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Review Article

THE USE OF *IN-SITU* HYDROGEL IN OCULAR DRUG DELIVERY

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Abstract

Ocular drug delivery has remained as one of the most challenging and interesting task for pharmaceutical scientists. The conventional ocular drug delivery systems like solutions, suspensions, ointments, polymeric insert show drawbacks such as lack patient compliance, increased precorneal elimination, and blurred vision. In situ-forming hydrogels are liquid based upon phase transition in the ocular cul-de-sac to form viscoelastic gel and this provides a response to environmental changes. In the past few years, an impressive number of novel temperature, pH, and ion induced in situ-forming systems have been reported for sustain ophthalmic drug delivery. This review includes effect of polymers, temperature and pH in situ-forming polymeric systems used to achieve prolonged contact time of drugs with the cornea and increase their bioavailability.

Keywords: - : In situ gelling system, hydrogel, change of pH, Polymer

Introduction

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist. The anatomy, physiology, and biochemistry of the eye render this organ highly impervious to foreign substances. A significant challenge to the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage. Development of newer, more sensitive diagnostic techniques and novel therapeutic agents continue to provide ocular delivery systems with high therapeutic efficacy. The ophthalmic formulation such as solution, suspension, and ointments, available in market shows drawbacks such as increased precorneal elimination, high variability in efficiency, and blurred vision. The major problem with the conventional dosage forms is bioavailability of drug, which was improved ion last three decades by common method i.e. adding viscosity-enhancing agent or mucoadhesive polymers into drug formulation. The goal of pharmacotherapeutics is to treat a disease in a consistent and predictable fashion. An assumption is made that a correlation exists between the concentration of a drug at its intended site of action and the resulting pharmacological effect. The specific aim of designing a therapeutic system is to achieve an optimal concentration of a drug at the active site for the appropriate duration. Ocular disposition and elimination of a therapeutic agent is dependent upon its physicochemical properties as well as the relevant ocular anatomy and physiology. Ophthalmic solutions are available for multidose or single-dose administration in a wide variety of glass and plastic dropper bottles, which deliver drops with a volume between 25 and 70 µL. Upon administration of topically applied eye drops, removal from the eye is rapid because of tear production and the blinking processes occurring simultaneously. The precorneal volume is about 7 µL, but volumes up to 20 to 30 µL can be held in this area before spillage occurs. Instillation of volumes greater than this will result in simply spilling out onto the cheek or rapid loss with the tears through drainage into the nasolachrymal duct. Also, the instilled product is diluted by normal tear production, with tear production rates in man reported as 1 µL/min under resting conditions. In practice, the introduction of any eye drop product, but particularly products causing irritation, is likely to stimulate the tear production rate and increase the rate of drug removal from the eye. The removal of material by dilution is also aided by the blink reflex

where each blink pumps approximately 2 µL of tear fluid into the nasolachrymal duct. Therefore only small amount of drug actually penetrates the cornea and reaches intraocular tissue. Due to these limitations, Controlled drug delivery to the eye is restricted imposed by the efficient protective mechanism. An ideal ophthalmic drug delivery must be able to release the drug in sustained manner and to remain in the area of front of the eye for prolong period of time. The in-situ activated gel forming systems can be administered in drop form and create considerably fewer problems with vision so that it is most preferable type of delivery system. Furthermore, In-situ gel systems provide better sustained release properties than drops. This type of dosage forms are used now a day in various type of eye disease like glaucoma, dry eye syndrome, eye infection etc. **[1-4]**

Anatomy and Physiology of the eye

Eye is the organ of the sense of sight situated in the orbital cavity and it is supplied by the optic nerve (2nd cranial nerve). Human eyeball is approximately globe shaped with a diameter of about 24 mm. It is slightly flattened from above downward. Eyeball is made up of two segments, an anterior part and posterior part. The radius of this part is about 8 mm. The posterior wall of this part is lined by the light sensitive structure called retina. [5-6]

Eyebrows: The two eyebrows are arched structures placed horizontally over the superciliary ridge of the frontal bone, separated from each other by a smooth hairless prominent area known as glabella. The surface of the eyebrows is covered by hair which project obliquely from the skin and form an important part of the eyebrows. They protect the eyeball from sweat, dust and other foreign bodies. [7]

Eyelids: Eyelids protect the eyeball from foreign particles coming in contact with its surface and cutoff the light during sleep. The eyelids are opened and closed voluntarily as well as reflexly. They distribute the tear fluid over the eye, providing an optically smooth surface over the cornea.

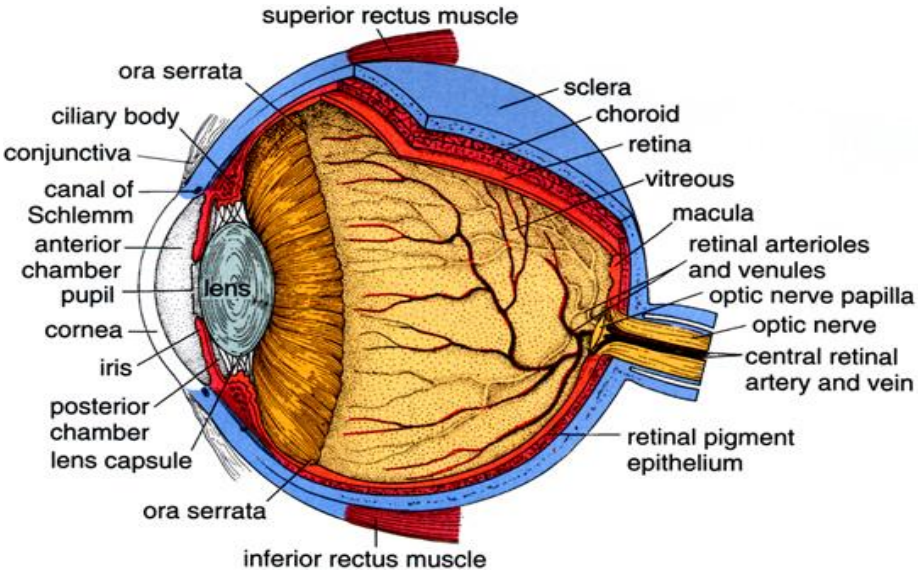

Fig.1 Human eye

Conjunctiva: It is a thin mucous membrane, which covers the exposed part of the eye. After covering the anterior surface, the conjunctiva is reflected into the inner surface of the eyelids. The surface of conjunctiva is lubricated by thin film of tear secreted by lacrimal gland. [6]

Lacrimal apparatus: The lacrimal apparatus comparises the structures concerned with the formation and drainage of tears. The nasolachrymal drainage system consists of three parts: the secretory system, the distributive system and the excretory system. The secretory system consists of basic secretors that are stimulated by blinking and temperature change due to tear evaporation and reflex secretors that have an efferent parasympathetic nerve supply and secrete in response to physical or emotional stimulation. The distributive system consists of the eyelids and the tear meniscus around the lid edges of the open eye, which spread tears over the ocular surface by blinking, thus preventing dry areas from developing. The excretory part of the nasolachrymal drainage system consists of the

lachrymal puncta, the superior, inferior and common canaliculi; the lachrymal sac; and the nasolachrymal duct. In humans, the two puncta are the openings of the lachrymal canaliculi and are situated on an elevated area known as the lachrymal papilla. It is thought that tears are largely absorbed by the mucous membrane that lines the ducts and the lachrymal sac; only a small amount reaches the nasal passage. [7]

The eyeball: The eyeball comprises three coats: [5]

- Outer (fibrous coat): sclera and cornea,
- Middle (vascular coat): choroid, ciliary body and iris,
- Inner (nervous coat): retina.

The outer fibrous coat: It is dense strong walls which protect the intraocular contents. Anterior one sixth of the fibrous coat is transparent and is called cornea. The posterior $5/6^{th}$ opaque part is called sclera. Junction of the cornea and scalera is called limbus.

Cornea: The cornea is transparent, avascular, watchglass-like structure with a smooth shining surface. The average diameter of cornea is 11-12 mm. Its thickness in the central part is 0.52 mm and in the peripheral part 0.67 mm. Nerve supply of cornea is purely sensory, derived from the ophthalmic division of the 5^{th} cranial nerve.

Sclera: The sclera, or white of the eye, forms the outermost layer of tissue of the posterior and lateral aspects of the eyeball and is continuous anteriorly with the transparent cornea. It consists of a firm fibrous membrane that maintains the shape of the eye and gives attachment to the extraocular or extrinsic muscles of the eye. Anteriorly the sclera continues as a clear transparent epithelial membrane, the cornea. Light rays pass through the cornea to reach the retina. The cornea is convex anteriorly and is involved in refracting or bending light rays to focus them on the retina. [7]

Iris: The iris works in the same way as the pupil of the eye. It is located in front of the crystalline lens and its size can be changed from 1.5mm to 8mm in diameter. These changes are made in order to adapt the energy for image formation and to prevent the retina from damage. [8]

Ciliary body: The Ciliary body is the anterior continuation of the choroid consisting of ciliary muscle (smooth muscle fibres) and secretory epithelial cells. It gives attachment to the suspensory ligament which, at its other end, is attached to the capsule enclosing the lens. Contraction and relaxation of the ciliary muscle changes the thickness of the lens which bends, or refracts light rays entering the eye to focus them on the retina. The epithelial cells secrete aqueous fluid into the anterior segment of the eye, i.e. the space between the lens and the cornea (anterior and posterior chambers). The ciliary body is supplied by parasympathetic branches of the oculomotor nerve (3rd cranial nerve). Stimulation causes contraction of the smooth muscle and accommodation of the eye.

Choroids: It is a dark brown highly vascular layer situated in between sclera and retina. It supplies nutrition to the outer layers of retina.

The inner nervous coat (retina): Retina, the innermost tunic of the eyeball, is a thin, delicate, transparent membrane. It is concerned with the visual functions.

Interior of eyeball: Interior of the eyeball contains, from anterior to posterior—the aqueous humour, lens and vitreous.

Aqueous humour: The anterior segment of the eye, i.e. the space between the cornea and the lens, is incompletely divided into anterior and posterior chambers by the iris. Both chambers contain a clear aqueous fluid (humour) secreted into the posterior chamber by ciliary glands. It circulates in front of the lens, through the pupil into the anterior chamber and returns to the venous circulation through the sclera venous sinus (canal of Schlemm) in the angle between the iris and cornea. There is continuous production and drainage but the intraocular pressure remains fairly constant between 10 to 20 mmHg. An increase in this pressure causes glaucoma. Aqueous fluid supplies nutrients and removes waste from the transparent structures in the front of the eye that have no blood supply, i.e. the cornea, lens and lens capsule.

Vitreous humour: Behind the lens and filling the posterior segment (cavity) of the eyeball is the vitreous body (humour). This is a soft, colourless, transparent, jelly-like substance composed of 99% water, some salts and mucoprotein. It maintains sufficient intraocular pressure to support the retina against the choroid and prevent the walls of the eyeball from collapsing. The eye keeps its shape because of the intraocular pressure exerted by the

vitreous body and the aqueous fluid.It remains fairly constant throughout life.

Lens: The lens is a transparent, biconvex, crystalline structure placed between the iris and the vitreous. It consists of fibres enclosed within a capsule and it is suspended from the ciliary body by the suspensory ligament. Its thickness is controlled by the ciliary muscle through the suspensory ligament. The lens bends (refracts) light rays reflected by objects in front of the eye. It is the only structure in the eye that can vary its refractory power, achieved by changing its thickness. [5, 7]

Advantages of ocular drug delivery systems [9-10]

- Easy convenience and needle free drug application
- Good penetration of hydrophilic, low molecular weight drugs can be obtained through the eye.
- To increase the ocular bioavailability of drug by increasing the corneal contact time. This can be achieved by effective adherence to corneal surface.
- Avoidance of hepatic first pass metabolism and thus potential for dose reduction compared to oral delivery.

Ocular Drug Delivery Systems [11, 10-12]

Conventional Ophthalmic Drug Delivery Systems

- Aqueous Solutions
- Suspensions
- Ointments

Novel Ophthalmic Drug Delivery Systems

- Ocular Inserts
- Liposomes
- Microemulsions
- In-situ hydrogel

Conventional Ophthalmic Drug Delivery Systems

Aqueous Solutions

Majority of topical ophthalmic preparations available today are in the form of aqueous solutions. A homogeneous Solution dosage form offers many advantages including the simplicity of large scale manufacture. The factors that must be taken into account while formulating aqueous solution include selection of appropriate salt of the drug substance, solubility, therapeutic concentration required, ocular toxicity, pKa and the effect of pH. Other parameters includes solubility, tonicity, buffer capacity, viscosity,stability compatibility with other formulation ingredients as well as packaging components, choice of preservative, ocular comfort and ease of manufacturing. However, solution eye drops do have the disadvantage of being rapidly drained from the eye, with corresponding loss of drug. The inclusion of viscosity-increasing agents in the formulation, such as hypromellose, hydroxyethylcellulose, polyvinyl alcohol, povidone, or dextran, can be used to increase the tear viscosity, which decreases drainage, thereby prolonging precorneal retention of the drops in the eye. Various studies have shown that an increase in product viscosity increases the residence time in the eye, but there is a danger that high-viscosity products may not be well tolerated in the eye. For this reason, most ophthalmic products are formulated within the range of 10 to 25 cP by the addition of viscosity-increasing agents. Certain viscosity-increasing materials, such as hyaluronic acid and its derivatives, or carbomer, have been shown to be more effective in achieving precorneal retention because of their mucoadhesive properties.

Suspensions

Aqueous or oily suspension eye drop formulations may be considered for drugs that are poorly water soluble, or because of poor aqueous drug stability. The drug particle size must be reduced to less than 10 µm levels to avoid irritation of the eye surface, leading to blinking and excessive lachrymation. One possible advantage of ophthalmic suspensions is that they should prolong the residence time of drug particles in the eye, allowing time for dissolution in the tears and an increase in ocular bioavailability. Some of the difficulties that a formulator should overcome during the development of a suspension are non-homogeneity of the dosage form, settling, cake formation, aggregation of the suspended particles, resuspendability, effective preservation, and ease of manufacture. The understanding of interfacial properties, wetting, particle interaction zeta potential, aggregation, sedimentation and rheological concepts are required for formulating an effective and elegant suspension.

Ointments

Eye ointments are sterile semisolid preparations intended for application to the conjunctiva. They are

attractive because of their increased contact time and better bioavailability compared to solutions. They can be very useful for night time application; however, they are not always well accepted by patients because upon application they often cause blurred vision due to refractive index difference between the tear and the non-aqueous nature of the ointment and inaccurate dosing. [11-13]

Novel Ophthalmic Drug Delivery Systems

Ocular Inserts

In 1975, the first controlled-release ophthalmic dosage form was marketed in United States by Alza Corporation. The Ocusert is an elliptical shaped membrane which is soft and flexible and designed to be placed in the cul-de-sac between the sclera and the eyelid and continuously release drug at a steady rate (20 and 40 μg/h) for 1 week.

Liposomes

It may increase the ocular bioavailability of certain drugs by increasing the association of the drug with the cornea by means of an increased lipophilic liposomal bilayer interaction with the corneal epithelium. Several other potential advantages of using liposomes as drug carriers for ophthalmic drug delivery have been reported. They can accommodate both hydrophilic and lipophilic drugs, they are biocompatible and biodegradable, they can protect the encapsulated drug from metabolic degradation; and they can act as a depot, releasing the drug slowly. Liposomes, however, have the disadvantages of reduced physical stability and difficulties in sterilizing the product. Temperatures required for autoclaving can cause irreversible damage to vesicles, while filtration is only applicable to vesicles less than 0.2 μm. [11]

Microemulsions

Microemulsions are dispersions of water and oil facilitated by a combination of surfactant and co-surfactant in a manner to reduce interfacial tension. These systems are usually characterized by higher thermodynamic stability, small droplet size (~100 nm) and clear appearance. Microemulsions possess low surface tension and therefore exhibit good wetting and spreading properties. While the presence of surfactants is advantageous due to an increase in cellular membrane permeability, which facilitates drug absorption and bioavailability, Caution needs to be taken in relation to the amount of surfactant incorporated, as high concentrations can lead to ocular toxicity. In general, nonionic surfactants are preferred over ionic ones, which are generally too toxic to be used in ophthalmic. Surfactants most frequently utilized for the preparation of Microemulsions are poloxamer, polysorbate, and polyethylene glycol derivatives.

Nanosuspensions

This can be defined as sub-micron colloidal system which consists of poorly water-soluble drug, suspended in an appropriate dispersion medium stabilized by surfactants. Nanosuspenisons usually consist of colloidal carriers like polymeric resins which are inert in nature. They help in enhancement of drug solubility and thus bioavailability. Unlike microemulsions, they are also popular because of their non irritant nature. [13- 14]

In-situ Hydrogel [11, 13]

Ophthalmic delivery systems can be developed containing polymers that undergo a phase change from liquid to semisolid as a result of changes in temperature, pH, or ionic strength in the tear film. These formulations are liquid formulations upon administration, but gel on contact with the eye to provide extended retention times. In situ gel formers also have the advantage of ease of administration, and improved patient compliance, because they can be instilled as a liquid drop.

Advantages of hydrogels [15]

- Sustained and prolonged action in comparison to conventional drug delivery systems
- Decreased dose of administration.
- Decreased side-effects.
- Improved patient compliance.
- Drug targeting to specific site.
- Protection of mucosa from irritating drugs.
- Drug loss is prevented by extensive first pass metabolism.
- Lower cost of therapy.

TYPES OF HYDROGELS [16-17]

a) Temperature induced in-situ gel systems

Gelling of the solution is triggered by change in temperature, thus sustaining the drug release. This can be achieved by using a polymer that is a solution at room temperature (<25°C) and a gel at body temperature. Thermosetting polymer is used for this type of gelling system and can be used up to 20-30%. An increase in concentration of poloxamer (Thermosetting polymer) increases contact time, increases elasticity of the gel and

decreases the sol-gel transition temperature. Poloxomer has mucomimetic properties and optical clarity therefore it can be successfully used as a tear substitute. It can be used in combination with hyaluronic acid and Carbopol. Ocular bioavailability of drug can be increased more readily by altering both the rheological characteristics of the delivery systems containing pluronic and by using a smaller dose volume. Carbopol (0.3%) and pluronic (14%) in combination shows a better retention of drugs than either alone.

b) pH induced in situ gel systems

Gelling of the solution is triggered by a change in pH. At pH 4.4 the formulation is a free-running solution which undergoes coagulation when the pH is raised by the tear fluid to pH 7.4. The pH change of about 2.8 units after instillation of the formulation (pH 4.4) into the tear film leads to an almost instantaneous transformation of the highly fluid latex into a viscous gel. Cellulose acetate phthalate latex, cross-linked polyacrylic and derivatives of Carbomers are used. Preliminary investigations of the pH sensitive latex system for ophthalmic administration began in the early 1980s. A Carbopol formulation has been shown to be therapeutically efficacious, stable, non irritant and provide sustained release of drug over 8 hours. Hydroxy ethyl cellulose was found to increase viscosity and prolong drug release.

c) Osmotically induced in situ gel systems:

Gelling of the solution can also be triggered by a change in ionic strength. It is assumed that the rate of gelation depend on the osmotic gradient across the surface of the gel. It is therefore likely that the osmolality of the solution might have an influence on the rate of the sol-gel transition occurring in the eye. The aqueous polymer solution forms a clear gel in the presence of the mono or divalent cations typically found in the tear fluids. The electrolyte of the tear fluid and especially Na, Ca and Mg cations are particularly suited to initiate gelation of the polymer when instilled as a liquid solution in the conjunctival cul-de-sac. The osmotically induced polymer Gelrite shows improvement in the ocular absorption of drug. Using hypotonic solutions of Gelrite, the gel can remain in the human eye for 20 hours.

Stimuli sensitivity of hydrogels

External stimuli	Mechanism	Examples
Temperature	Formulation is liquid at room temperature (20°– 25° c) which undergoes gelation with contact to body fluids (35° – 37°c) temperature increases the degradation of polymer chain which leads to formation of hydrophobic domains and transition of an aqueous liquid to hydrogel network	Poloxamer/pluronics, Polyester, Xyloglucan, Cellulose derivatives.
Ionic interactions	Formulation undergoes liquid-gel transition under influence of an increase in ionic strength, Gel formation takes place because of complexation with polyvalent cations (like ca^{+2}) in lacrimal fluid.	Chitosan, Gallen gum, Alginates
Ph-change	Sol to gel transition when ph raised from 4.2 – 7.4 (eye ph). At higher ph polymer forms hydrogen bonds with mucin which leads to formation of hydrogel networks	Pseudolatexes, Acrylates (carbopols), Cellulose acetate phthalate (cap).

Conclusions:

The development of ophthalmic drug delivery systems is easy because we can easily target the eye to treat ocular diseases and complicated at the same time because the eye has specific characteristics, which make the development of ocular drug delivery systems extremely difficult. The most widely In situ developed drug delivery system is represented by the polymeric hydrogels. Hydrogels generally offer a moderate improvement of ocular drug bioavailability despite their favorable bioadhesive properties. One of the disadvantages is that hydrogel may result in blurred vision as well as foreign body sensation to patients. activated gel-forming systems seem to be

preferred as they can be administered in drop form and create significantly less problems with vision. Moreover, they provide good sustained release properties. Over the last decades, an impressive number of novel temperature, pH, and ion induced in-situ forming solutions have been described in the literature. Each system has its own advantages and drawbacks. The choice of a particular hydrogel depends on its intrinsic properties and envisaged therapeutic use.

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