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A Brief Insight into Rational and Novel Approaches to Ocular Drug Delivery

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ABSTRACT

As an isolated organ, eye is very difficult to study from a drug delivery point of view. Ophthalmic drug delivery is extremely interesting and highly challenging endeavours. In recent scenario, most eye-diseases are treated with topical application of eye-drops. But these conventional eye-drops have two major problems. 1) It needs frequent administration at every 4 hours or 1 hour if the infection is severe and 2) Formation of crystalline deposits on cornea due to its pH-dependent solubility which is very low. In order to provide the solution to above problems many new formulations have been developed, which include nanosuspension, nanoemulsion, inserts, hydrogels, in-situ gel, etc. The poor bioavailability of ophthalmic solution caused by dilution and drainage from the eye can be overcome by using in-situ forming ophthalmic drug delivery system prepared from polymers that exhibit reversible liquid-gel phase transition. The developed formulation provides better drug product effectiveness, reliability, stability, safety, non-irritancy and prolonged release. Thus, it's a viable alternative to conventional eye-drops by virtue of its ability to enhance bioavailability through its longer pre-corneal residence time & ability to provide prolonged drug release upto 8 hours. The main important factor is the reduced frequency & the ease of installation resulting in better patient acceptance.

Keywords: Ophthalmic delivery, in-situ gel, polymers, liquid-gel phase transition, pre-corneal residence time, prolonged drug release.

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INTRODUCTION:

Eye is the window of soul. The eye is unique organ from anatomical and physiological point of view. Without eye we cannot enjoy the beauty of nature. The eye has special attributes that allows local drug delivery and non-invasive clinical assessment of disease and but also makes understanding of disease pathogenesis and ophthalmic drug delivery challenges. Eye ailment can cause distress and anxiety in the patient, with the ultimate fear of loss of vision or even facial disfigurement. Many parts of the eye are relatively inaccessible to systematically administered drugs and as a result, topical drug delivery remains the preffered route in most delivery systems. Drugs may be delivered to treat the pre-corneal region for such infections as conjuctivitis and blepheritis, or to provide intraocular treatment via the cornea for diseases such as gloucoma and uveitis.[1-2]

The main problem in ocular drug delivery system is rapid and extensive elimination of conventional eye drops from the eye, thus resulting in extensive loss of drug. Only a few amount of drug can penetrate the corneal layer and reached to the internal tissue of the eye. The main region of drug loss includes lacrymal drainage and drug dilution by tears. This super fluity reduces the bioavailability and lead to unwanted toxicity and side effects. [3-7]

The following characteristics are required to optimize ocular drug delivery systems.

- A good corneal penetration.
- A prolonged contact time of drug with corneal tissue.
- Simplicity of installation and removal for the patient.
- A non-irritative and at ease form (the viscous solution should not irritate lachrymation and reflex flashing) and
- Appropriate rheological properties.

Over last two decades valuable attention is to be made on development of sustained and controlled release drug delivery system. The aim of such system based on localization on site of action so as to avoid the dose frequency and improvement in the drug effectiveness.[8]

ANATOMY OF HUMAN EYE:

The eye is a sensory organ that converts light to an electric signal that is treated and interpreted by the brain. Briefly, the eye ball is covered by three layers: an outer fibrous protective layer (sclera and cornea), a middle vascular layer(choroid),and an inner nervous layer (retina) as depicted in **figure 1**(Anatomy of human eye).

The cornea is a clear, transparent, thin avascular tissue that is composed of five layers: epithelium, bowmans‘s layer, stroma, Descemet‘s membrane and endothelium. The stroma is the

only hydrophilic layer. The eye is generally divided into two parts: the anterior and the posterior segments. The anterior segment includes the cornea, sclera, ciliary body, and the lens; these structures delimit a cavity: the anterior chamber filled with the aqueous humor. The posterior segment includes all the structures between the lens and the optic nerve that delimit a cavity: the vitreous filled with an aqueous gel (the vitreous humor).[9-13] There are many anatomical and physiological features which affect the administered drug. These are as follows:

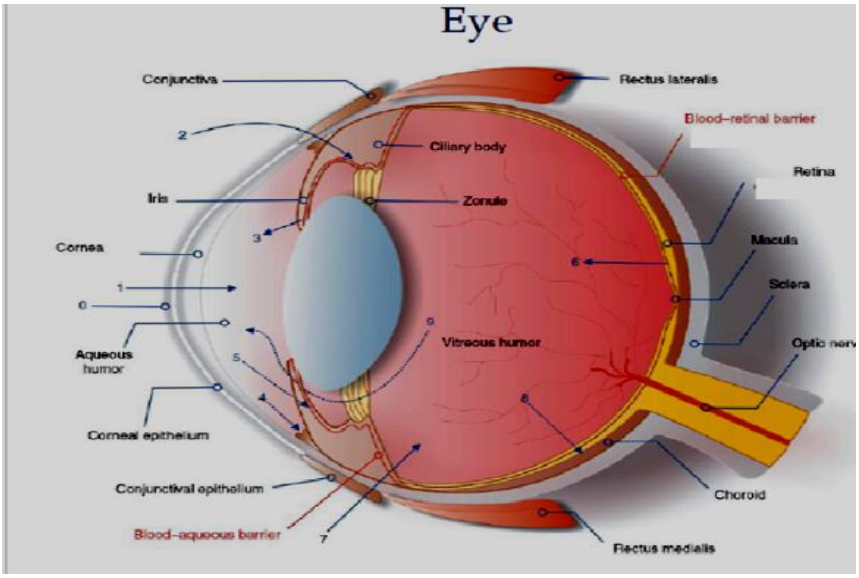


Figure 1:The anatomy of human eye.

- Blinking of eye
- Tear secretion
- Nasolachrimal drainage

Upon reflex blinking lid closure provides protection against external problems. Tears wash the surface of eye. It contains lysozyme and immunoglobulin which exert an anti-infectious activity to eye. The lachrymal fluid drained out through nasolachrimal rout, pharynx and esophagus. In addition binding of drug to conjunctival mucin and tears proteins also inactivate the drug.[14-16]

OPHTHALMIC DISORDERS

1.EYE INFECTIONS

Eyes can get infections from bacteria, fungi or viruses. Eye infections can occur in different parts of the eye and can affect just one eye or both. Common eye infections are Conjunctivitis, Corneal ulcers & Endophthalmitis.

a.Conjunctivitis- Conjunctivitis is swelling (inflammation) or infection

of the membrane lining the eyelids (conjunctiva).It is characterized by cellular infiltration and exudation. Staphylococcus aureus is the most common cause of bacterial conjunctivitis and

blepharo-conjunctivitis. Many other organisms like Haemophilus influenza, Streptococcus pneumoniae also cause conjunctivitis. Conjunctivitis can be classified as (1) Infective – Acute, Sub acute & Chronic (2) Allergic conjunctivitis.

b.Corneal ulcers / Keratitis- Inflammation of cornea (Keratitis) is characterized by corneal edema, cellular infiltration & ciliary congestion. Being the most anterior part of eyeball, cornea is exposed to atmosphere & hence prone to get infected easily.Bacterial corneal ulcers are the most commonly caused by virulent organism. Common bacteria associated with corneal ulceration are Staphylococcus aureus, Pseudomonas pyocyanea, E.coli, Proteus etc.

c.Endophthalmitis / Iritis- It is severe form of intraocular inflammation (purulent uveitis) involving ocular cavities & inner coats of eyeball. Causative organisms include Streptococci, E.coli, Pseudomonas, etc. Accordingly, the armamentarium of available antimicrobials used in the prevention and treatment of these infections includes antivirals, antifungals, and antibacterials.[17-18]

2. DRY EYE SYNDROME- The inadequate wetting of the ocular surface.

3.Glaucoma- The build up of the pressure in the anterior and posterior chambers of the choroid layer that occurs when the aqueous humour fails to drain properly.[2]

4.Diabetic retinopathy- Diabetes Mellitus is the inability of the body to use and store sugar, properly resulting in high blood sugar levels. It results in changes in veins, arteries and capillaries in the body. It could develop cataracts (clouding of the naturally clear lens in the eye), glaucoma, or retinopathy (damage occurs to the fragile blood vessels inside the retina).[19]

BARRIERS FOR OCULAR DELIVERY

Topical instillation of an active compound is the first method of choice of delivery in ocular therapy. However, due to the innate protective characteristics of the eye against the entry of foreign compounds, the bioavailability of an instilled compound is generally low. The eyeball consists of two anatomical regions: the anterior segment, in which the cornea and conjunctiva are the main prominent structures, and the posterior segment, in which the retina plays the most important function(i.e.transduction and adaptation to different levels of light).[20] The cornea is a non-vascularized barrier consisting of five to seven layers, which exhibits high resistance to passive diffusion of ions and molecules and withstands the intraocular pressure.[21] This tissue has a smaller surface area compared to the conjunctiva which, moreover, is a leakier epithelium than the cornea.[22] Traditionally the role of the conjunctiva has been considered to be mainly protective and functioning as a passive physical barrier. However, nowadays it is known that there are several transporters (e.g. P-glycoprotein, amino acid, etc) which play a critical role in

achieving influx and efflux transport of drugs in the conjunctiva. As a consequence, the feasibility for intraocular drug delivery via the conjunctival route is now well documented.[20,22] Nevertheless, it should also be taken into account that the presence of lymphatic and blood vessels can lead to significative systemic absorption.[23] Covering both corneal and conjunctival surfaces and forming part of the tearfilm, is a mucus layer, which is secreted by the goblet cells of the conjunctiva. The lachrymal film plays a multifunctional role, since it hydrates, cleanses, lubricates and serves as a defense against the pathogens; but also, it involves an additional obstacle to any drug penetration.[1] Moreover, the lachrymalfilm is a dynamicfluid that undergoes a constant renewal and therefore limits the time of residence of the drugs on the surface of the eye. In addition to the physical barriers, ocular tissues contain metabolic enzymes, such as esterases, aldehyde and keton reductases,[24] which may degrade and reduce the efficacy of the drugs. As a result of these anatomical and physiological constraints after topical application, a major fraction of the administered drug is lost by different mechanisms, resulting in very low ocular bioavailability.[23,25] Thus they are classified as follow:

A. Drug loss from the ocular surface- After instillation, the flow of lacrimal fluid removes instilled compounds from the surface of the eye. Even though the lacrimal turnover rate is only about 1 µl/min the excess volume of the instilled fluid is flown to the nasolacrimal duct rapidly in a couple of minutes. Another source of non-productive drug removal is its systemic absorption instead of ocular absorption. Systemic absorption may take place either directly from the conjunctival sac via local blood capillaries or after the solution flow to the nasal cavity.

B. Lachrymal fluid-eye barriers- Corneal epithelium limits drug absorption from the lacrimal fluid into the eye. The corneal epithelial cells form tight junctions that limit the paracellular drug permeation. Therefore, lipophilic drugs have typically at least an order of magnitude higher permeability in the cornea than the hydrophilic drugs. In general, the conjunctiva is leakier epithelium than the cornea and its surface area is also nearly 20 times greater than that of the cornea.

C. Blood-ocular barriers- The eye is protected from the xenobiotics in the blood stream by blood-ocular barriers. These barriers have two parts: blood-aqueous barrier and blood-retina barrier. The anterior blood-eye barrier is composed of the endothelial cells in the uvea (The middle layer of the eye beneath the sclera. It consists of the iris, ciliary body, and choroid). This barrier prevents the access of plasma albumin into the aqueous humor, and also limits the access of hydrophilic drugs from plasma into the aqueous humor. The posterior barrier between blood stream and eye is comprised of retinal pigment epithelium (RPE) and the tight walls of retinal

capillaries. Unlike retinal capillaries the vasculature of the choroid has extensive blood flow and leaky walls. Drugs easily gain access to the choroidal extravascular space, but thereafter distribution into the retina is limited by the RPE and retinal endothelia.[25, 26]

ROUTES OF OCULAR DRUG DELIVERY

There are several possible routes of drug delivery into the ocular tissues as shown in **figure 2**(Routes of ocular drug delivery). The selection of the route of administration depends primarily on the target tissue.

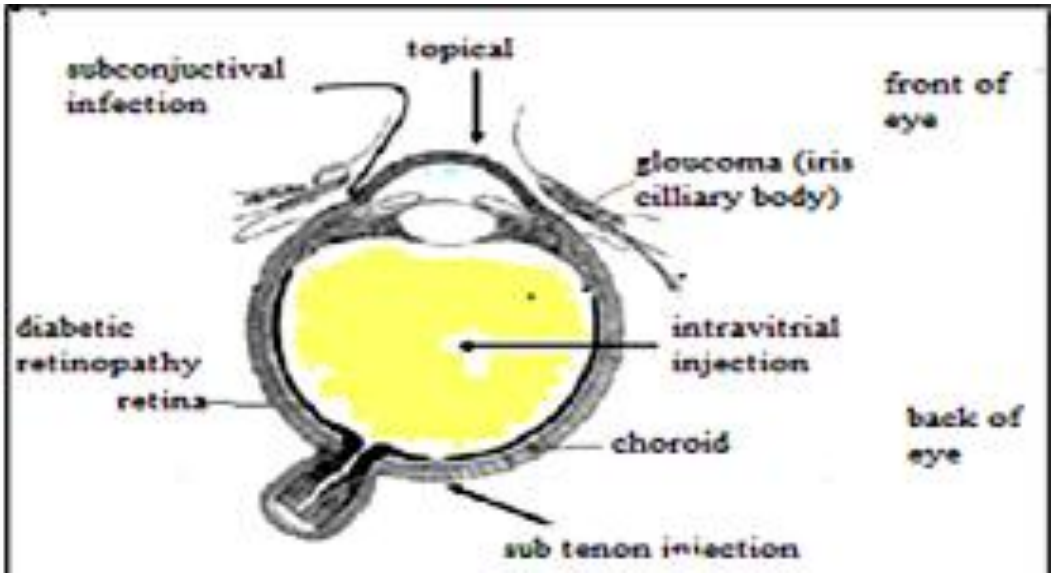


Figure 2: Routes of ocular drug delivery

A. Topical route- Typically topical ocular drug administration is accomplished by eye drops, but they have only a short contact time on the eye surface. The contact, and thereby duration of drug action, can be prolonged by formulation design (e.g. gels, jellifying formulations, ointments, and inserts).

B. Subconjunctival administration- Traditionally subconjunctival injections have been used to deliver drugs at increased levels to the uvea. Currently this mode of drug delivery has gained new momentum for various reasons. The progress in materials sciences and pharmaceutical formulation have provided new exciting possibilities to develop controlled release formulations to deliver drugs to the posterior segment and to guide the healing process after surgery.

C. Intravitreal administration- Direct drug administration into the vitreous offers distinct advantage of more straightforward access to the vitreous and retina. It should be noted; however that delivery from the vitreous to the choroid is more complicated due to the hindrance by the RPE (Retinal Pigment Epithelium) barrier. Small molecules are able to diffuse rapidly in the vitreous but the mobility of large molecules, particularly positively charged, is restricted.[25]

Mechanism of ocular drug absorption

Drugs administered by instillation must penetrate the eye and do so primarily through the cornea followed by the non-corneal routes. These non-corneal routes involve drug diffusion across the conjunctiva and sclera and appear to be particularly important for drugs that are poorly absorbed across the cornea.

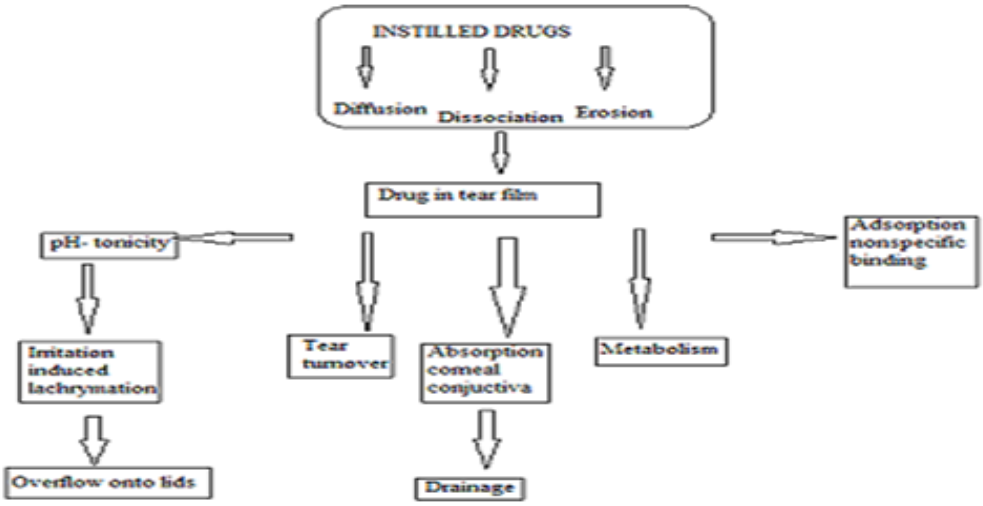


Figure 3- Ocular drug absorption

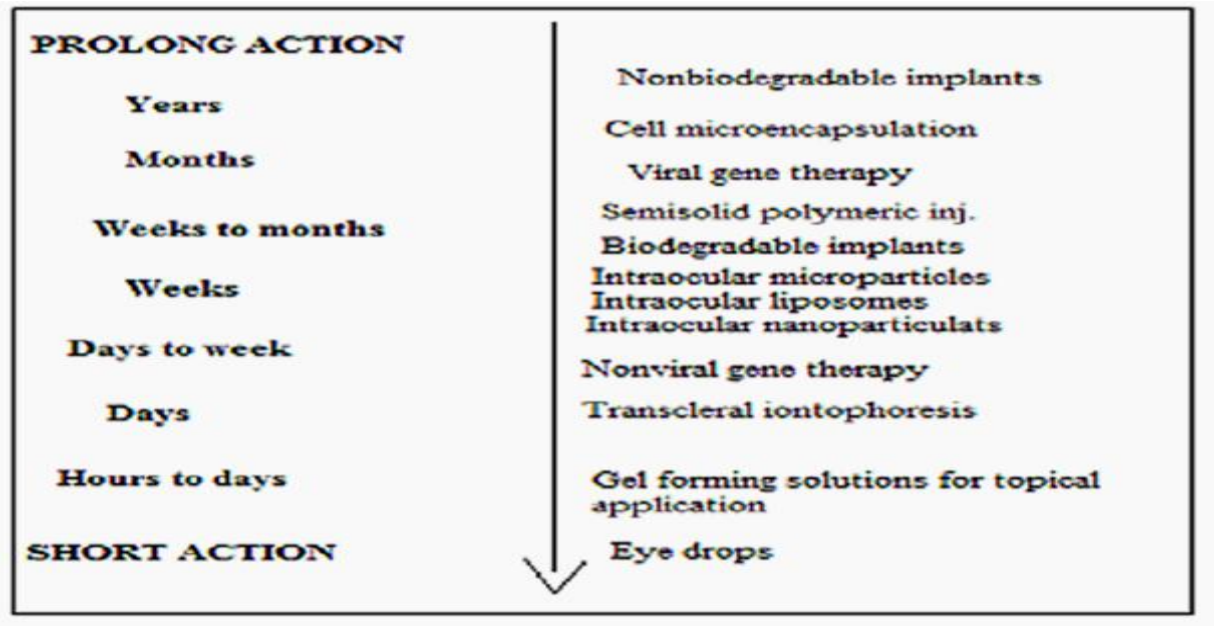
A. Corneal permeation- The permeation of drugs across the corneal membrane occurs from the precorneal space. Thus, the mixing and the kinetic behaviour of drug disposition in tears have a direct bearing on efficiency of drug absorption into the inner eye. The productive absorption of most ophthalmic drugs results from diffusion process across corneal membrane. The efficiency of absorption process is a function of rate and extent at which the transport processes occur. The flux of any drug molecule across the biological membrane depends on the physicochemical properties of the permeating molecule and its interaction with the membrane. The extent to which the transport or absorption process occurs is also function of physiological mechanism of precorneal fluid drainage or turnover. In terms of transcorneal drug permeation, the cornea can be considered to consist of three primary layers (epithelium, stroma and endothelium). The epithelium and endothelium contain on the order of a 100 fold greater amount of lipid material than the stroma. Consequently, depending on the physicochemical properties of a diffusing drug, the resistance offered by the individual layers varies greatly. Epithelium, being lipoidal, represents a diffusion barrier offering high resistance to ionic or other aqueous soluble or polar species. In contrast, compounds with relatively low polarity encounter a greater diffusional resistance in the hydrophilic stroma layer. This frequently cited concept of drug permeation across the corneal membrane is referred to as ―differential solubility concept.

B. Non-corneal permeation- Primary mechanism of drug permeation is the sclera is likely to be diffusion across the intercellular aqueous media in the case of structurally similar corneal stroma. Therefore the possibility of partitioning mechanism cannot be eliminated. Although like cornea, the conjunctiva is composed of an epithelial layer covering an underlying stroma, the conjunctival epithelium offers substantially less resistance than the corneal epithelium.[27]

Challenges of ophthalmic drug delivery system

Ophthalmic drug delivery is one of the most interesting and challenging endeavours facing the pharmaceutical scientist.[18] The landscape of ophthalmic drug delivery is highly competitive and rapidly evolving. New classes of pharmaceuticals and biologics are fuelling the demand for novel drug delivery. The main aim of pharmacotherapeutics is the attainment of effective drug concentration at the site of action for the sufficient period of time to elicit a response.

The challenge is to provide a system with improved ocular drug bioavailability and prolonged duration of activity, but still with a minimum risk of ocular complications. A major problem of ophthalmic drug delivery is not the lack of efficient drugs but the attainment of their optimal concentration at the site of their optimal concentration at the site of action.[28] The emergence of new and innovative means for improving therapeutic efficacy suggests that a greater choice of dosage forms will be provided to physicians and patients in the next decade. Most of the formulation efforts aim at maximizing ocular drug absorption through prolongation of the drug residence time in the cornea and conjunctival sac, as well as to slow drug release from the delivery system and minimize precorneal drug loss. Various ophthalmic formulations and their residence time period in the ocular cavity are given below.



(**Figure 4- Duration of ocular drug absorption**) [29]

BRIEF LAYOUT OF DIFFERENT OCULAR FORMULATIONS

A. Based on the physical form of the formulation

A multitude of ocular dosage forms are available for delivery of drugs to the eye. These can be classified on the basis of their physical forms as follow.

1. **Liquids-** solutions, sol to gel forms, sprays.
2. **Solids-** ocular inserts, contact lenses, corneal shields, artificial tear inserts, filter paper strips.
3. **Semisolids-** ointments, gels.
4. **Miscellaneous-** ocular iontophoresis, vesicular systems, mucoadhesive dosage forms, particulates.

B. Conventional ophthalmic formulations

1. 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.[30] The reported maximal attainable ocular absorption is only about 10% of the dose.[31]

2. Ointment and Gels-

Prolongation of drug contact time with the external ocular surface can be achieved using ophthalmic ointment vehicle but, the major drawback of this dosage form like, blurring of vision and matting of eyelids can limits its use. It is reported that ointments and gels vehicles can prolong the corneal contact time of many drugs administered by topical ocular route, thus prolonging the duration of action and enhancing ocular bioavailability of drugs.[32]

3. Ocuserts-

Ocular insert (Ocusert) are sterile preparation that prolong residence time of drug with a controlled release manner and negligible or less affected by nasolacrimal damage.[33]

4. Liposomes-

Liposomes are biocompatible and biodegradable lipid vesicles made up of natural lipids and about 25–10 000 nm in diameter.[34] They are having an intimate contact with the corneal and conjunctival surfaces which is desirable for drugs that are poorly absorbed, the drugs with low partition coefficient, poor solubility or those with medium to high molecular weights and thus increases the probability of ocular drug absorption.[35]

5. Niosomes-

Niosomes are developed as they are chemically stable as compared to liposomes and can entrap both hydrophobic and hydrophilic drugs. Niosomes are non-ionic surfactant vesicles that have potential applications in the delivery of hydrophobic or amphiphilic drugs.[36]

6. Pharmacosomes-

This term is used for pure drug vesicles formed by the amphiphilic drugs. Any drug possessing a free carboxyl group or an active hydrogen atom can be esterified to the hydroxyl group of a lipid molecule, thus generating an amphiphilic prodrug. The amphiphilic prodrug is converted to pharmacosomes on dilution with water. The pharmacosomes show greater shelf stability, facilitated transport across the cornea, and a controlled release profile.[37]

C. Controlled ophthalmic drug delivery

1. Implants- .

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.[38]

2. Iontophoresis-

In Iontophoresis direct current drives ions into cells or tissues. For iontophoresis the ions of importance should be charged molecules of the drug.[39] The positively charges of drug are driven into the tissues at the anode and vice versa. The ocular iontophoresis delivery is not only fast, painless and safe but it can also deliver high concentration of the drug to a specific site. Iontophoretic application of antibiotics in eye not only increases their bactericidal activity but also reduce the severity of disease.[40]

3. Dendrimer-

Dendrimer can successfully be used for different routes of drug administration and has better water solubility, bioavailability and biocompatibility. They determined the influence of size, molecular weight and number of amine, carboxylate and hydroxyl surface groups in several series of dendrimers. The residence time was longer for the solutions containing dendrimers with carboxylic and hydroxyl surface groups.[41]

4. Cyclodextrin-

Cyclodextrin (CDs) are cyclic oligosaccharides capable of forming inclusion complexes with many guest molecules. This complexation of CD does not interrupt the biological membrane compared to conventional permeation enhancer like benzalkonium chloride. Due to inclusion, the free drug is not available, so drugs with inherent irritant properties can be successfully

delivered by this approach. CD molecules are inert in nature and were found to be non-irritant to the human and animal eye.[42]

5. Contact lenses-

Water soluble drugs soaked in drug solutions can be absorbed through Contact lenses. The drug saturated contact lenses are placed in the eye which releases the drug in eye for a long period of time. For prolongation of ocular residence time of the drugs, hydrophilic contact lenses can be used.[43]

6. 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.[44]

7. Nanosuspension-

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.[45]

8. Microneedle-

As an alternative to topical route researchers have developed microneedle to deliver drug to posterior segment and it had shown prominent in vitro penetration into sclera and rapid dissolution.[46]

9. Prodrug-

The ideal prodrug for ocular therapy not only has increased lipophilicity and a high partition coefficient, but it must also have high enzyme susceptibility to such an extent that after corneal penetration or within the cornea they are either chemically or enzymatically metabolized to the active parent compound.[47]

10. Mucoadhesive Polymers-

They are basically macromolecular hydrocolloids with plentiful hydrophilic functional groups, such as hydroxyl, carboxyl, amide and sulphate having capability for establishing electrostatic interactions, and treatment of gloucoma.[48]

11. Phase Transition Systems/In-situ gel system-

Phase transition of the formulation from the liquid form to the gel or solid phase occurs when these systems instilled into the cul-de-sac of eye lead to increase the viscosity of a drug formulation in the precorneal region results in increased bioavailability, due to slower drainage from the cornea. These systems can be influenced by pH, temperature or by ion activation.[49]

D. Advanced ophthalmic drug delivery system

1. Cell Encapsulation
2. Gene Therapy
3. Stem cell Therapy
4. Protein and Peptide therapy
5. Scleral Plug therapy
6. Aptamer (oligonucleotide ligands)
7. Ribozyme therapy

Polymeric drug delivery for ophthalmic

Hydrogels are one of the upcoming classes of polymer based controlled release drug delivery system.[50] Polymeric drug delivery systems have been extensively studied in order to solve the potential problems associated with drugs or bioactive molecules including toxicity, site dependence, low effectiveness, poor solubility, short half-life, rapid degeneration and rapid clearance from the body. Considering various properties such as flexibility, structure, biocompatibility, and hydrophilicity, three dimensional matrices, hydrogels, are being extensively used as drug delivery carriers.[51]

Advantages of polymeric drug delivery

- Reduce toxic effects on the healthy tissue and reach sites that are conventionally inaccessible due to the presence of various barriers[25] by targeted drug delivery.
- Increase the half-life of drugs, preventing their rapid degradation, and reduce the rate of elimination, thus maintaining drug concentration within a therapeutically effective window.
- Reduce the amount of drug required to achieve therapeutic efficacy.
- Cut down the number of repeated invasive dosage required for certain conditions and thus helps to improve patient‘s compliance and offers better living.[52]

Types of polymeric systems / Different types of gels

A:Gels and hydrogels

Technically, gels are semi-solid systems comprising small amounts of solid, dispersed in relatively large amounts of liquid, yet possessing more solid-like than liquid-like character.[53] sometimes, hydrogels are also described as aqueous gels because of the prefix ‘hydro’. Although the term ‘hydrogel’ implies material already swollen in water, in a common misinterpretation in polymer science is the use of the terms ‘gel’ and ‘hydrogel’ synonymously. As polymeric networks, both gels and hydrogels might be similar chemically, but they are physically distinct.

In true sense hydrogels are a cross-linked network of hydrophilic polymers. They possess the ability to absorb large amounts of water and swell, while maintaining their three-dimensional (3D) structure.[54]

This definition differentiates hydrogels from gels, which are polymeric networks already swollen to equilibrium, and the further addition of fluids results only in dilution of the polymeric network **(figure 5-** polymeric structure of gel and hydrogel**)**. Although some of the gels are rigid enough to maintain their structure under a small stress, after exceeding the yield-value, gel fluidity is observed with loss of polymer structure.[55)]

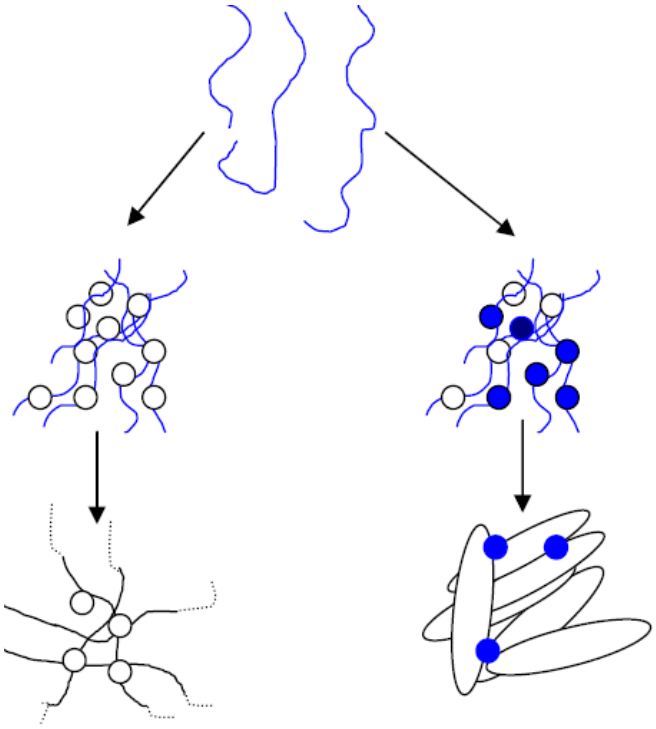


Figure 5 : Polymeric system for gels and hydrogels

B:In situ hydrogels

Hydrogels are polymeric networks that absorb large quantities of water while remaining insoluble in aqueous solutions due to chemical or physical crosslinking of individual polymer chains. They resemble natural living tissue more than any other class of synthetic biomaterials due to their high water content; furthermore, the high water content of the materials contributes to their biocompatibility.[56] Hydrogels show minimal tendency to adsorb proteins from body fluids because of their low interfacial tension. Further, the ability of molecules of different sizes to diffuse into (drug loading) and out of (drug release) hydrogels allows the possible use of dry or swollen polymeric networks as drug delivery systems for oral, nasal, buccal, rectal, vaginal, ocular and parenteral routes of administration.[57] These are polymers endowed with an ability to swell in water or aqueous solvents and induce a liquid–gel transition.[58]

Currently; two groups of hydrogels are distinguished, namely preformed and in situ forming gels preformed hydrogels can be defined as simple viscous solutions which do not undergo any modifications after administration. The use of preformed hydrogels still has drawbacks that can limit their interest for ophthalmic drug delivery or as tear substitutes. They do not allow accurate and reproducible administration of quantities of drugs and, after administration; they often produce blurred vision, crusting of eyelids, and lachrymation. Thus in situ hydrogels can be instilled as eye drops and undergo an immediate gelation when in contact with the eye. In situ-forming hydrogels are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form viscoelastic gel and this provides a response to environmental changes. Three methods have been employed to cause phase transition on the surface, change in temperature, pH, and electrolyte composition. Increase in solution viscosity by using polymers improves retention of product on the corneal surface. The polymers selected should meet some specific rheological characteristics.[59, 60]

C:Smart hydrogels (stimuli-sensitive hydrogels)

'Smart' hydrogels or stimuli-sensitive hydrogels are very different from inert hydrogels in that they can 'sense' changes in environmental properties such as pH and temperature and respond by increasing or decreasing their degree of swelling. The volume changing behaviour of 'smart' hydrogels is particularly useful in drug delivery applications as drug release can be triggered upon environmental changes. These intelligent‖ or 'smart' polymers play important role in drug delivery since they may dictate not only where a drug is delivered, but also when and with which interval it is released. The stimuli that induce various responses of the hydrogel systems include physical (temperature) or chemical (pH, ions) ones.[59]

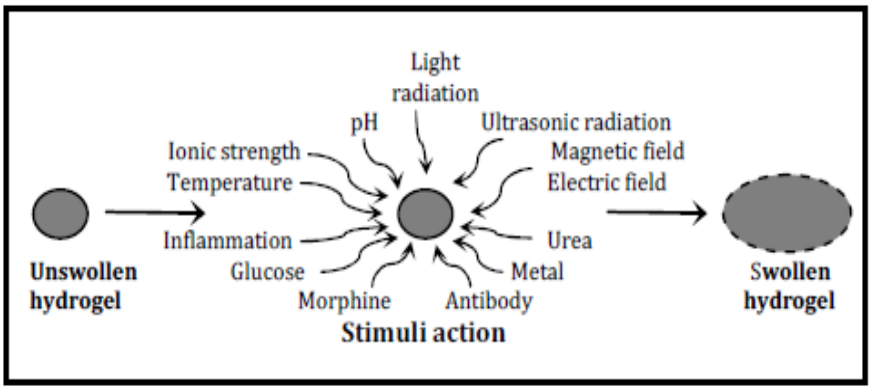


Figure 6: stimuli sensitive swelling[55]

Types of in-situ gelling system (approaches of in-situ gelling system)

There are three broadly defined mechanisms used for triggering the in situ gel formation of biomaterials.

- Physiological stimuli (e.g., temperature and pH),
- Physical changes in biomaterials (e.g., solvent exchange and swelling),
- Chemical reactions (e.g., enzymatic, chemical and photo-initiated polymerization).

1. In situ formation based on physiological stimuli

A. Thermally trigged system

Temperature-sensitive hydrogels are probably the most commonly studied class of environment-sensitive polymer systems in drug delivery research. The use of a biomaterial whose transitions from sol-gel is triggered by increase in temperature is an attractive way to approach in-situ formation. The ideal critical temperature range for such system is ambient and physiologic temperature, such that clinical manipulation is facilitated and no external source of heat other than that of body is required for trigger gelation. A useful system should be tolerable to account for small differences in local temperature, such as might be encountered in appendages at the surface of skin or in the oral cavity.

B. pH triggered systems

Another formation of in situ gel based on physiologic stimuli is formation of gel is induced by pH changes. All the pH-sensitive polymers contain pendant acidic or basic groups that either accept or release protons in response to changes in environmental pH. The polymers with a large number of ionizable groups are known as polyelectrolytes. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups. The most of anionic pH sensitive polymers are based on PAA (Carbopol®, carbomer) or its derivatives.

2. In situ formation based on physical mechanism

A. Swelling In situ formation may also occur when material absorbs water from surrounding environment and expand to occur desired space. One such substance is myverol 18-99 (glycerol mono-oleate), which is polar 1400 lipid that swells in water to form lyotropic liquid crystalline phase structures. It has some bioadhesive properties and can be degraded in vivo by enzymatic action.

B. Diffusion : This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N-methyl-pyrrolidone (NMP) has been shown to be useful solvent for such system.

3. In situ formation based on chemical reactions

Chemical reactions that results in situ gelation may involve precipitation of inorganic solids from supersaturated ionic solutions, enzymatic processes, and photo-initiated processes.

A. Ionic cross linking

Polymers may undergo phase transition in presence of various ions. Some of the polysaccharides fall into the class of ion-sensitive ones .While k-carrageenan forms rigid, brittle gels in reply of small amount of K+, carrageenan forms elastic gels mainly in the presence of $Ca^{2+.}$ Gellan gum commercially available as Gelrite® is an anionic polysaccharide that undergoes in situ gelling in the presence of mono- and divalent cations, including $Ca^{2+,}$ Mg^{2+}, K^{+} and Na^{+}. Gelation of the low-methyl pectins can be caused by divalent cations, especially $Ca^{2+.}$ Likewise, alginic acid undergoes gelation in presence of divalent/polyvalent cations e. g. Ca^{2+} due to the interaction with glucuronic acid block in alginate chains.

B. Enzymatic cross-linking

In situ formation catalysed by natural enzymes has not been investigated widely but seems to have some advantages over chemical and photochemical approaches. For example, an enzymatic process operates efficiently under physiologic conditions without need for potentially harmful chemicals such as monomers and initiators. Intelligent stimuli-responsive delivery systems using hydrogels that can release insulin have been investigated. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to blood glucose level releasing the entrapped insulin in a pulsatile fashion. Adjusting the amount of enzyme also provides a convenient mechanism for controlling the rate of gel formation, which allows the mixtures to be injected before gel formation.

C. Photo-polymerisation

Photo-polymerisation is commonly used for in situ formation of biomaterials. A solution of monomers or reactive macromer and initiator can be injected into a tissues site and the application of electromagnetic radiation used to form gel. Acrylate or similar polymerizable functional groups are typically used as the polymerizable groups on the individual monomers and macromers because they rapidly undergo photo polymerisation in the presence of suitable photo initiator. Typically long wavelength ultraviolet and visible wavelengths are used. Short wavelength ultraviolet is not used often because it has limited penetration of tissue and biologically harmful. A ketone, such as 2, 2dimethoxy-2-phenyl acetophenone, is often used as the initiator for ultraviolet photo- polymerization, whereas camphorquinone and ethyl eosin initiators are often used in visible light systems. These systems can be designed readily to be degraded by chemical or enzymatic processes or can be designed for long term persistence in-vivo. Photo polymerizable systems when introduced to the desired site via injection get photo cured in-situ gel with the help of fibre optic cables and then release the drug for prolonged period

of time. The photo-reactions provide rapid polymerization rates at physiological temperature. Furthermore, the systems are easily placed in complex shaped volumes leading to an implant formation.[61]

CONCLUSION

The primary requirement of a successful controlled release product focuses on increasing patient compliance which the in situ gels offer. Exploitation of polymeric in-situ gels for controlled release of various drugs provides a number of advantages over conventional dosage forms. Sustained and prolonged release of the drug, good stability and biocompatibility characteristics make the in-situ gel dosage forms very reliable. These are easy to instill at the same time improves ocular bioavailability by increasing the duration of contact with corneal tissue, thereby reducing the frequency of administration required in case of conventional ophthalmic solutions, thus optimizing ocular therapy. Use of biodegradable and water soluble polymers for the in situ gel formulations can make them more acceptable and excellent drug delivery systems.

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