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INNOVATION IN OCULAR DRUG DELIVERY SYSTEM

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ABSTRACT

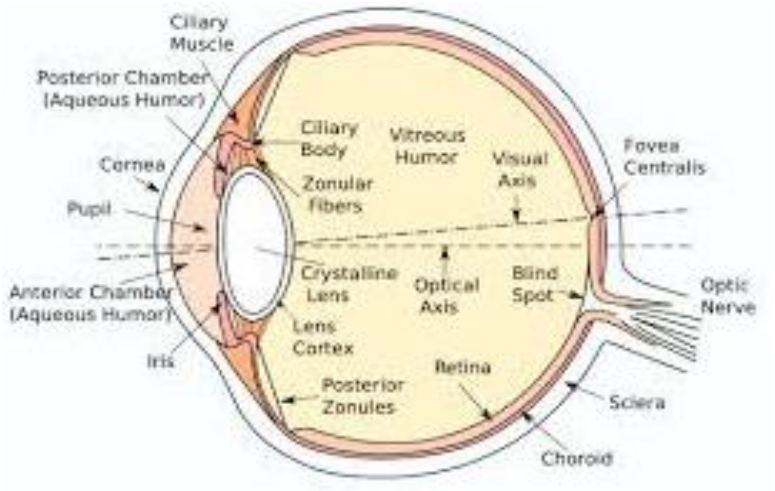
Ocular drug delivery is one of the most fascinating and challenging tasks facing the Pharmaceutical researchers. One of the major barriers of ocular medication is to obtain and maintain a therapeutic level at the site of action for prolonged period of time. Ocular drug delivery is hampered by the barriers protecting the eye. The bioavailability of the active drug substance is often the major hurdle to overcome. Conventional ocular dosage form, including eye drops, are no longer sufficient to combat ocular diseases. This article reviews the constraints with conventional ocular therapy and explores various approaches like eye ointments, gel, viscosity enhancers, prodrug, penetration enhancers, microparticles, liposomes, niosomes, ocular inserts, implants, intravitreal injections, nanoparticles, nanosuspension, microemulsion, in situ-forming gel, iontophoresis and periocular injections to improve the ocular bioavailability of drug and provide continuous and controlled release of the drug to the anterior and posterior chamber of the eye and selected pharmacological future challenges in ophthalmology. In near future, a great deal of attention will be paid to develop noninvasive sustained drug release for both anterior and posterior segment eye disorders. Current momentum in the invention of new drug delivery systems hold a promise toward much improved therapies for the treatment of vision-threatening disorders.

KEYWORDS: Ocular drug delivery system.

INTRODUCTION

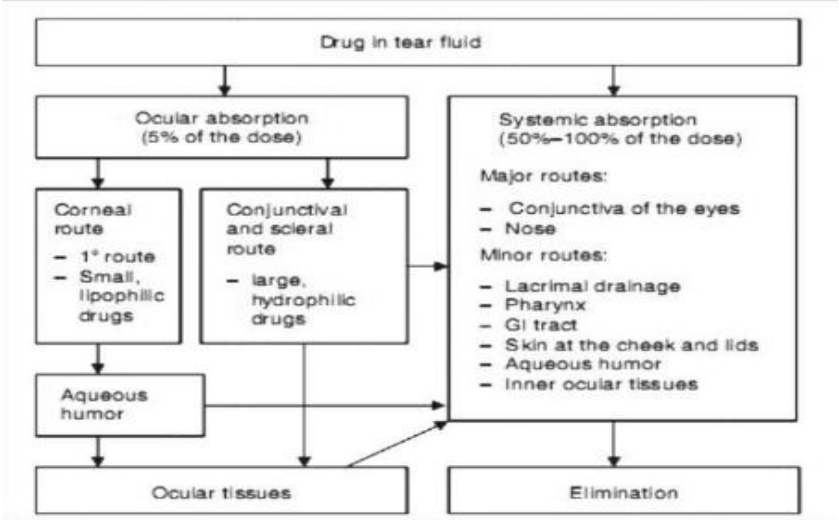
The eye is a complex organ with an unique anatomy and physiology. The structure of eye can be divided into two main parts: anterior segment and posterior segment. Anterior segment of the eye occupies approximately one-third while the remaining portion is occupied by the

posterior segment. Tissues such as cornea, conjunctiva, aqueous humor, iris, ciliary body and lens make up the anterior portion. Back of the eye or posterior segment of the eye include sclera, choroid, retinal pigment epithelium, neural retina, optic nerve and vitreous humor. The anterior and posterior segment of eye is affected by various vision threatening diseases. Diseases affecting anterior segment include, but not limited to glaucoma, allergic conjunctivitis, anterior uveitis and cataract. While, age-related macular degeneration (AMD) and diabetic retinopathy are the most prevalent diseases affecting posterior segment of the eye. Topical instillation is the most widely preferred non-invasive route of drug administration to treat diseases affecting the anterior segment. Conventional dosage forms such as eye drops account for 90% of the marketed ophthalmic formulations. The reason may be attributed to ease of administration and patient compliance. Nonetheless, the ocular bioavailability is very low with topical drop administration. Numerous anatomical and physiological constraints such as tear turnover, nasolachrymal drainage, reflex blinking, and ocular static and dynamic barriers pose a challenge and impede deeper ocular drug permeation. Hence, less than 5% of topically applied dose reaches to deeper ocular tissue. Also, it is difficult to achieve therapeutic drug concentration into posterior segment ocular tissues following topical eye drops instillation because of the above mentioned barriers. The drug can be delivered to the posterior segment ocular tissues by different mode of administrations such as intra vitreal injections, periocular injections, and systemic administration. However, small volume of eye compared to whole body and presence of blood retinal barriers; makes systemic administration an impractical approach. Intra vitreal injection is the most common and widely recommended route of drug administration to treat posterior ocular diseases. Though, the need of repeated eye puncture with intra vitreal injections causes several side effects such as endophthalmitis, hemorrhage, retinal detachment and poor patient tolerance. The transscleral drug delivery with periocular administration route is evolved as an alternative mode of drug delivery to the posterior ocular tissues. Although transscleral delivery is comparatively easy, less invasive and patient compliant, drug permeation is compromised by ocular static and dynamic barriers. Ocular barriers to transscleral drug delivery include: static barriers *i.e.*, sclera, choroid and retinal pigment epithelium (RPE), and dynamic barriers, *i.e.*, lymphatic flow in the conjunctiva and episclera, and the blood flow in conjunctiva and choroid.



To overcome the ocular drug delivery barriers and improve ocular bioavailability, various conventional and novel drug delivery systems have been developed such as emulsion, ointments, suspensions, aqueous gels, nanomicelles, nanoparticles, liposomes, dendrimers, implants, contact lenses, nanosuspensions, microneedles, and *in situ* thermosensitive gels for the earlier mention ocular diseases. This review will provide an overview on various conventional and novel ophthalmic drug delivery systems developed to deliver drug to diseased ocular tissues for the treatment of ocular diseases.

Ocular absorption pathway

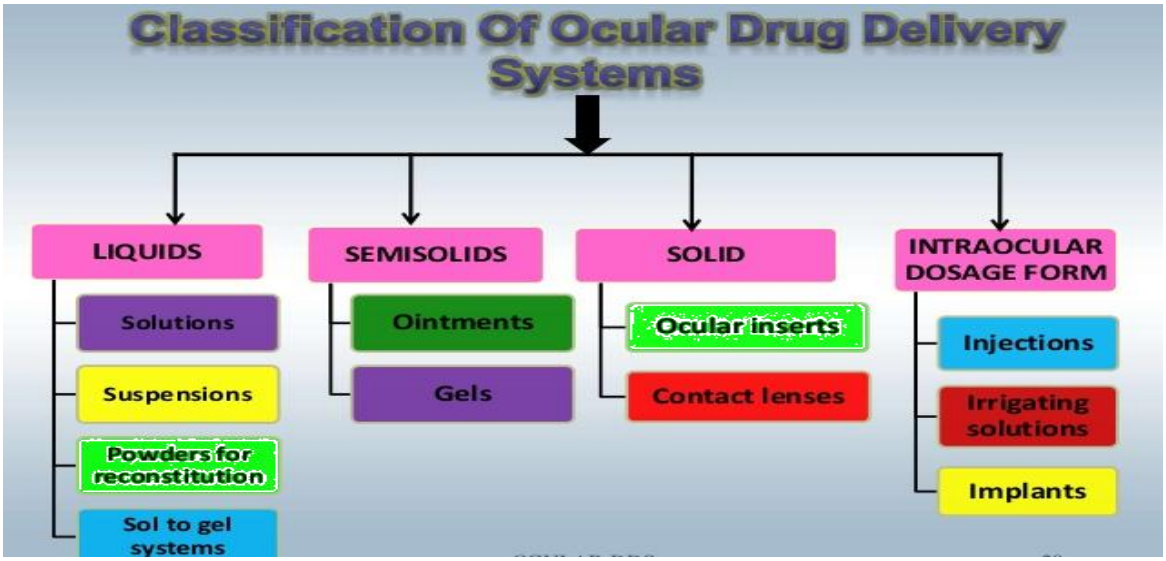


Ophthalmic dosages form

Ophthalmic preparations are sterile products essentially free from packaged dosage from foreign particles, suitably compounded and packaged for instillation in to the eye. Ocular drug delivery presents unique challenges and opportunities. Eye tissues can be accessed directly with relative ease using topical eye drops. However, the loading and ocular

absorption of drugs are limited using traditional solution and suspension formulation particularly for compounds with low aqueous solubility. For such compounds, delivery to the posterior ocular tissues including the retina and choroid, can be particularly problematic. The need for formulations that increase the topical ocular absorption of poorly soluble compounds remains largely unmet, precluding the development of otherwise peomising medicines for glaucoma, age-related macular degeneration(AMD), diabetic retinopathy, infections, and other eye diseases.

Ocular drug delivery system



Eye drops

- Drugs which are active at eye or eye surface are widely administered in the form of Solutions, Emulsion and Suspension.
- Various properties of eye drops like hydrogen ion concentration, osmolality, viscosity and instilled volume can influence retention of a solution in the eye.
- Less than 5% of the dose is absorbed after topical administration into the eye.
- Eye drops are saline-containing drops used as an ocular route to administer.

Advantages and disadvantages of eye drops

Dosages form	Advantage	Disadvantage
Solution	Convenience Usually do not interfere with vision of patient.	Rapid precorneal elimination. Non sustained action. To be Administered at frequent intervals.
Emulsion	Prolonged release of drug from vehicle	Blurred vision. patient non compliance.

Suspension	Patient compliance. Best for drug with slow dissolution. Longer contact time	Drug properties decide performance loss of both solutions and suspended particles. Irritation potential due to the particle size of the drug.

Recent work done in eye drops

New Eye Drops Can Dissolve Cataracts With No Need For Surgery

Zhang and his research team went on to develop eye drops that contained lanosterol as a drug treatment for cataracts.

Ointment

- Eye ointments can deliver medicine directly to your eyes, keep your eyes moist and help with redness, itching and watering and prolongation of drug contact time with the external ocular surface.
- Ointment base is sterilized by heat and filtered while molten to remove foreign particulate matter.
- The entire ointment may be passed through a previously sterilized colloid mill.
- It is important to be sure the dropper or tube is clean. Do not let it touch the eye, eyelid, lashes or any surface. This will keep it free from bacteria.

Advantages

1. Longer contact time and greater storage stability.
2. Flexibility in drug choice.
3. Improved drug stability.

Disadvantages

1. Sticking of eyes lids.
2. Blurred vision.
3. Poor patient compliance
4. Interfere with the attachment of new corneal epithelial cells to their normal base.
5. Matting of eyelids

Gels

- Gels are defined as a substantially dilute cross-linked system, which exhibits no flow when in the steady-state.

- By weight, gels are mostly liquid, yet they behave like solids due to a three-dimensional cross-linked network within the liquid.
- Ophthalmic gels are composed of mucoadhesive polymers that provide localized delivery of an active ingredient to the eye.
- These polymers extend the contact time of the drug with the biological tissues and improve ocular bioavailability.
- Most commonly used polymers in ocular gels are gellan gum, alginic acid, xyloglucan, pectin, chitosan, poloxamer, gellan gum, sodium alginate.

Advantages

1. Longer contact time.
2. Greater storage stability.

Disadvantages

1. Blurred vision but less then ointment.
2. Poor patient compliance.

Recent work done

A new eye gel containing sodium hyaluronate and xanthan gum for the management of post-traumatic corneal abrasions.

Francesco Faraldi and et. al. investigate the effects of an ophthalmic gel containing sodium hyaluronate and xanthan gum in addition to the antibiotic netilmicin in the management of traumatic corneal abrasions.

- **Vesicular system**

LIPOSOMES

- Liposomes are biocompatible and biodegradable lipid vesicles made up of natural lipids and about 25 –10 000 nm in diameter.
- They are having an intimate contact with the corneal and conjunctival surfaces which is desirable for drugs that are poorly absorbed, low partition coefficient, poor solubility or high molecular weights and thus increases the ocular drug absorption.
- These formulations are mainly composed of phosphatidylcholine and other constituents such as cholesterol and lipid-conjugated hydrophilic polymers. Phospholipids used-

Phosphotidylcholine, Phosphotidic acid, Sphingomyline, Phosphotidyleserine, Cardiolipine.

- Liposomes are Biodegradable, Non-toxic and biocompatible in nature.
- Current approaches for topical delivery of liposomes are focused in improving the corneal adhesion and permeation by incorporating various bioadhesive and penetration enhancing polymers.

Types

1. MLV
2. ULV-SUV (upto 100 nm)
3. LUV (more than 100 nm)

Advantages

1. Drugs delivered intact to various body tissues.
2. Liposomes can be used for both hydrophilic and hydrophobic drug.
3. Possibility of targeting and decrease drug toxicity.
4. The size, charge and other characteristics can be altered according to drug and desired tissue.

Disadvantages

1. Costly preparation.
2. Stability problem and oxidative degradation.
3. Requires special packaging and storing facility.

Recent work done

Development and in vitro/in vivo Evaluation of Liposomal Gels for the Sustained Ocular Delivery of Latanoprost.

Soliman G.M. and et.al. found Latanprost Liposomes for Glaucoma Treatment Decelopment and in vitro/in vivo Liposomes Delivery of Latanoprost.

Niosomes

- The major limitations of liposomes are chemical instability, oxidative degradation of phospholipids, cost and purity of natural phospholipids.

- To avoid limitations of liposomes niosomes are developed as they are chemically and can entrap both hydrophobic and hydrophilic drugs.
- Niosomes are nonionic surfactant vesicles that have potential applications in the delivery of hydrophobic or amphiphilic drugs.
- Niosomes are non-ionic surfactant based multilamellar (>0.05µm), small unilamellar (0.025-0.05µm) or large unilamellar vesicles (>0.1µm) in which an aqueous solution of solute(s) is entirely enclosed by a membrane resulted from organization of surfactant macromolecules as bilayers.
- They are non toxic and do not require special handling techniques.

STRUCTURAL COMPONENTS USED

- Surfactants (dialkyl polyoxy ethylene ether non ionic surfactant)
- Cholesterol.

Advantages

1. Niosomes can entrap both hydrophilic and lipophilic drug.
2. Enhance skin penetration therapy improving bioavailability of drug.
3. Niosomes are depository for releasing drug in sustained or prolonged manner.
4. More stable than liposomes.
5. Better patient compatibility better therapeutic effect than conventional.
6. Bio degradable, bio compatible and non immunogenic to the body.

Disadvantages

1. Physical instability.
2. Aggregation.
3. Leaking of entrapped drug.
4. Controlled release.

Recent work done

Niosomes encapsulated with Gatiflaxacin for ocular drug delivery

Hitendra S Mahajan and et. al. was to formulate and evaluate non-ionic surfactantvesicles (niosomes) as carriers for the delivery of Gatiflaxacin. Niosomal formulations.

Pharmacosomes

- A novel approach based on lipid drug delivery system has evolved, pharmacosomes.

- Pharmacosomes are colloidal, nanometric size micelles, vesicles drug dispersions attached covalently to the phospholipid. This term is used for pure drug vesicles formed by the amphiphilic drugs.
- This type of vesicular system improves permeation of drugs across the biomembranes and thus results in an improvement in the bioavailability and can also improve the pharmacodynamic properties of various types of drug molecules.

Advantages

1. Delayed elimination of rapidly metabolized drugs facilitate sustained release.
2. These system reduces the adverse effects and provide better targeting to body tissues and specific sites.

Discomes

- Soluble surface active agents when added in critical amount to vesicular dispersion leads to solubilization or breakdown of vesicles & translates them into mixed micellar systems

e.g: Egg yolk phosphatidyl choline liposomes by the addition of non ionic surfactants of poly oxy ethylene cetyl ether till the lamellar and mixed lamellar coexist.

Advantages

1. Minimal opacity imposes no hinderance to vision
2. Increased patient compliance
3. Zero order release can be easily attained.

Ocular inserts

Types of ocular inserts

Erodible inserts	The fabrication polymer is hydrophobic but biodegradable. Drug is released through the erosion of the surface of the insert.
Soluble inserts	The fabrication polymer is hydrophilic and water soluble. Drug release characteristics: Diffusion control for soluble drugs. Dissolution control for less soluble drugs.
Hydrophilic but water insoluble inserts	The fabrication polymer is hydrophilic but water-insoluble. Drug release characteristics: Diffusion control for soluble drugs. Dissolution control for less soluble drugs.
Inserts using osmotic system	A polymeric matrix in which the drug is dispersed as discrete small domains. Upon placement in the cul-de-sac, tears are imbibed into the matrix because of an osmotic pressure gradient created by the drug, where upon the drug is dissolved and released.

Membrane-controlled diffusional inserts	The drug core is surrounded by a hydrophobic polymer membrane; this controls the diffusion of the drug from from the core to the outside.

Non erodible

1. **OCUSERT**

- The Ocusert therapeutic system is a **flat, flexible, elliptical device** designed to be placed in the inferior cul-de-sac between the sclera and the eyelid and to release Pilocarpine continuously at a steady rate for 7 days.
- The device consists of 3 layers…..

a. Outer layer - ethylene vinyl acetate copolymer layer.

b. Inner Core - Pilocarpine gelled with alginate main polymer.

c. A retaining ring - of EVA impregnated with titanium di oxide

ADVANTAGES

1. Increased contact time and thus improved bio-availability.
2. Lack of explosion.

DISADVANTAGES

1. The inserts may be lost immediately.
2. A leakage may occur.
3. Dislocation of the device in front of the pupil.
4. Expensive.

Recent work done

Preparation of Fluconazole b-Cyclodextrin Complex Ocuserts: In Vitro and In Vivo Evaluation.

Hindustan Abdul Ahad and et. al. developed ocuserts containing fluconazole b- cyclodextrin.

Erodible inserts

- The solid inserts absorb the aqueous tear fluid and gradually erode or disintegrate. The drug is slowly leached from the hydrophilic matrix.
- They quickly lose their solid integrity and are squeezed out of the eye with eye movement and blinking.
- Do not have to be removed at the end of their use.

Three types

1. Lacriserts
2. Sodi
3. Minidisc

LACRISERTS

- Sterile rod shaped device made up of hydroxyl propyl cellulose without any preservative.
- For the treatment of dry eye syndromes.
- It weighs 5 mg and measures 1.27 mm in diameter with a length of 3.5 mm.
- It is inserted into the inferior fornix.

SODI

- Soluble ocular drug inserts.
- Small oval wafer.
- Sterile thin film of oval shape.
- Weighs 15-16 mg.
- Use – glaucoma.
- Advantage – Single application.

MINIDISC

- Countered disc with a convex front and a concave back surface.
- Diameter – 4 to 5 mm.

Advantages

- Effective.
- Flexibility in drug type & dissolution rate.
- Need only be introduced into eye and not removed.

Disadvantage

- Patient discomfort.
- Require patient insertion.

Contact lens

Contact lenses are among the fastest progressing topics in optometry and the last decade has seen a number of significant developments occurring in the field. Among these has been the

increasing dominance of soft lens materials in the market, albeit with substantial differences between countries. Optical designs have improved, allowing the optimisation of distance vision through the use of aspherics, enhanced range of clear focus with multifocals and more predictable toric designs for astigmatic correction. Silicone hydrogel technology has increased oxygen permeability to the eye, with improved corneal and ocular surface physiology being the result. Due, however, to their mechanical properties, deposition profiles and care system interactions, clinical problems have not been entirely absent, especially with non-compliant wearers. Efforts to eliminate end of day discomfort, a major cause of drop-out, have included incorporating viscous solutions into lens materials, as well as manipulating both multipurpose care solutions and agents within the blister-packaging in which lenses are delivered.

- Contact lenses can be a way of providing extended release of drugs into the eye.
- Conventional hydrogel soft contact lenses have the ability to absorb some drugs and release them into the post lens lachrymal fluid, minimizing clearance and sorption through the conjunctiva.
- Their ability to be a drug reservoir strongly depends on the water content and thickness of the lens, the molecular weight of the drug, the concentration of the drug loading solution and the time the lens remains in it.

Contact lenses- latest technology

New contact lenses are launched all the time but one of the most exciting advances in contact lens technology in recent years has been the development of orthokeratolgy (Ortho K) or overnight vision correction. This treatment uses specially designed overnight contact lenses to alter the shape of the eye while sleeping. The changes at a microscopic level, correct myopia (short-sightedness). The main advantage is that contact lenses or glasses are not needed during the day making lots of everyday activities easier, especially sports.

Since it is possible to see both with and without overnight contact lenses, they correct the vision around the clock, meaning that the wearer is never without full 20/20 vision. In fact eyesight is better than 20/20 especially in the first part of the day.

Overnight contact lenses are ideal for sport as they offer short-sighted athletes a new way to achieve perfect natural vision without special prescription sports eyewear. The latest contact lenses, however, benefit from new high oxygen permeable materials, state of the art computer

mapping techniques that accurately measure the eye's surface and computerised laithes which replicate this map and produce a bespoke contact lens design manuafactured to fit an individuals eye shape at microcopic levels.

It is impossible to wear glasses or daytime contact lenses for many contact sports such as football, rugby, martial arts or boxing and extremely difficult for most water sports. If you cycle, run or ski then conventional contact lenses are susceptible to environmental hazards such as wind, rain and dust and they can move or fall out.

OVC® contact lenses are only worn at night and they correct your eyesight while you sleep therefore special prescription sports glasses or presciption goggles are not needed.

It is not recommended to wear contact lenses for sports like swimming or other water sports due to the risk of infection from microbes picked up in the water.

iGO overnight contact lenses are now worn by a professional boxer, an England rugby player, a Great Britain canoeist plus many more recreational and amateur sports people.

New Contact Lenses for Dry Eyes

New contact lenses are launched regularly in an effort to improve comfort. They have come a long way since the original RGP hard contact lens which today is still considered by most opticians to be the healthiest option and the one which give the best clarity of vision. However, with the invention of silicon hydrogel materials came daily disposable contact lenses which were both more comfortable and more hygienic. There are now also extended wear lenses that can be worn consistantly for one month. However, an even better alternative for dry eye sufferers are overnight contact lenses because they are worn for fewer hours and leave the eyes free to lubricate and oxygenate for the whole day.

New Bionic Contact Lenses Could Make Glasses Obsolete

Your eyesight may be about to get a huge boost if a new bionic lens makes it to market. Invented by an optometrist in Canada, the Ocumetics Bionic Lens promises to enhance eyesight to a level that's three times better than 20/20 - the universal standard for normal vision.

These aren't lenses you pop in and out, though - the lens developed by Gareth Webb is inserted into the eye via a painless procedure that takes less than 10 minutes (Webb says the

process is a lot like cataract surgery). The lenses don't degrade over time so you'll never have a problem with cataracts or failing vision no matter how long you live.

The Ocumetics Bionic Lens incorporates a patented miniature optics system that works like a tiny digital camera: powered by the body, it can shift focus from close range objects to objects any distance away faster than the human eye is able to.

Such technology isn't invented in a day, of course - the lens has been eight years in the making and has cost US$3 million to develop so far. "This is vision enhancement that the world has never seen before," Webb told CBC News. "If you can just barely see the clock at 10 feet, when you get the Bionic Lens you can see the clock at 30 feet (9 metres) away."

Ocumetics Technology Corp, which owns the technology, says it's safe and durable. The implanted lens feels natural and won't cause headaches or any kind of eyestrain. Nevertheless, there's a way to go before it hits the market: a launch has been tentatively set for 2017, after extensive clinical trials have been completed.

Control delivery system

Implants

- Implants have been widely employed to extend the release of drugs in ocular fluids and tissues particularly in the posterior segment.
- Implants can be broadly classified into two categories based on their degradation properties:

(1) Biodegradable

(2) Nonbiodegradable

- With implants, the delivery rate could be modulated by varying polymer composition.
- Implants can be solids, semisolids or particulate-based delivery systems.
- For chronic ocular diseases like cytomegalo virus (CMV) retinitis, implants are effective drug delivery system. Earlier non biodegradable polymers were used but they needed surgical procedures for insertion and removal.
- Presently biodegradable polymers such as Poly Lactic Acid (PLA) are safe and effective to deliver drugs in the vitreous cavity and show no toxic signs.

Intophorosis

- In Iontophoresis direct current drives ions into cells or tissues. For iontophoresis the ions of importance should be charged molecules of the drug.
- If the drug molecules carry a positive charge, they are driven into the tissues at the anode; if negatively charged, at the cathode.
- Requires a mild electric current which is applied to enhance ionized drug penetration into tissue.
- Ocular iontophoresis offers a drug delivery system that is fast, painless, safe, and results in the delivery of a high concentration of the drug to a specific site.
- Ocular iontophoresis has gained significant interest recently due to its non-invasive nature of delivery to both anterior and posterior segment.
- Iontophoretic application of antibiotics may enhance their bactericidal activity and reduce the severity of disease.
- Can overcome the potential side effects associated with intraocular injections and implants.
- Iontophoresis is useful for the treatment of bacterial keratitis.

Dendrimer

- Dendrimers can successfully used for different routes of drug administration and have better water-solubility, bioavailability and biocompatibility.

Microemulsion

- Microemulsion is dispersion of water and oil stabilized using surfactant and co- surfactant to reduce interfacial tension and usually characterized by small droplet size (100 nm), higher thermodynamic stability and clear appearance.
- Selection of aqueous phase, organic phase and surfactant/co-surfactant systems are critical parameters which can affect stability of the system.

Nanosuspensions

- Nanosuspensions have emerged as a promising strategy for the efficient delivery of hydrophobic drugs because they enhanced not only the rate and extent of ophthalmic drug absorption but also the intensity of drug action with significant extended duration of drug effect.

- For commercial preparation of nanosuspensions, techniques like media milling and high-pressure homogenization have been used.

Marketed formulation for ocular drug delivery system

Sr. NO	DISEASE	PRODUCT	BRAND NAME	MFG BY	DOSAGE FORM
1	Inflammation	Ketorolac	ACUVAIL	Allergan	Eye-drops
		Diclofenac			
2	Inflammation	Chloramphenicol	VOLTARIN	Novartis	Eye- drops
		Pilocarpin Hcl			
3	Infection	Ganciclovir	CHLOPTIC	Allergan	Eye-drops
4	Miotics	Gatifloxacin			
		Dexamethasone	PILOPINI	Alcon	Gel
5	Viral	Laxobetolol Hcl	ZIRGAN	Alliance	Gel
		Flurometholone			
6	Infection	Azithromycin	ZYMER	Allergan	Eye-drops
		Bipostain			
7	Inflammation	Besifloxacin	TOBRADEX	Alcon	Eye Ointment
8	Glaucoma	Betaxolol	BETAXON	Alcon	Eye- drops
9	Inflammation	Ciprofloxacin	FML	Allergan	Susoension
10	Conjunctivitis	Ciprofloxacin	AZASITE	Catalent	Eye-drops
			BESIVANCE	Baush	Suspension

- **Patents on ocular formulations**

Sr no.	Formulation	Patent Application no	Title of patent
1	Eye drops	US 14/512,365	Antioxidant eye drops
2	Opthalmic ointment	US 06/505,984	Eye ointment formulation including the disodium salt of 1,3-bis(2-carboxychromon-5-yloxy)propan-2-ol
3	Opthalmic gel	US 08/092,574	Opthalmic gel composition and method of treating eye infections
4	Ocular liposomes	PCT/EP2011/052061	Liposome system for ocular administration
5	Ocular inserts	US 05/520,277	Ocular inserts

CONCLUSION

The complexity of the eye in terms of anatomic barriers and lacrimal drainage presents a number of unique challenges for ocular drug delivery. In this scenario, drug delivery to the posterior part of the eye becomes all the more challenging due to the anatomical and physiological barriers that seperate the posterior and anterior segments. Systemic use of glucocorticoids cause a series of adverse and toxic effects as withdrawal symptoms, suppression of hypothalamus-pituitary axis, electrolyte imbalance. These needs have generated interest and development in the novel techniques of ophthalmic drug delivery systems that can increase bioavailability, prolong action, minimize local and systemic side effects and achieve better patient compliance.

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