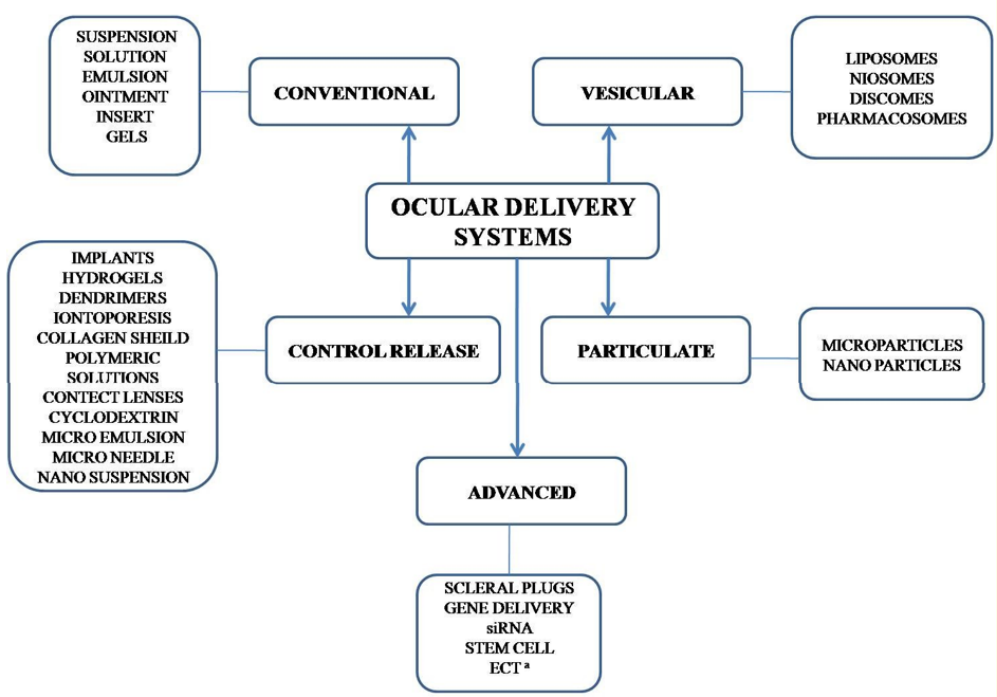

Figure 1: Different drug delivery systems for ocular therapy.

Topical delivery systems	Intraocular delivery	Reference
Solutions	Inserts	11
Suspensions	Implant	12
Gels - degradable - in situ-forming gels	- degradable - non-degradable	13
Ointments	Micro/nanoparticulates	14
Mucoadhesive polymers		
Conjunctival inserts		
Contact lenses		
Micro/nanoparticulates		

Table 1: Main Types of Ocular Delivery Systems.

Control delivery systems

Implants in ocular drug delivery

Implants represent a significant advancement in ocular drug delivery, offering a targeted and sustained-release approach that addresses some of the limitations associated with conventional delivery systems. These devices, typically small and biocompatible, are strategically placed within or around the eye to provide controlled release of therapeutic agents over an extended period. The utilization of implants has gained prominence in the treatment of chronic eye conditions, providing a promising alternative to frequent administration and improving patient compliance [15].

Types of ocular implants

Intravitreal implants

- Implanted into the vitreous humor of the eye.
- Provide sustained release of drugs directly to the retina.
- Commonly used for conditions like diabetic macular edema and retinal vein occlusion.

Scleral implants

- Placed in the sclera, the outer white layer of the eye.
- Offer localized drug delivery while avoiding the complexities of intravitreal administration.
- Used for conditions such as uveitis and glaucoma.
- Subconjunctival Implants:
- Positioned beneath the conjunctiva, the clear membrane covering the white part of the eye.
- Release drugs into the subconjunctival space for gradual absorption.
- Suitable for treating conditions like inflammation and infections [16].

Iontophoresis

Iontophoresis is an innovative and non-invasive technique employed in ocular drug delivery, utilizing the application of a low electrical current to enhance the penetration of therapeutic agents across ocular tissues. This method has garnered attention for its ability to overcome barriers that limit traditional drug delivery, offering a promising solution to improve drug permeation and bioavailability within the eye [17].

Mechanism of iontophoresis

During iontophoresis, a small electric current is applied to the ocular surface, typically through an electrode-containing drug reservoir. The electric field generated facilitates the movement of charged drug molecules across the cornea and other ocular barriers. This process can enhance drug penetration, enabling more efficient delivery to targeted tissues within the eye [18].

Key features of iontophoresis

Enhanced drug permeation

- Iontophoresis improves the permeability of ocular tissues, overcoming natural barriers that limit drug absorption [18,19].

Controlled drug delivery

- The application of an electric current allows for precise control over the rate and duration of drug delivery, optimizing therapeutic outcomes.

Reduced systemic exposure

- By directly targeting ocular tissues, iontophoresis minimizes systemic exposure, lowering the risk of side effects in other parts of the body [19].

Non-invasiveness

- Iontophoresis is a non-invasive method, eliminating the need for injections or surgical procedures, which can enhance patient acceptance [19,20].

Versatility

- This technique is adaptable for a wide range of drugs, making it suitable for treating various ocular conditions.

Dendrimers

Dendrimers, a class of hyperbranched, well-defined, and three-dimensional macromolecules, have emerged as promising nanocarriers in the field of ocular drug delivery. These nanostructures,

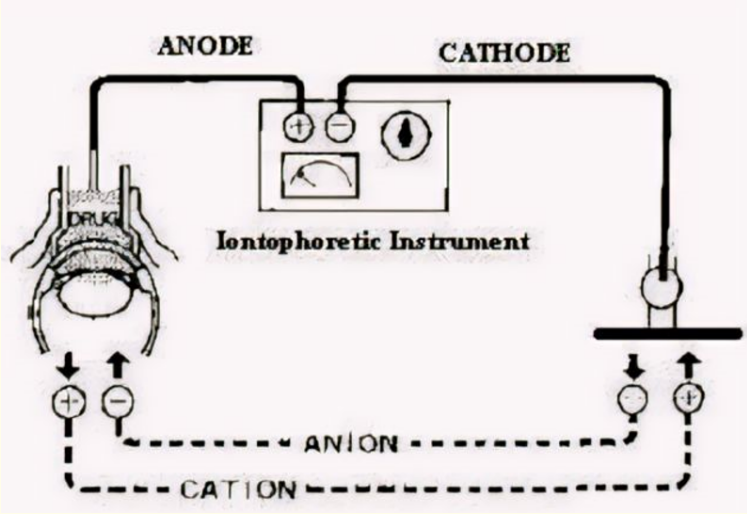

Figure 2: Diagram of ocular iontophoresis delivering a positively charged drug.

characterized by a central core, repeating units, and terminal functional groups, offer unique properties that make them suitable for encapsulating and delivering therapeutic agents to the eyes [20].

Key characteristics of dendrimers

- **Nanostructure**: Dendrimers possess a well-defined and compact nanostructure, allowing for precise control over size, shape, and surface functionality.
- **Multivalency:** Terminal functional groups enable multivalent interactions, facilitating drug encapsulation and controlled release.
- **Biocompatibility:** Dendrimers can be engineered to be biocompatible and exhibit low cytotoxicity, essential for applications in ocular drug delivery [21].
- **Versatility:** Dendrimers can encapsulate a variety of therapeutic agents, including small molecules, peptides, and nucleic acids, making them versatile carriers for different types of drugs.
- **Cyclodextrins:** Cyclodextrins, a family of cyclic oligosaccharides composed of glucose units, have found significant applications in the realm of ocular drug delivery. Their unique molecular structure, characterized by a hydrophobic central cavity and hydrophilic outer surface, enables them to form inclusion complexes with a variety of drugs. This property makes cyclodextrins versatile carriers for enhancing the solubility, stability, and bioavailability of therapeutic agents, particularly those with limited water solubility [22].

Key characteristics of cyclodextrins

- **Inclusion Complex Formation:** Cyclodextrins can form inclusion complexes with lipophilic drugs, increasing their aqueous solubility and bioavailability [23].
- **Biocompatibility:** Generally recognized as safe (GRAS) by regulatory authorities, cyclodextrins are biocompatible and suitable for various pharmaceutical applications.
- **Surface modification:** The outer surface of cyclodextrins allows for functionalization, enabling targeted drug delivery and controlled release.
- **Versatility:** Cyclodextrins can encapsulate a wide range of drugs, including small molecules, peptides, and proteins [24].

- **Contact:** Contact lenses, traditionally used for vision correction, have evolved into innovative platforms for ocular drug delivery. These devices offer a non-invasive and patient-friendly approach, providing sustained and controlled release of therapeutic agents directly to the ocular surface. The integration of drug-releasing materials into contact lenses addresses the challenges associated with traditional ocular drug delivery methods and enhances patient compliance [25].

Key features of drug-releasing contact lenses

- **Material selection:** Contact lenses are made from materials that allow for the incorporation of drug-releasing components, such as nanoparticles or hydrogels.
- **Sustained drug release**: Drug-releasing contact lenses provide controlled and prolonged release of therapeutic agents, reducing the need for frequent administration.
- **Customizable design**: Contact lenses can be engineered to release different drugs at specified rates, catering to the requirements of specific eye conditions.
- **Comfortable wear:** Patients find drug-releasing contact lenses comfortable to wear, promoting better compliance compared to other ocular drug delivery methods [26].
- **Collagen shield:** A collagen shield, also known as a collagen corneal shield or collagen bandage, is a medical device made from collagen materials that is designed to protect and support the cornea, particularly after certain eye surgeries or in cases of corneal injuries. These shields are thin, transparent, and conformable, resembling a contact lens, and they can be placed directly onto the surface of the eye [27].

Key Features and Applications of Collagen Shields

- **Material Composition:** Collagen shields are typically composed of purified collagen derived from animal sources, such as bovine or porcine collagen.
- **Conformability:** These shields are flexible and conform to the shape of the cornea, providing a comfortable fit.
- **Biodegradability:** Collagen shields are biodegradable, gradually breaking down over time as the cornea heals.
- **Moisture retention:** The collagen material retains moisture, helping to prevent dryness on the ocular surface and promoting a suitable environment for corneal healing.
- **Protection and support:** Collagen shields are used to protect the cornea from mechanical irritation, such as blinking, and to provide support during the healing process after surgery or injury [28].
- **Microemulsions:** Microemulsions are thermodynamically stable colloidal systems composed of water, oil, and surfactant, often with the addition of a co-surfactant. These nanoscale droplets of oil dispersed in water (or vice versa) form transparent and isotropic solutions, offering unique properties that make them highly effective carriers for ocular drug delivery [29].

Key Characteristics of Microemulsions:

- **Nanoemulsion Structure:** Microemulsions consist of nanosized droplets (typically 10-100 nm) stabilized by surfactants, forming a thermodynamically stable and transparent system.
- **Enhanced Solubilization:** Microemulsions can solubilize both hydrophobic and hydrophilic drugs, overcoming the limitationof drug solubility in traditional formulations.
- **Improved Bioavailability:** The nanoscale droplets increase the surface area available for drug absorption, leading to enhanced bioavailability.
- **Thermodynamic Stability:** Microemulsions exhibit long-term stability without phase separation, ensuring consistent drug delivery over time [30].

Nanosuspensions: Nanosuspensions are submicron colloidal dispersions of drug particles in a liquid medium stabilized by surfactants or polymers. In ocular drug delivery, nanosuspensions have gained attention as effective carriers to overcome challenges related to poor drug solubility, low bioavailability, and limited penetration into ocular tissues [31].

Microneedles: Microneedles are minimally invasive devices with tiny needle-like structures that can penetrate the skin or mucosal surfaces, including the ocular surface, for the delivery of therapeutic agents. In ocular drug delivery, microneedles offer a novel approach to bypass barriers, such as the corneal epithelium, and deliver drugs directly to the targeted ocular tissues [32].

Key features and applications of microneedles include

- **Drug Delivery:** Microneedles are utilized to enhance transdermal drug delivery, enabling medications to be delivered through the skin in a less invasive manner compared to traditional injections.

- They can improve the bioavailability of certain drugs by bypassing barriers in the skin and targeting specific tissue layers.
- **Vaccination:** Microneedle-based vaccine delivery is being explored as an alternative to traditional needle and syringe injections. It offers potential advantages such as improved patient compliance, reduced needle phobia, and simplified administration.
- **Diagnostics:** Microneedles can be incorporated with sensors for diagnostic purposes. By collecting interstitial fluid or blood, they can provide real-time information about biomarkers or other analytes.
- **Cosmetic Applications:** Microneedle rollers or patches are used in cosmetic procedures to improve the absorption of skincare products and promote collagen production.
- **Research and Sampling:** In research settings, microneedles are employed for collecting small quantities of interstitial fluid or extracting biomolecules for analysis.
- **Pain Reduction:** Due to their smaller size and reduced nerve stimulation compared to traditional needles, microneedles may offer a less painful experience for patients.
- **Patch Technologies:** Microneedle patches, which typically consist of an array of microneedles on a patch, are being developed for various applications, including vaccine administration and continuous glucose monitoring.
- **Fabrication Techniques:** Microneedles can be fabricated using different materials and methods, including silicon, metals, and polymers. Fabrication techniques include lithography, micromolding, and laser cutting [33].

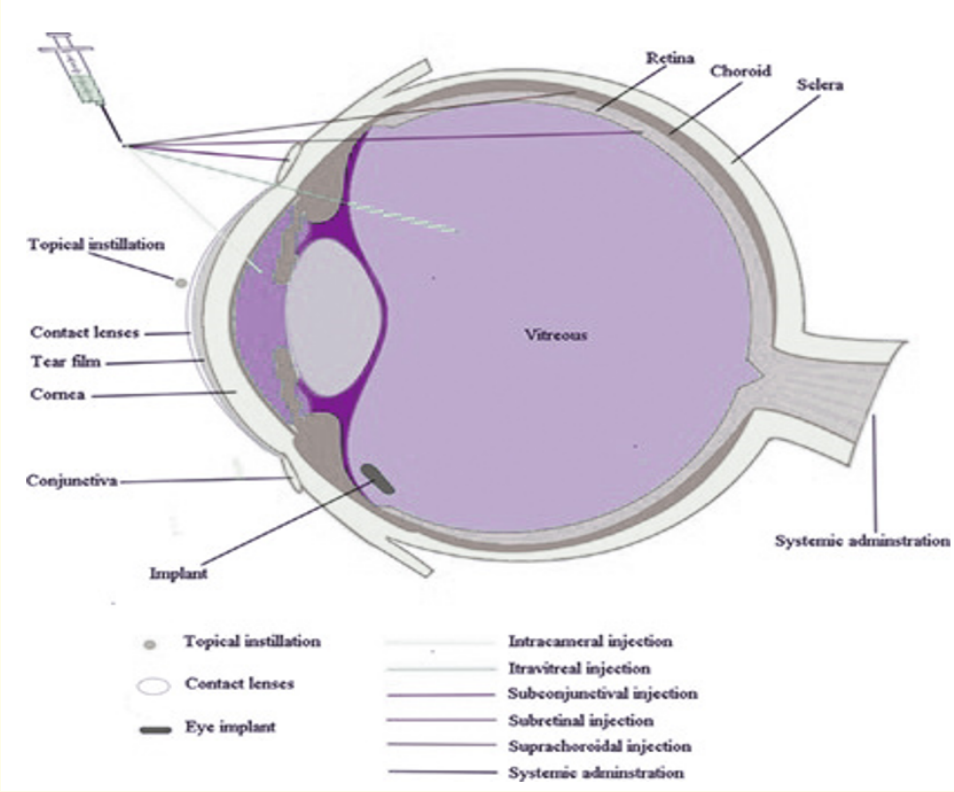

Figure 3: Ocular routes for drug delivery systems.

Prodrugs

Prodrugs are pharmacologically inactive compounds that undergo biotransformation in the body to release the active drug. In ocular drug delivery, prodrugs play a strategic role in improving the bioavailability, stability, and penetration of drugs to target tissues within the eye. The design of prodrugs allows for enhanced drug delivery while addressing challenges such as limited solubility, rapid metabolism, and poor tissue permeability [34].

Key features of prodrugs

Chemical modification: Prodrugs involve the chemical modification of the parent drug to create a derivative that is inactive or less active until it undergoes a specific enzymatic or chemical transformation in the body.

Enhanced lipophilicity or hydrophilicity: Prodrugs can be designed to enhance the lipophilicity or hydrophilicity of the drug, influencing its pharmacokinetics and tissue distribution [20].

Improved stability: Prodrugs can enhance the stability of the active drug, protecting it from degradation and improving its shelf life.

Targeted drug delivery: Prodrugs allow for targeted drug delivery by facilitating the release of the active drug at the desired site or within specific tissues [35].

Penetration

Penetration enhancers, also known as permeation enhancers or absorption enhancers, are compounds that improve the delivery of drugs across biological barriers. In ocular drug delivery, penetration enhancers play a crucial role in enhancing the permeability of drugs across the cornea and other ocular tissues. These enhancers can be employed to overcome the challenges associated with the protective barriers of the eye, such as the corneal epithelium, and improve the bioavailability of therapeutic agents [36].

Mucoadhesive

Mucoadhesive polymers are substances that adhere to mucosal surfaces, providing sustained contact and facilitating the delivery of drugs to these tissues. In ocular drug delivery, mucoadhesive polymers are utilized to enhance the residence time of therapeutic agents on the ocular surface, particularly the cornea and conjunctiva. This prolonged contact improves drug absorption and bioavailability, making mucoadhesive polymers valuable components in the development of ophthalmic formulations [37].

Key points about mucoadhesives

Applications

- **Drug delivery:** Mucoadhesive materials are commonly used in pharmaceuticals for controlled drug release. They can enhance the residence time of a drug at the site of administration, leading to improved absorption and bioavailability.
- **Medical devices:** Mucoadhesive properties are exploited in the development of medical devices, such as patches, gels, and films, that adhere to mucosal surfaces for prolonged therapeutic effects.
- **Topical formulations:** Mucoadhesive materials are used in various topical formulations, including gels and ointments, to improve adhesion and drug retention on mucosal surfaces.

Types of mucoadhesives

- **Synthetic polymers:** Synthetic polymers such as poly (acrylic acid) and polyethylene glycol can be modified to possess mucoadhesive properties.
- **Natural polymers:** Natural polymers like chitosan, alginate, and hyaluronic acid exhibit inherent mucoadhesive characteristics and are widely used in pharmaceutical formulations.
- **Thiolated polymers:** Polymers modified with thiol groups, such as thiolated chitosan, can enhance mucoadhesion due to interactions with mucin proteins.

Mechanisms of mucoadhesion

- **Adsorption:** Mucoadhesive materials can adhere to mucosal surfaces through non-specific interactions, such as hydrogen bonding, van der Waals forces, and electrostatic interactions.
- **Covalent bonds:** Some mucoadhesives form covalent bonds with mucosal proteins, leading to a stronger and more durable adhesion.
- **Hydration:** Swelling and hydration of mucoadhesive polymers can contribute to adhesion by facilitating interactions with the mucosal surface.

Benefits

- **Improved bioavailability:** Mucoadhesive drug delivery systems can enhance the absorption of drugs, leading to increased bioavailability.

- **Prolonged action:** The prolonged contact time provided by mucoadhesion allows for sustained release of drugs, reducing the frequency of administration.
- **Targeted delivery:** Mucoadhesive formulations can target specific mucosal sites, improving the therapeutic outcome [38].

Challenges

- **Variability in mucosal surfaces:** Mucosal surfaces can vary in composition and characteristics, making it challenging to design universal mucoadhesive formulations.
- **Biocompatibility:** Ensuring the biocompatibility of mucoadhesive materials is crucial to prevent irritation or adverse reactions at the application site.

In situ gel systems

In situ gel systems, also known as phase transition systems, are formulations that undergo a phase transition from a liquid to a gel state under specific physiological conditions. In ocular drug delivery, these systems are designed to improve the residence time of drugs on the ocular surface, enhancing drug absorption and bioavailability. The transition from a liquid to a gel phase can be triggered by factors such as temperature, pH, or the presence of ions, allowing for controlled and sustained drug release [39].

Key Features of *In Situ* gel systems

Thermosensitivity: *In situ* gel systems can exhibit thermosensitive properties, undergoing gelation in response to the temperature of the ocular surface.

pH-Dependent gelation: Some formulations undergo gelation in response to the pH of the tear fluid or ocular surface, leading to increased viscosity and prolonged drug retention.

Ion-Induced gelation: Certain formulations can undergo gelation in the presence of specific ions found in tears, providing a mechanism for *in situ* gel formation.

Ease of administration: These systems are often administered as liquid drops, ensuring ease of application, and then undergo a phase transition to form a gel [40].

Particulates (Nanoparticles and microparticles)

The maximum size limit for microparticles for ophthalmic administration is about 5-10 mm above which a scratching feeling in the eye can result upon ocular instillation. That is why microspheres and nanoparticles are promising drug carriers for ophthalmic application.39 Nanoparticles are prepared using bioadhesive polymers to provide sustained effect to the entrapped drugs. An optimal corneal penetration of the encapsulated drug was reported in presence of bioadhesive polymer chitosan.40 Similarly Poly butyl cyanoacrylate nanoparticles [41,42].

Advanced delivery system

Cell encapsulation

Cell encapsulation has shown promise as a novel approach in ocular drug delivery, offering unique advantages in protecting therapeutic cells and facilitating controlled release of therapeutic agents. While the field is still evolving, researchers are exploring the potential applications of cell encapsulation for treating various ocular diseases. Here are some key aspects of cell encapsulation in ocular drug delivery [43].

Gene therapy

Along with tissue engineering, gene therapy approaches stand on the front line of advanced biomedical research to treat blindness arising from corneal diseases, containing pilocarpine into collagen shields, showed greater retention and activity characteristics with respect to the controls. Nanospheres made up of poly lactic acid (PLA) coated with Poly Ethylene Glycol (PEG) shown better efficacy compared to conventional dosage form of Acyclovir for the treatment of ocular viral infections. Microspheres of poly lacto gylcolic acid (PLGA) for topical ocular delivery of a peptide drug vancomycin were prepared by an emulsification/spray-drying technique modified human RPE cells secretes ciliary neurotrophic factor into the vitreous humour of the patients' eyes [39]. ECT can potentially serve as a delivery system for chronic ophthalmic diseases like neuroprotection in glaucoma, anti-angiogenesis in choroidal neovascularization, anti-inflammatory factors for uveitis which are second only to cataract as the leading cause of vision loss. Several kinds of viruses including adenovirus, retrovirus, adeno-associated virus, and herpes simplex virus, have been manipulated for use in gene transfer and gene therapy applications. Topical delivery to the eye is the most expedient way of ocular gene delivery. However, the challenge of obtaining substantial gene expression following topical administration has led to the prevalence of invasive ocular administration [44].

Stem cell therapy in ocular regenerative medicine

Stem cell therapy holds significant promise in the field of ocular regenerative medicine, offering potential treatments for various eye diseases and conditions. Stem cells possess the unique ability to differentiate into different cell types, making them a valuable resource for repairing damaged tissues and promoting regeneration. In ocular applications, stem cell therapy is being explored for its potential to treat conditions affecting the cornea, retina, and other components of the eye [45].

Protein and peptide therapy in ocular diseases

Protein and peptide therapy is a rapidly evolving field with promising applications in the treatment of various ocular diseases. Proteins and peptides offer targeted therapeutic approaches, addressing specific molecular pathways involved in ocular disorders. Here's an overview of the use of protein and peptide-based therapies in ocular medicine [46].

Anti-VEGF therapies

- **Purpose:** Anti-vascular endothelial growth factor (VEGF) therapies are designed to inhibit abnormal blood vessel growth, a hallmark in conditions like age-related macular degeneration (AMD), diabetic retinopathy, and macular edema.
- **Examples:** Bevacizumab, ranibizumab, and aflibercept are monoclonal antibodies used to neutralize VEGF and are administered through intravitreal injections.

Neuroprotective peptides

- **Purpose:** Neuroprotective peptides aim to prevent or limit damage to retinal ganglion cells, offering potential therapeutic strategies for conditions like glaucoma.
- **Examples:** Brimonidine, a neuroprotective alpha-2 adrenergic agonist, has been investigated for its neuroprotective effects in glaucoma.

Corticosteroids

- **Purpose:** Corticosteroids have anti-inflammatory and immunosuppressive properties, making them useful in treating inflammatory conditions of the eye, such as uveitis.
- **Examples:** Dexamethasone and prednisolone are corticosteroids that can be administered topically or through intravitreal injections.

Growth factors

- **Purpose:** Growth factors play a role in tissue repair and regeneration. They are investigated for their potential in promoting healing and regeneration in ocular tissues.
- **Examples:** Epidermal growth factor (EGF) and fibroblast growth factor (FGF) are among the growth factors studied for their ocular therapeutic potential.

Peptide-based drug delivery systems

- **Purpose:** Peptide-based drug delivery systems enhance the delivery of therapeutic agents to specific ocular tissues, improving bioavailability and reducing systemic side effects.
- **Examples:** Peptide carriers, such as cell-penetrating peptides (CPPs), have been explored to improve the transport of drugs across ocular barriers.

Antimicrobial peptides

- **Purpose:** Antimicrobial peptides are investigated for their potential in treating ocular infections by disrupting the membranes of microbial pathogens.
- **Examples:** LL-37 is an antimicrobial peptide with broad-spectrum activity against bacteria and fungi [47].

Ribozymes

Ribozymes, with their ability to specifically target and cleave RNA molecules, have been explored as a potential therapeutic strategy for various ocular diseases. The targeted RNA cleavage offered by ribozymes presents an opportunity to modulate gene expression, inhibit the replication of specific RNA sequences, and potentially address molecular abnormalities associated with ocular disorders. Here are some key considerations and applications of ribozymes in the context of ocular diseases [48,49].

Retinal diseases

- **Angiogenesis inhibition:** Abnormal angiogenesis is a hallmark of retinal diseases such as diabetic retinopathy and neovascular age-related macular degeneration (AMD). Ribozymes can be designed to target RNA sequences associated with the overexpression of angiogenic factors, potentially inhibiting abnormal blood vessel formation.

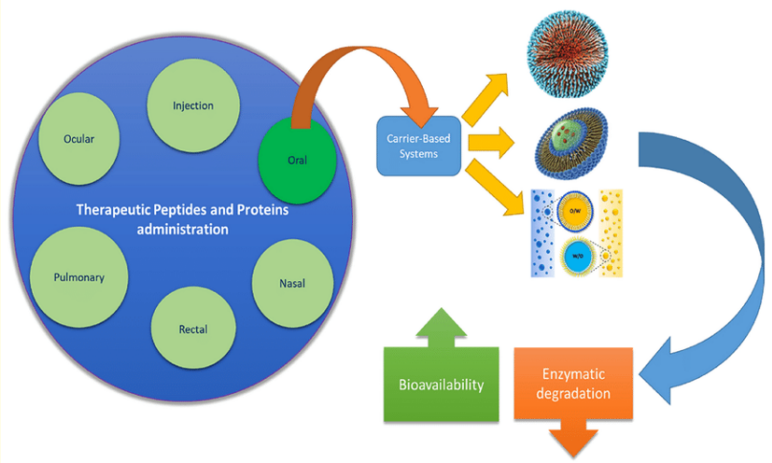

Figure 4: Protein and Peptide Therapy in Ocular Diseases.

Genetic disorders

- **Genetic mutation correction:** Inherited genetic disorders affecting the eye, such as certain forms of retinitis pigmentosa, involve specific mutations in RNA sequences. Ribozymes can be tailored to target and cleave mutant RNA, potentially correcting the genetic defect or reducing the expression of deleterious proteins.

Antiviral strategies

Viral RNA inhibition: Ocular viral infections, including those caused by herpes simplex virus (HSV) or cytomegalovirus (CMV), may be targeted using ribozymes. Designing ribozymes to cleave viral RNA can potentially inhibit viral replication and limit the progression of viral-induced ocular diseases [50].

Scleral plug therapy

Scleral plug can be implanted using a simple procedure at the pars plana region of eye, made of biodegradable polymers and drugs, and it gradually releases effective doses of drugs for several months upon biodegradation. The release profiles vary with the kind of polymers used, their molecular weights, and the amount of drug [51].

siRNA therapy

For various angiogenesis-related diseases, the use of siRNA is considered as a promising approach. Feasibility of using siRNA for treatment of choroidal neovascularization has been demonstrated using siRNA directed against vascular endothelial growth factor (VEGF) or VEGF receptor 1 (VEGFR1), and both of these approaches are being tested in clinical trials. Topical delivery of siRNAs directed against VEGF, or its receptors has also been shown to suppress corneal neovascularisation. siRNA has become a valuable tool to explore the potential role of various genes in ocular disease processes [52].

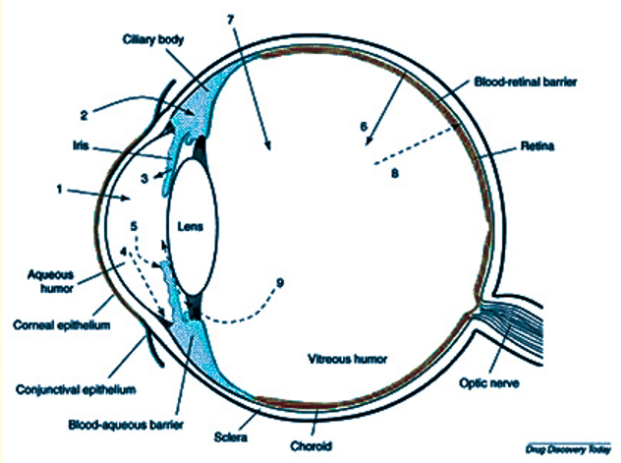

Figure 5: siRNA therapy.

Aptamer

Aptamers are oligonucleotide ligands that are used for high-affinity binding to molecular targets. They are isolated from complex libraries of synthetic nucleic acid by an iterative process of adsorption, recovery, and reamplification. They bind with the target molecules at a very low level with high specificity. One of the earliest aptamers studied structurally was the 15 meters [53].

Delivery platform	Drug	Method of delivery	Developmental stage	REFERECNCE
Clearside Biomedical	Triamcinolone acetonide	Suprachoroidal injection	P2(TYBEE) P3(PEACHTREE)	54
Microcannulation	Stem cell (CNTO 2476)	Suprachoroidal injection	P1/2	55
Microcannulation	Iluvien	Suprachoroidal injection	Ex-US P1	56
Encapsulated cell technology	Ciliary neurotrophic factor (CNTF)	Intravitreal implant	P2	57
Retiset	Fluocinolone acetonide	Intravitreal implant	Launched	58
Iluvien	Fluocinolone acetonide	Intravitreal implant	Launched	59
Ozurdex	Dexamethasone	Intravitreal implant	Launched	60
PLGA nanoparticles	Bevacizumab	Intravitreal implant	Pre-clinical	61
PLGA microparticles	Bevacizumab	Intravitreal implant	Pre-clinical	62
Graybug vision GB-102	Sunitinib malate	Intravitreal implant	P1/2a	63
Ocular therapeutix OTX-IVT	Aflibercept	Intravitreal implant	Pre-clinical	64
Ocular therapeutix OTX-TKI	Tyrosine kinase inhibitor	Intravitreal implant	Ex-US P1	65
Thermoresponsive hydrogel	Bevacizumab or ranibizumab	Intravitreal implant	Pre-clinical	66
In situ hydrogel	Bevacizumab	Intravitreal implant	Pre-clinical	67
Microsphere-thermoresponsive composite system	Bevacizumab, ranibizumab, or aflibercept	Intravitreal implant	Pre-clinical	68
Port delivery system	Ranibizumab	Intravitreal implant	P2	69

Table 2: Ocular drug delivery systems in clinical trials or in development.

Conclusion

Ocular drug delivery systems provide local as well as systemic delivery of the drugs. The novel advanced delivery systems offer more protective and effective means of the therapy for the nearly inaccessible diseases or syndromes of eyes. The latest available targeted drug delivery systems focus on the localised delivery of the drugs as well as certain macromolecular substances like proteins, genes like DNA, siRNA to the internal parts of the eye. Further developments are preferable which will eliminate the cons of these available advanced delivery systems and readily acceptable with the regulatory authorities as well.

Bibliography

1. Hughes PM and Mitra AK. "Overview of ocular drug delivery and iatrogenic ocular cytopathologies". In: Mitra AK. Ophthalmic Drug Delivery Systems. 2nd edition. New York: M. Dekker Inc (1993): 1-27.

2. Bourlais CL., *et al*. "Ophthalmic drug delivery systems- recent advances". *Progress in Retinal and Eye Research* 17 (1988): 33-58.

3. Kaur IP., *et al*. "Vesicular systems in ocular drug delivery: an overview". *International Journal of Pharmaceutics* 269 (2004): 1-14.

4. Wadhwa S., *et al*. "Nanocarriers in ocular drug delivery: An update review". *Current Pharmaceutical Design* 15 (2009): 2724-2750.

5. Mueller WH and Deardroff DL. "Ophthalmic vehicles: The effect of methyl cellulose on the penetration of Homatropine hydro bromide through the cornea". *Journal of the American Pharmacists Association* 45 (1956): 334-341.

6. Urtti A., *et al*. "Controlled drug delivery devices for experimental ocular studies with timolol, Ocular and systemic absorption inrabbits". *International Journal of Pharmaceutics* 61 (1990): 241-249.

7. Geroski DH and Edelhauser HF. "Drug delivery for posterior segment eye diseases". *Investigative Ophthalmology and Visual Science* 41 (2000): 961-964.

8. Sultana Y., *et al*. "Review of Ocular Drug Delivery". *Current DrugDelivery* 3 (2006): 207-217.

9. Mishra DN and Gilhotra RM. "Design and characterization of bioadhesive *in-situ* gellingocular insert of gatifloxacin sesquihydrate". *DARU* 16 (2008): 1-8.

10. Lawrenson JG., *et al*. "Comparison of the efficacy and duration of action of topically applied proxymetacaine using a novel ophthalamic delivery system versus eye drops in healthy young volunteers". *British Journal of Ophthalmology* 77 (1993): 713-715.

11. Ebrahim S., *et al*. "Applications of liposomes in ophthalmology". *Survey of Ophthalmology* 50 (2005): 167-182.

12. Kaur IP., *et al*. "Vesicular systems in ocular drug delivery: An overview". *International Journal of Pharmaceutics* 269 (2004): 1-14.

13. Shek PN and Barber RF. "Liposomes are effective carriers for the ocular delivery of prophylactics". *Biochimica et Biophysica Acta* 902 (1987): 229-236.

14. Vyas SP., *et al*. "Discoidal niosome based controlled ocular delivery of timolol maleate". *Pharmazie* 53.7 (1998): 466-469.

15. FF Behar-Cohen., *et al*. "Transscleral Coulombcontrolled iontophoresis of methyl prednisolone into the rabbit eye: Influence of duration of treatment, current intensity and drug concentration on ocular tissue and fluid levels". *Experimental Eye Research* 74.1 (2002A): 51-59.

16. BC Hayden., *et al*. "Pharmacokinetics of systemic versus focal carboplatin chemotherapy in the rabbit eye: possible implication in the treatment of retinoblastoma". *Investigative Ophthalmology and Visual Science* 45 (2009): 3644-3649.

17. M Voigt., *et al*. "Ocular aspirin distribution: a comparison of intravenous, topical, and coulomb-controlled iontophoresis administration". *Investigative Ophthalmology and Visual Science* 43.10 (2002): 3299-3306.

18. RF Jones and DM Maurice. "New methods of measuring the rate of aqueous flow in man with fluorescein". *Experimental Eye Research* 5 (1966): 208-220.

19. R Grossman., *et al*. "Regional ocular gentamicin levels after transcorneal and transscleral iontophoresis". *Investigative Ophthalmology and Visual Science* 31 (1990): 909-916.

20. J Frucht-Pery., *et al*. "The distribution of gentamicin in the rabbit cornea following iontophoresis to the central cornea". *Journal of Ocular Pharmacology and Therapeutics* 15.3 (1999): 251-256.

21. J Frucht-Pery., *et al*. "Efficacy of iontophoresis in the rat cornea". *Graefe's Archive for Clinical and Experimental Ophthalmology* 234 (1996): 765-769.

22. GA Fischer., *et al*. "OcuPhor-the future of ocular drug delivery". *Drug Delivery Technology* 2 (2002): 50-52.

23. TM Parkinson., *et al*. "Tolerance of ocular iontophoresis in healthy volunteers". *Journal of Ocular Pharmacology and Therapeutics* 19.2 (2003): 145-151.

24. TM Parkinson., *et al*. "The effects of *in vivo* iontophoresis on rabbit eye structure and retinal function". *Investigative Ophthalmology and Visual Science* 41 (2000): S772

25. DL Vollmer., *et al*. "*In vivo* transscleral iontophores is of amikacin to rabbit eyes". *Journal of Ocular Pharmacology and Therapeutics* 18.6 (2002): 549-558.

26. MS Hastings., *et al*. "Visulex: advancing iontophoresis for effective noninvasive back-to-the-eye therapeutics". *Drug Delivery Technology* 4.3 (2004): 53-57.

27. E Eljarrat-Binstock., *et al*. "Transcorneal and transscleral iontophoresis of dexamethasone phosphate in rabbits using drug loaded hydrogel". *Journal of Controlled Release* 106.3 (2005): 386-390.

28. E Eljarrat-Binstock., *et al*. "Hydrogel probe for iontophoresis drug delivery to the eye". *Journal of Biomaterials Science. Polymer Edition* 15.4 (2004): 397-413.

29. E Eljarrat-Binstock., *et al*. "Delivery of gentamicin to the rabbit eye by drug-loaded hydrogel iontophoresis". *Investigative Ophthalmology and Visual Science* 45.8 (2004): 2543-2548.

30. J Frucht-Pery., *et al*. "Iontophoresisgentamicin delivery into the rabbit cornea, using a hydrogel delivery probe". *Experimental Eye Research* 78.3 (2004): 745-749.

31. F Brouneus., *et al*. "Diffusive transport properties of some local anesthetics applicable for iontophoretic formulation of the drugs". *International Journal of Pharmaceutics* 218.1-2 (2001): 57-62.

32. CR Anderson., *et al*. "Effects of iontophoresis current magnitude and duration on dexamethasone deposition and localized drug retention". *Physical Therapy* 83.2 (2003): 161-170.

33. SS Kamath and LP Gangarosa. "Electrophoretic evaluation of the mobility of drugs suitable for iontophoresis". *Methods and Findings in Experimental and Clinical Pharmacology* 17.4 (1995): 227-232.

34. D Monti., *et al*. "Effect of iontophoresis on transcorneal permeation Fin vitro_ of two beta-blocking agents, and on corneal hydration". *International Journal of Pharmaceutics* 250.2 (2003): 423-429.

35. O Camber., *et al*. "Permeability of prostaglandin F2 and prostaglandin F2 esters across cornea *in vitro*". *International Journal of Pharmaceutics* 29 (1986): 259-266.

36. PH Fishman., *et al*. "Iontophoresis of gentamicin into aphasic rabbit eyes". *Investigative Ophthalmology and Visual Science* 25 (1984): 343-345.

37. TB Choi and DA Lee. "Transscleral and transcorneal iontophoresis of vancomycin in rabbit eyes". *Journal of Ocular Pharmacology* 4.2 (1988): 153-164.

38. DS Rootman., *et al*. "Pharmacokinetics and safety of transcorneal iontophoresis of tobramycin in the rabbit". *Investigative Ophthalmology and Visual Science* 29.9 (1988): 1397-1401.

39. J Frucht-Pery., *et al*. "Iontophoretic treatment of experimental pseudomonas keratitis in rabbit eye using gentamicinloaded hydrogel, (submitted for publication) (2009).

40. Fujiwara T., *et al*. "Enhanced depth imaging optical coherence tomography of the choroid in highly myopic eyes". *American Journal of Ophthalmology* 148 (2009): 445-450.

41. Ramrattan RS., *et al*. "Morphometric analysis of Bruch's membrane, the choriocapillaris, and the choroid in aging". *Investigative Ophthalmology and Visual Science* 35 (1994): 2857-2864.

42. Spraul CW., *et al*. "Histologic and morphometric analysis of the choroid, Bruch's membrane, and retinal pigment epithelium in postmortem eyes with age-related macular degeneration and histologic examination of surgically excised choroidal neovascular membranes". *Survey of Ophthalmology* 44.1 (1999): S10-32.

43. Hewitt AT and Newsome DA. "Altered synthesis of Bruch's membrane proteoglycans associated with dominant retinitis pigmentosa". *Current Eye Research* 4 (1985): 169-174.

44. Hewitt AT., *et al*. "Analysis of newly synthesized Bruch's membrane proteoglycans". *Investigative Ophthalmology and Visual Science* 30 (1989): 478-486.

45. Farboud B., *et al*. "Development of a polyclonal antibody with broad epitope specificity for advanced glycation end products and localization of these epitopes in Bruch's membrane of the aging eye". *Molecular Vision* 5 (1999): 11.

46. Handa JT., *et al*. "Increase in the advanced glycation end product pentosidine in Bruch's membrane with age". *Investigative Ophthalmology and Visual Science* 40 (1999): 775-779.

47. Yamada Y., *et al*. "The expression of advanced glycation endproduct receptors in rpe cells associated with basal deposits in human maculas". *Experimental Eye Research* 82 (2006): 840-848.

48. Candiello J., *et al*. "Biomechanical properties of native basement membranes". *FEBS Journal* 274 (2007): 2897-2908.

49. Mordenti J., *et al*. "Comparisons of the intraocular tissue distribution, pharmacokinetics, and safety of 125I-labeled full-length and Fab antibodies in rhesus monkeys following intravitreal administration". *Toxicologic Pathology* 27 (1999): 536-544.

50. Heiduschka P., *et al*. "The tubingen Bevacizumab study, G. penetration of Bevacizumab through the retina after intravitreal injection in the monkey". *Investigative Ophthalmology and Visual Science* 48 (2007): 2814-2823.

51. Dib E., *et al*. "Subretinal bevacizumab detection after intravitreous injection in rabbits". *Investigative Ophthalmology and Visual Science* 49 (2008): 1097-1100.

52. Sakurai E., *et al*. "Effect of particle size of polymeric nanospheres on intravitreal kinetics". *Ophthalmic Research* 33 (2001): 31-36.

53. Bourges JL., *et al*. "Ocular drug delivery targeting the retina and retinal pigment epithelium using polylactide nanoparticles". *Investigative Ophthalmology and Visual Science* 44 (2003): 3562-3569.

54. Cunha-Vaz J. "The blood-ocular barriers". *Survey of Ophthalmology* 23 (1979): 279-296.

55. Schnitzer JE., *et al*. "Endothelial caveolae have the molecular transport machinery for vesicle budding, docking, and fusion including VAMP, NSF, SNAP, annexins, and GTPases". *Journal of Biological Chemistry* 270 (1995): 14399-14404.

56. Simionescu M., *et al*. "Transcytosis of plasma macromolecules in endothelial cells: A cell biological survey". *Microscopy Research and Technique* 57 (2002): 269-288.

57. Hosny KM. "Ciprofloxacin as ocular liposomal hydrogel". *AAPS PharmSciTech* 11 (2010): 241-246.

58. Zhang J., *et al*. "Freezedried liposomes as potential carriers for ocular administration of cytochrome c against selenite cataract formation". *Journal of Pharmacy and Pharmacology* 61 (2009): 1171-1178.

59. Zhang J and Wang S. "Topical use of coenzyme Q10-loaded liposomes coated with trimethyl chitosan: Tolerance, precorneal retention and anti-cataract effect". *International Journal of Pharmaceutics* 372 (2009): 66-75.

60. Aggarwal D and Kaur IP. "Improved pharmacodynamics of timolol maleate from a mucoadhesive niosomal ophthalmic drug delivery system". *International Journal of Pharmaceutics* 290 (2005): 155-159.

61. Kaur IP., *et al*. "Improved ocular absorption kinetics of timolol maleate loaded into a bioadhesive niosomal delivery system". *Graefe's Archive for Clinical and Experimental Ophthalmology* 248 (2010): 1467-1472.

62. Guinedi AS., *et al*. "Preparation and evaluation of reverse-phase evaporation and multilamellar niosomes as ophthalmic carriers of acetazolamide". *International Journal of Pharmaceutics* 306 (2005): 71-82.

63. Aggarwal D., *et al*. "Study of the extent of ocular absorption of acetazolamide from a developed niosomal formulation, by microdialysis sampling of aqueous humor". *International Journal of Pharmaceutics* 338 (2007): 21-26.

64. Abdelbary G and El-Gendy N. "Niosome-encapsulated gentamicin for ophthalmic controlled delivery". *AAPS PharmSciTech* 9 (2008): 740-747.

65. Garg G., *et al*. "Cubosomes: An overview". *Biological and Pharmaceutical Bulletin* 30 (2007): 350-353.

66. Gan L., *et al*. "Self-assembled liquid crystalline nanoparticles as a novel ophthalmic delivery system for dexamethasone: Improving preocular retention and ocular bioavailability". *International Journal of Pharmaceutics* 396 (2010): 179-187.

67. Han S., *et al*. "Novel vehicle based on cubosomes for ophthalmic delivery of flurbiprofen with low irritancy and high bioavailability". *Acta Pharmacologica Sinica* 31 (2010): 990-998.

68. Klang SH., *et al*. "Evaluation of a positively charged submicron emulsion of piroxicam on the rabbit corneum healing process following alkali burn". *Journal of Controlled Release* 57 (1999): 19-27.

69. Abdulrazik M., *et al*. "Ocular delivery of cyclosporin A. II. Effect of submicron emulsion's surface charge on ocular distribution of topical cyclosporin A". Paris: Editions de sante (2001).