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Research Article

in-situ GEL SYSTEM FOR OPHTHALMIC PREPARATION

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ABSTRACT

Recently, controlled and sustained drug delivery has become the standard in modern Pharmaceutical design and an intensive research have been undertaken in achieving much better drug product effectiveness, reliability and safety. This interest has been sparked by the advantages shown by *in situ* forming polymeric delivery systems such as ease of administration and reduced frequency of administration, improved patient compliance and comfort. The formation of gels depends on factors like temperature modulation, pH change, presence of ions and ultra violet irradiation, from which the drug gets released in a sustained and controlled manner. Various biodegradable polymers that are used for the formulation of in situ gels include gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly (DLlactic acid), poly (DL-lactide-co-glycolide) and poly-caprolactone. Mainly *in situ* gels are administered by oral, ocular, rectal, vaginal, injectable and intraperitoneal routes. The *in situ* gel forming polymeric formulations offer several advantages like sustained and prolonged action in comparison to conventional drug delivery systems. From a manufacturing point of view, the production of such devices is less complex and thus lowers the investment and manufacturing cost. This comprehensive article contains approaches, polymers, anatomy of eyes, factor affecting gels and recent advances of in situ gel.

Keywords: Biodegradable polymers, controlled release, in situ gels, poly (lactic-co-glycolic acid), sustained release.

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 exquisitely impervious to foreign substances. The challenge to the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage. The primitive ophthalmic solutions, suspensions and ointment dosage forms are clearly no longer sufficient to combat some present virulent diseases. Due to tear drainage, most of the administered dose passes via the naso-lacrimal duct into the GI tract, leading to side effects. Rapid elimination of the eye drops administered often results in a short duration of the therapeutic effect making a frequent dosing regimen necessary. Ocular therapy would be significantly improved if the precorneal residence time of drugs could be increased. Several new preparations have been developed for ophthalmic use, not only to prolong the contact time of the vehicle on the ocular surface, but also to slow down drug elimination. However, these preparations have some disadvantages such as poor compliance, especially by elderly people and many patients sometimes lose the device without noticing it. From the point of view of patient acceptability, a liquid dosage form is preferable. This problem can be overcome by the use of polymeric solutions, which change to a gel as a result of exposure to the physiological temperature, pH or ionic composition of the lacrimal fluid. Such a system can be formulated as a liquid dosage form suitable to be administered by instillation into the eye, which upon exposure to physiological conditions, changes to the gel phase thus increasing the pre-corneal residence time of the delivery system and enhancing ocular bioavailability. [46-48]

Sodium alginate, the sodium salt of alginic acid, is a natural hydrophilic polysaccharide containing two types of monomers, β-Dmannuronic acid (M) and α-L- guluronic acid (G). The polymer forms three-dimensional hydrogel matrices and the high G content alginate forms a low viscosity, free-flowing liquid at concentrations suitable for gel formation in the lacrimal fluid. Sodium Alginate was chosen as a vehicle for ophthalmic formulations since it exhibits several favorable biological properties such as biodegradability and non-toxicity. A prolonged precorneal residence of formulations containing alginic acid was looked for, not only based on its ability to gel in the eye but also because of its mucoadhesive properties. [49]

Current research and development strategy focus on development of drug delivery system that makes clinically established drugs to their therapeutic best rather than search for new drug in the traditional hit or miss way.

Ophthalmic products, like most other product in the medical armamentarium are currently undergoing a process termed optimization. New modes of delivering a drug to the eye are being activity explored, ranging from a solid hydrophobic device that is inserted into the ophthalmic cul-de-sac, to conventionally applied dosage from which due to their formulation characteristic markedly increases the drug residence time in the orbit of eye, thus providing drug for absorption for prolonged periods are for absorption for prolonged periods are reducing the frequency of drug administration. [1]

Poor bioavailability of many drugs from topical ophthalmic preparation limits therapeutic drug delivery. Furthermore treatment of several posterior segment disorders requiring therapeutic intravitreal drug level necessitate repeated injections off drugs due to the short residence time of drug in the vitreous cavity. Substantial effort has been directed towards the development of ocular and intraocular drug delivery of ocular and intraocular drug delivery system that would prolong the drug retention allowing the drug to remain in the contact with ocular milieu for longer duration and thus maximize bioavailability. Beyond the issue of bioavailability, patient compliance and dexterity issue for drug installation are other important consideration that may impact therapeutic drug delivery.

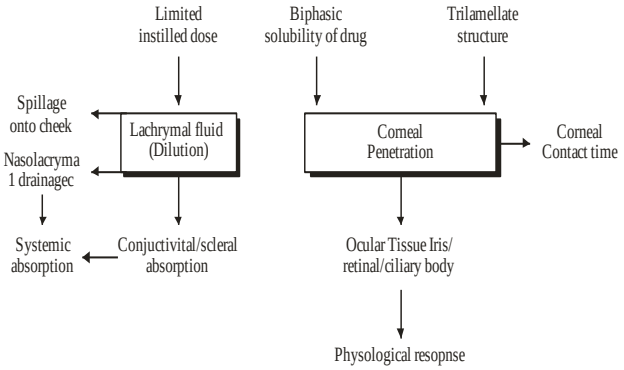
Delivery of an optimal drug delivery system for eye is most challenging and Complex because the eye is one of the sense organ most sensitive to external stimuli.

Although for ophthalmic formulation the total amount of dose instilled into the eye can be determined, major amount of formulation is lost. It is known that only a fraction of total applied dose is bioavailability to target site within the eye from a simple solution type dosage form. Actually corneal permeability of a drug is quit law and the reason for an early entry of a drug followed by rapid decline of drug concentration in the tear has to do with the enormous loss of drug from the front of the eye. [2]

These processes lead to a typical corneal contact time of about 1 to 2 min. in human for an instilled solution and ocular bioavailability that is commonly less than 10%.

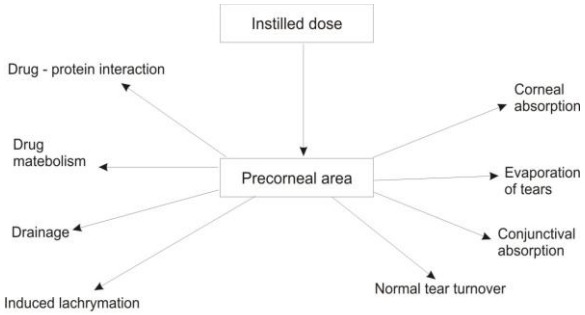
- Eye can accommodate only 7.0µl of drug and major portion of drug is lost I lachrymal secretion and rapid nasolacrimal drainage resulting in low ocular bioavailability.

- Systemic absorption of drug drained through the nasolacrimal duct result in some undesirable side effect.
- To maintain the desired therapeutic level it require frequent instillation of drug into the eye.



Factors attributing to poor bioavailability of an opthalmic formulation

Fig. 1: Factor attributing to poor bioavailability of an ophthalmic formulation



Drug elimination pathways from the Corneal Area

Fig. 2: Drug elimination pathways from the corneal area

The various ophthalmic drug delivery system has been devised which offer some Improvement over a conventional liquid dosage form by modifying the pulse entry of drugs. These include:-

- Suspension
- Ointments
- Soluble Polymeric gels
- Pre soaked soft contact lens
- Bio erodible ocular inserts
- Emulsion
- Diffusional devices (Non-erodible inserts)
- Osmotic system
- Ion exchange resins
- Colloidal system including liposomes
- Nanoparticles

These ocular drug delivery system offer some improvement over conventional dosage from but because of blurred vision (ointment) and lack of patient compliance (inserts) they have not been universally accepted.

As a result a good ocular bioavailability following topical delivery of drug to eye remains a challenger gets to be satisfactory resolved.

One of the primary performance characteristics desired of ocular drug delivery System is their ability to be retained at delivery site for prolonged period of time. This would result in achieving maximum drug bioavailability. [3]

From the point of view of patient acceptability a liquid dosage from that can sustain drug release and remain in contact with cornea of eye for extended period of time is ideal.

If the precorneal residence time of a drug could be improvement only modestly say to one or two hours then following things can be achieved:

- Improvement local bioavailability
- Reduced dose concentration
- Less total drug
- Improvement patient acceptability
- Reduced dosage frequently

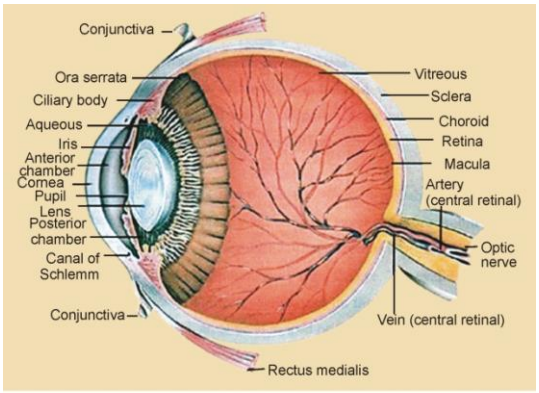
This relatively modest but important improvement can be achieved by delivery system based on the concept of *IN-SITU* GELLING SYSTEM. [4]

Such delivery system consists of phases transition systems that are instilled in a liquid from and shift to the gel or sol phases once in the cul-de-sac of the eye.

THE EYE

ANATOMY OF EYE

The human eye is a remarkable organ that is able; distinguish from, color and distant and with the aid of brain, translate this information into what we refer to as vision. This complex process require a highly developed organ, the with its relatively unique architecture and physiologic processes. Not surprisingly the eye has numerous protective mechanisms maintain normal functions, but, at times, because of anatomic physiologic abnormalities or to frank pathologic condition vision is compromised.



The Human Eye

Fig. 3: The Human Eye

It is important to recognize the pathologic or abnormal process, which may be well tolerated elsewhere in the body, can threaten vision when they occur in the eye. For example, a modest inflammation in most areas, of the body will generally be resolved quickly with little, if any after effects. A similar inflammation of the cornea can lead vascularization with possible vision impairment. It is useful therefore to being an examination of the eye with the realization that it is extremely sensitive organ, often requiring prone medical treatment for pathologic conditions, and always with significant need for optimal drug therapy.

RELEVANT ANATOMY AND PHYSIOLOGY

It is convenient to consider the eye as four fluid-fill components:

- Tear chamber
- Anterior chamber
- Posterior chamber
- Vitreous chamber

THE TEAR CHAMBER

This is the portion of the eye that interface with the outside world. It

sometimes to as the precorneal area. At its anterior surface are two movable "wind-shield wiper" like tissues, the eyelids, which open to the atmosphere. At its posterior surface lie the corner and conjunctiva all tissues in this chamber are continually bathed by tear.

The Eyelids: The eyelids are two thin, movable flaps of tissue covering the eye, with the upper being the larger and more mobile of the two. At the tip of both eyelids are eyelashes that serve in a protective fashion to sweep foreign objects and perspiration away from the eye. The eyelid is lined on the inside by a layer of tissue. The conjunctiva and on the outside by muscle and skins. when the lids are opened an almond shaped orifice is created. This orifice is referred to as the palpebral fissure. Contained on the nasal side of the palpebral fissure are two small opening, one on each lid, termed the puncta. The puncta are initial conduits though which tear normally drain away from the eye very important to normal movement of tears in the tear chamber as well for drug bioavailability of topical instilled drugs, is eyelid closure. Squeezing or closing the lid causes tears or drug-containing fluids to leave the tear chamber. There are three distinct types of eyelid: -

- Blinking
- Voluntary winking
- Blepharospasm (or the involuntary rapid closing of the eyelids)

Blinking, which occurs in humans at a rate of approximately 15 to 20 times per minute forces removal of drug away from the eye area, as dose forcible closing of the lid ? [5]

The conjunctiva: The conjunctiva is a loose flap of tissue that can be manually pulled away from the globe of the eye because it is attached to the anterior surface of the lid at one end and to the scleral tissue near the cornea at the other end.

The sclera: The white portion of the eye, next to the cornea and beneath the conjunctiva is referred to as the sclera. This is a dense fibrous tissue that is very rigid and vascular.

The Cornea: The curved transparent window of the eye, the cornea, allows light rays to enter the eye and become focused as image on the retina to give rise to the to the vision processes ; naturally this tissue is very important to adequate vision and must be maintained in a healthy state by a variety of bioavailability and physiologic process. It is critical to vision that is, the tears, cornea aqueous humor, lens and vitreous humor are optically transparent. And provide the correct refractive index..

There are three principle layers in the cornea each of which is separated from the other by a thin membrane.

- Epithelium
- Substantial propria or stroma
- Endothelium

The two membranes separating the various layers – are Bowman's membrane, which separate the epithelium and stroma, and; Descemet's membrane which separate the stroma and endothelium.

Tears: To keep the cornea surface with the correct refractive index and in a proper state of health, the surface is continuously bathed with tears. Tears are formed from several different sources in the precorneal portion of eye with the largest part coming from the lachrymal gland located in the upper fornix. A number of accessory gland contribute lipid, mucous and other substrate to the tears. Under normal circumstance tears to not move by themselves across the cornea but must be assisted by blinking. Tears then collect and are moved to the drainage apparatus for elimination from eye.

Purpose of tears

- Flush the eyes to remove foreign object.
- Maintain corneal moistness so that an optically clear window is present
- Destroy bacteria and other pathogenic substances entering the tear chamber
- Maintain the correct degree of corneal hydration as well as a proper supply of oxygen.

ANTERIOR CHAMBER

Immediately at the black of the cornea is the anterior chamber. It is bounded anterior by the lens and the iris and contains the transparent fluid aqueous humor.

The Iris: (The iris is a tissue that expands (leading to a constraints pupil- miosis) and contracts' (leading to a dilated pupil-mydriasis), when exposed to light and chemicals, thus faltering the size of the pupil. Biochemical events in iris muscles, as well as the action of the drugs, account for the miosis and mydriasis that are observed. Iris tissue is porous and very vascular.

The ciliary processes: The ciliary body contain muscles which change the degree of curvature of the lens surface to accommodate light that is, they adjust the refractive capacity of the crystalline lens for the varying distance of near vision. Moreover, the ciliary processes contribute to formulation of aqueous humor.

The lens: The lens, like the cornea must remain optically transparent and must have the correct index of refraction for near vision it must be more rounded for great refraction or bending of light rays. This tissue is very dense and like the cornea is avascular so that nutrients must be supplied by the bathing fluid. Because of a very limited oxygen supply to the lens, its principle metabolic activity is anaerobic glycoside which accounts for some 86% of glucose use. The lens is composed of about 65% water with the remainder being protein. The water content of the lens decreases with age and the lens becomes less pliable and therefore less responsive to the suspensory ligament of the ciliary muscle. This leads to impairment of a near vision, that is, presbyopia.

The aqueous humor: Contained within the anterior chamber is crystal clear fluid referred to as aqueous humor. The aqueous humor serves two main functions…

Maintenance of intraocular pressure so that the cornea retains an optically useful shape.
Nourishment of the lens and cornea under normal circumstances there is about 0.3 ml of fluid in the anterior chamber and about 0.057 ml in the chamber aqueous humor is continually formed by an active process in the ciliary body and is filtered into the posterior chamber fluid in the posterior chamber them travels past the iris into the anterior chamber where it mixes with whatever humor is already present. Once in the anterior chamber a portion of these fluid continually drains away from the eye.

THE POSTERIOR CHAMBER

The posterior chamber is a narrow space between the iris and the lens containing aqueous Humor. Communication between anterior chamber and the posterior chamber is around the lens.

THE VITREOUS CHAMBER

The vitreous chamber contains a transparent, material that keeps the eyeball in Its rounded shape. This assures proper form to the retinal tissue at the rear of the eyeball. [6]

Table 1 Anatomical and Physiological Features of Human Eye

S. No.	Factor	Human Eye
1.	Tear volume (HC)	7.30
2.	Tear turn over rata (µl/min)	.5-2.2
3.	Spontaneous dining rate	6-15 times/min
4.	Nictating membrane	Absent
5.	Lachrymal puncta	2
6.	pH of lachrymal fluids	7.3-7.7
7.	Miliosmolarity of tears	305
8.	Corneal thickness (nm)	0.52
9.	Corneal diameter(nm)	0.52
10.	Corneal surface area (cm^2)	1.04
11.	Ratio of conjuctival Surface and corneal surface	17

12.	Aqueous humor volume (me)	0.1-0.25
13.	Aq. humor turnover rate (µl/min)	2-3

CLASSIFICATION OF OCULAR DRUG DELIVERY SYSTEMS

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

- Liquids: solutions, suspensions, sol to gel systems, Sprays
- Solids: Ocular inserts, Contact lenses, corneal shield, Artificial tear, Filter paper Strips.
- Semi-solids: Ointments, Gels
- Miscellaneous: Ocular iontophoresis, Vesicular systems, Mucoadhesive dosage Forms, Particulates, Ocular penetration enhancers.

LIQUID DOSAGE FORMS

Liquids are the most popular an desired state of dosage forms for the eye. This is because the drug absorption is fastest from this state. The slow release of the drug from the suspended solid provides sustained effect for a short duration of time.

Solution and Suspensions: Solutions are the pharmaceutical forms most widely used to administer drugs that must be active on the eye surface or in the eye after passage through the cornea or the conjunctiva. The drug in the solution is in the solved state and may be immediately active. This form also have disadvantage; the very short time the solution stays at the eye surface, its poor bioavailability (a major portion i.e. 75% is lost via nasolacrimal drainage), the instability of the dissolved drug, and the necessity of using preservatives. A considerable disadvantage of using eye drops is the rapid elimination of the solution and their poor bioavailability. The retention of a solution in the eye is influenced by viscosity, hydrogen ion concentration, the osmolality and the instilled volume.

Sol to gel system: The concept of producing gel in situ (e.g. in the cul-de-sac of the eye) was suggested for the first time in the early 1980s. It is widely accepted that increasing the viscosity of a drug formulation in the precorneal region will leads to an increased bioavailability, due to slower drainage from the cornea. Several concepts for the in situ gelling systems have been investigated. These systems can be triggered by pH, temperature or by ion activation. An anionic polymeric dispersion shows a low viscosity up to pH 5.0 and will coacervate in contact with tear fluid due to presence of a carbonic buffer system which regulates the pH of tears. In situ gelling by a temperature change is produced when the temperature of polymeric dispersion raised from 25 to 37%. Ion activation of polymeric dispersion occurred due to the presence of cations in the tear fluid.

Vadnere et al studied a number of pluronic polyols with the aim of determining factor which influence the transition temperature of the hydrogels. All of the pluronic polyols studied showed endothermic enthalpy change for sol-gel process. The presence of sodium chloride, potassium chloride and sodium sulphate decreased the transition temperature whereas the opposite effect was observed with urea, alcohol and sodium dodecylsulfate. The enthalpy of gel formation was significantly changed by the added substances that entropy plays the major role in the gelation process. Rozier et al formulated 0.6% w/v GelriteÒ solution and compared its effect with equiviscous hydroxyl ethyl cellulose (HEC) solution on timolol bioavailability. An enhanced drug bioavailability and longer retention time was obtained in case of GelriteÒ solution as compared to HC solution in the rabbit's eye. Middleton and Robinson prepared sol to gel system with mucoadhesive property to deliver the steroid fluorometholone to the eye. The formulation gave better release of drug over a long period of time in the rabbit's eye, as compared to conventional eye drops. Lindell and Engstrom studied in-vitro release rate was retarded with in-situ gelling polymer GelriteÒ compare to non-gelling ethyl hydroxy ethyl cellulose system. Kumar et al developed in-situ forming gel for ophthalmic drug delivery which increased residence time of drug in the eye. A solution containing 1.5% methyl cellulose and 0.3% carbopol at pH 4.0 and 25°C was found to be an easily flowing liquid capable of administration as drop and showed an increase in viscosity and conversion to a gel on changing pH to 7.4 by addition of 0.5 M NaOH. Kumar and Himmelstein investigated that in-situ gelling behavior of carbopol Solution can be modified by addition of hydroxy propyl methyl cellulose. They found that hydroxy propyl methyl cellulose-polyacrlic acid could be formulated as an eye drop and upon instillation into the cul-de-sac of the eye can undergo in-situ transition to form gels capable of sustained drug release. [7]

Lin and sung contributed to the field of ophthalmic in situ gelling systems by the development and characterization of a series of carbopol and pluronic-based solutions by studying their rheological behavior. Gunning et al found that the ion activated in situ gelling systems of Gelrite for sezolamide and dorzolamide performed better then conventional deliveries.

Sprays: Although not commonly used, some practitioners use mydriatics or cycloplegics alone or in combination in the form eye spray. These sprays are used in the eye for dilating or for dilating the pupil or for cycloplegic examination.

SOLID DOSAGE FORMS

The concept of using solids for eye is based on providing sustained release characteristics.

Ocular inserts: Ocular inserts are solid dosage form and can overcome the disadvantage reported with traditional ophthalmic systems like aqueous solutions, suspensions and ointments. The typical pulse entry type drug release behavior observed with ocular aqueous solutions (eye drop), suspensions and ointments is replaced by more controlled, sustained and continuous drug delivery system. The eye drops provided pulse entry pattern of drug administration in the eye which is characterized by transient overdose, relatively short period of acceptable dosing, followed by prolonged periods of under dosing. The ocular maintain an effective drug concentration in the target tissues and yet minimize the number of applications consonant with the function of controlled release systems. Limited popularity of ocular inserts has been attributed to psychological factors, such as reluctance of patients to abandon the traditional liquid and semisolid medications, and to occasional therapeutic failures (e.g. unnoticed expulsion from the eye, membrane ruptures etc.). A number of ocular inserts were prepared utilization different techniques to make soluble, erodible, and hydrogel inserts.

Contact lenses: Contact lenses can absorb water soluble drug when soaked in drug solutions. These drug saturated contact lenses are placed in the eye for releasing the drug for long period of time. In humans, the Bionite lens which was made from hydrophilic polymer (2- hdroxy ethyl methacrylate) has been shown to produce a greater penetration of fluorescein.

Cornea shield: A non cross-linked homogenized, porcine sclera collagen slice is developed by a company {Bio-cor (Bausch and Lomb pharmaceuticals)}. Topically applied antibiotics have been used in conjunction with the shield to promote healing of corneal ulcers. Collagen shield arefabricated with foetal calf skin tissue and originally developed as a corneal bandage. These devices, once softened by the tear fluid, form a thin pliable film that confirms exactly to the corneal surface, and undergoes dissolution up to 10, 24 or 72 hours. Collages film proved as a promising carrier for ophthalmic drug delivery system because of its biological inertness, structural stability and good biocompatibility. Gussler et al investigation the delivery of trifluoro thymidine (TET) in collagen shield and in topically drops in the cornea of normal rabbits and corneas with experimental epithelial defects. It was found that highest drug concentration were found in the eyes treated with shields as compared to the eye drops.

Artificial tear inserts: A rod shaped pellet of hydroxypropyl cellulose without preservative is commercially available (Lacrisert). This device is designed as a sustained release artificial tear for the treatment of dry eye disorder. It was development by Merck, Sharp and Dohme 1981.

Filter paper strips: Sodium fluorescein and Rose Bengal dyes are commercially available as drug impregnated filter paper strips. These dyes are used diagnostically to disclose corneal injuries and infection such as herpes simplex, and dry eye disorder. [8]

SEMI SOLID DOSAGE FORMS

A wide variety of semi solids vehicles are used for typical ocular delivery which falls into two general categories: simple and compound bases. Simple bases refer to a single continuous phase. These include white petrolatum, lanolin and viscous gels prepared from polymers such as PVA, carbopol etc. Compound bases are usually of a biphasic type forming either water in oil (w/o) or oil in water (o/w) emulsions. A drug in either a simple or compound base provide an increase in the duration of action due to reduction in dilution by teas, reduction in drainage by way of a sustained release effect, and prolonged corneal contact time. The most commonly used semisolid preparation is ointments consisting of a solid drug in an appropriate vehicle base.

Semi-solid dosage forms are applied once or twice daily and provide sustained effects. The primary purpose of the ophthalmic ointment vehicle is to prolong drug contact time with the external ocular surface. But they present a disadvantage of causing blurring of vision and matting of eyelids. Ophthalmic gels are similar in viscosity and clinical usage to ophthalmic ointments. Pilocarpine HS is one of the ophthalmic preparations available in gel form and is intended to provide sustained action of pilocarpine over a period of 24 hours. Semi-solids vehicles were found to prolong the ocular contact time many ultimately leads to an enhanced bioavailability.

MISCELLANEOUS DOSAGE FORMS

Ocular iontophoresis: Iontophoresis is the process in which direct current driers ions into cells or tissues. When Iontophoresis is used for drug delivery, ions of importance are charged molecules of drug. If the drug molecules carry a positive charge, they are driven into the tissues at the anode; if negatively charged, at the cathode.

Ocular iontophoresis offers a drug delivery system that is fast, painful, safe and in most cases, results in the delivery of a high concentration of the drug to a specific site. Increased incidence of bacterial keratitis, frequently resulting in corneal scarring, offers a clinical condition that may benefit from drug delivery by iontophoresis. Iontophoretic application of antibiotic may enhance their bactericidal activity and reduce the severity of disease; similar application of anti-inflammatory agent could prevent or reduce vision threatening side effects. But the role of iontophoresis in clinical ophthalmology remains to be identified.

Vesicular systems: Vesicular systems have been developed to provide improvement in ocular contact time; providing sustained effect and reducing side effects of the drug(s) entrapped.

Liposomes: Liposomes are phospholipids-lipid vesicles for targeting the drugs to the specific sites in the body. Because of their structural versatility they can incorporate any kind of drug substance regardless of its solubility. They provide the controlled and selective drug delivery and improved bioavailability and their potential in ocular drug delivery appears greater for lipophilic than hydrophilic compounds. Liposomes are vesicles composed of a lipid membrane enclosing compounds. Liposomes offer the advantage of being completely biodegradable and relatively nontoxi but are less stable than particulate drug delivery systems. Liposomes were found to be potential delivery system for administration of a number of drugs to the eye. [9]

***in-situ* GEL SYSTEM**

HYDROGELS

Hydrogels are polymers endorsed with the ability to swell in water or aqueous solvent induced induce a liquid-gel transition. Currently, two group of hydrogels are distinguished (Fig) namely:

- Performed gels
- *In situ* forming gels

PERFORMED GELS

They can be defined as simple systems sets with do not undergo any modify after administrate e.g. Include cellulose, poly vinyl alcohol, hyaluronic acid, carbomer. They are also called bioadhesive polymers. They are usually macromolecular hydrocolloids with numerous hydrophilic groups. These polymers can improve drug delivery through optimum contact with absorbing surface in order to prolong residence time & reducing dosing frequency.

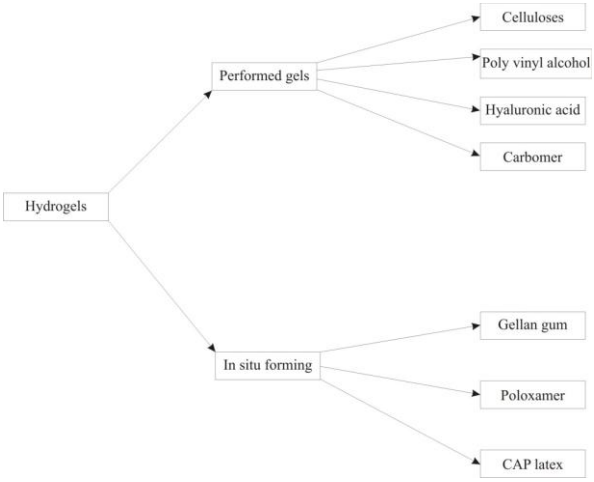


Fig. 4: Classification of ophthalmic hydro gel

***IN SITU* FORMING GELS**

In situ forming gels are formulation applied as solution, sols or suspension that undergoes gellation after installation due to physicochemical changes inherent to the eye. This new concept of providing a gel in-situ was suggested for the first time in early 1980's. [10]

Several concepts for in-situ gelling system have been investigated. These methods have been employed to cause transition on eye surface

- Change in pH
- Change in temperature
- Ion activation

pH triggered system

Example –

- Cellulose acetate phthalate latex.
- Polyacrylic acid polymers (Carbopol & polycarbophils)

pH Triggered *in situ* gelling systems, are low viscosity polymer dispersed in water which undergoes spontaneous coagulation and gelling after instillation in conjuctival cul-de-sac.

Cellulose acetate phthalate (CAP) an anionic polymer shows a very low viscosity up to pH-5 but forms a gel in few seconds when come in contact with tear fluid (pH 7.2 to 7.4). This system is however characterized by higher polymer concentration (30% CAP) that may cause discomfort to the patient.

Polyacrylic acid based polymers which include carbopol, a cross linked polyacrylic acid polymer are very sensitive to pH and shows a sol-to-gel transformation on changing pH from 4.0 to7.4. The polyacrylic acid polymers are effective in small concentration (0.5%).

Change in temperature

Example

- Pluronic
- Poloxamer F27

This system is based on polymers which changes from sol-to-gel at the temperature of eye (33 to 34°c). An example of this type of polymer is poloxamer F127 which is a polyoxyethylene linked with polyoxypropylene units. At room temperature the polyxamer remain in solution when solution is instilled into the eye surface. The elevated temperature causes the solution to become a gel thereby prolonging its contact with ocular surface.

Ion activation systems

Example:- Gomme "Gellen" (Gelrite)

These system show sol to gel transformation in the presence of ions. Gelrite, a polysaccharide, low acetyl gellan gum, which forms clear gel in the presence of mono or divalent cations (sodium ions in tear).

Advantage of in-situ gelling systems:

- Generally more comfortable than insoluble inserts.
- Less blurred vision as compared to ointment.
- Increased bioavailability due to

-Increased precorneal residence time.
-Decreased nasolacrymal drainage of drug.

- Chance of undesirable side effects arising due to systematic absorption of drug through nasolacrimal duct is reduced.
- Drug effect is prolonged hence frequent instillation of drug is not required.
- The carbomer polymeric gel base itself has been successfully to treat moderate to severe cases of dry eye such as kerato conjunction sicca (KCS).

APPLICATION OF *in-situ* GEL SYATEM

***In Situ* Gel Formulation For Gene Delivery: Release and Formulation**

The in vitro release of plasmid DNA and salmon sperm DNA from *IN SITU* gel formulation was investigation. Two *IN SITU* gel systems were studied (a) an interpolymeric complex (IPC) of water-soluble polymers polymethacrylic acid (PMA) and polyethylene glycol (PEG) and (b) a Hydroxypropylmethylcellulose carbopol system (H:C). Two-way analysis of variance with replication demonstrates that both gel composition and medium pH influence significantly the release of plasmid DNA from *IN SITU* gel formulation. When the release of both types of DNA was compared, higher release was observed for plasmid DNA compared to genomic salmon sperm DNA. Conformational analysis of the released plasmid DNA showed that DNA was released without degradation, but with remarkable conversion from super coiled (SC) to open circular (OC). In addition, the tested *IN SITU* gel systems demonstrate protection from DNAse I degradation. The myotoxicity of the injectable gelling solutions was assessed by the cumulative release of creatine kinase (CK) over 120 min from the isolated rodent extensor longus (EDL) muscle. A higher level of cumulative CK was observed for IPC when compared to H:C (2:1). These results demonstrate that the *IN SITU* gelling systems can be considered as a valuable injectable controlled-delivery system for pDNA in their role to provide protection from DNAse degradation. [11]

***in-situ* cartilage and bone tissue engineering with mesenchymal steam cells in hydro gels**

In recent years, biomaterials have begun to play an increasingly important role in developing a more effective therapy for the treatment of diseased tissue or organs, like osteoarthritis. Current biomaterial design encourages cohesive integration with an implant. The interface between a biomaterial and surrounding tissue is integral to its functionally and long-term performance, particularly with musculoskeletal implants, which has dense cellular matrix and Lacks the ability to self-repair, such as cartilage. Tissue engineering techniques have developed a minimally invasive strategy to place the hydrogel into a defect by macromer injection and prompt *IN SITU* photogelation. The liquid precursor and rapid solidification provide the feasibility for implant-defect steric appropriateness, as well as cell encapsulation. With this strategy, goat mesenchymal stem cells (gMSC) were introduced into a novel biodegradable phosphoester hydrogel and transplanted into the cartilage defect for 3-dimeensional in vitro cultivation until this substitute begins to integrate with the surrounding tissue. The development of the hydrogel-cartilage transplantation system will be real-timely and non-invasively monitored via nuclear magnetic resonance imaging (MRI) and eventually by osteo/chondrogenesis analysis. [12]

Engineered nanoparticles in cancer therapy

Intense research has led to a more comprehensive understanding of cancer at the genetic, molecular and cellular levels providing an avenue for methods of increasing antitumor efficacy of drugs while reducing systemic side effects. Nano-particulate technology is of particular use in developing a new generation of more effective cancer therapies capable of overcoming the many biological, biophysical and biomedical barriers that the body stages against a standard intervention. Nanoparticles show much promise in cancer therapy by selectively gaining access to tumor due to their small size and modifiability. Typically, through not exclusively, nanoparticles are defined as submicroscopic particles between 1 and 100 nm. Nanoparticles are formulated out of a variety of substance and engineered to carry an array of substance in a controlled and targeted manner. Nanoparticles are prepared to take advantage of fundamental cancer morphology and modes of development such as rapid proliferation of cells, antigen expression, and leaky tumor vasculature. In cancer treatment and detection nanoparticles serves many targeted functions in chemotherapy, radiotherapy, immunotherapy and anti-angiogenesis. Multifunctional nano-particles perform many of these tasks simultaneously such as targeted delivery of a potent anticancer drug at the same time as an imaging material to visualize the effectiveness of the drug utilized for treatment follow-up. [13]

Cell Encapsulation in Mammal Reproduction

Cell encapsulation is an evolving branch of biotechnology with numerous applications including the enhancing of reproductive performance humans and other mammal species. Over the last twenty years male and female gametes and embryos have been encapsulations with or without somatic cells, for different purpose, such as semen controlled release, in vitro gametogenesis, embryo culture after in vitro fertilization and cell preservation. The patents and papers underline a widespread use of alginate which is a natural anionic biocompatible, biodegradable polymer that mimics the extracellular matrix or the basal membrane and supports cell functions and metabolism. Gamete and embryo encapsulation techniques tend to fall into two main groupings: the "classical" three-step method, and the more recent one-step method. However all of these encapsulation techniques are moving towards new, interesting applications since they can be easily tailor-made to fit a variety of cell lines. [14]

***IN SITU* amplification of oestrogen receptor {alpha} mRNA in breast cancer cell lines and tumors**

The aim of this work was to develop a direct *IN SITU* reverse transcription polymerase chain reaction (*IN SITU* RT-PCR) assay for the detection of oestrogen receptor {alpha} (ER{alpha}) mRNA on in vitro cell lines and breast tumor cell smears. ER {alpha} mRNA amplification was performed on MCF-7 (ER {alpha} positive)and MDA-MB-231 (ER { alpha } negative)cell lines as well as on 51 cytological smears of breast tumor samples from patients. The *IN SITU* amplification of mRNA in cell lines and ex vivo breast tumors was successful. However, finding equilibrium between optimal cell morphology and PCR performance varied with each tumor, leading to difficulty in standardization for daily practice. Nonetheless, *IN SITU* RT-PCR is a useful tool for the detection of ER {alpha} mRNA in selected cases, both in vitro and ex vivo. [15]

Hydrogels formulated *IN SITU* gelation effective for drug delivery and wound healing

The high water content and soft consistency of hydrogels makes them similar to natural living tissue with numerous applications across the medical field. Under certain conditions it is desirable to prepare a hydrogel at the site of use; unfortunately most polymers

must be performed due to the extreme reaction conditions, which would not be compatible with the environment of use. Kiser and Roberts have overcome this problem with the creation of *IN SITU* gelling hydrogels. Two liquid-state prepolymers are mixed together under mild aqueous conditions to form a gel at room temperature and or body temperature.

This system is ideal for injectable drug delivery vehicle applications, and it is also possible to use this system in the presence of cells to make scaffolds for wound healing. [16]

DRUGS AND POLYMERS FOR *in-situ* GEL SYSTEM

POLYMERS

Carbomer 940 Hydroyproply methylcellulose

DRUGS

- Ciprofloxacin
- Norfloxacin

CARBOMER 940

Introduction: Carbomer is high molecular weight polymer of acrylic acid cross linked with allyl ether of sucrose.

Functional category: Suspending and / or viscosity-increasing agent, pharmaceutical aid.

Synonyms

Carboxypolymethylene; carboxyvinyl polymer; acrylic acid polymer; carbopol.

Empirical formula:- $(C_3H_4O_2)X.(-C_3H_5\text{-sucrose})Y$

Molecular weight: Carbomer 940: $4x10^6$

Method of manufacture: A synthetic, high molecular weight, cross-linked polymer of acrylic acid copolymerized with approximately 0.75-2% w/w of polyalkyl sucrose. The end product contain 56-68% carboxylic acid groups.

Description: A white, fluffy, acidic, hygroscopic powder with a slight characteristic odor.

Specific Graity: 1:4

Density, Bulk: 5 g/cm^3

Equilibrim Moisture Content: 8.0% (20°C and 40% RH)

Viscosity: 20.5-54.5P (0.2% Spindle 4)

305-394 (0.5% Spindle 6)

(Brookfield, at 20 rpm using neutralized sol at 25°C)

Stabiliy and stroage conditions: Dry powder forms of carbomer do not support the growth of molds and fungi; however, microorganism grows well in unpreserved aqueous dispersions. Carbopol gels posses good well in stability and do not support bacterial or fungal. Certain preservatives, such as benzoic acid, sodium benzoate and benzalkonium chloride, cause a decrease viscosity of the dispersion. Carbopol should be stored in tight containers.

Incompatibilities: Carbomer is incompatible with phenol cation polymers, strong acid and high concentration of electrolysis, and is dissolved by resorcinol. Exposure to light causes oxidation which is reflected in decrease in viscosity.

Safety: The highest dose tolerated on intragastric administrator resin equivalent to 125 mg/kg of dry carbopol resin administrator 1-2.5% solution in rats. Instillation of 1% solution of carbopol 940 resin does not produce ocular injury and safe for topical use as confirmed by human skin patch testing.

Application: Emulsifying agent, suspending agent, Gelling agent, Thickening agent in ointments and creams; tablet binder in sustained-release formulations.

The various grades of Carbomer available are Carbomer 907, 910, 934 P, 940 and 941. From these Carbomer 940 was selected due to various benefits, it offers, such as thickening efficiency, uniform performance, temperature stability, excellent shelf life, microbial resistance and safety.

Some marked preparation containing carbomer are Pilopine HS Gel (Alcon).

Lacrinorm (Framigea)

Thilo-tears (Alcon)

HYDROXYPROPYL METHYLCELLULOSE

Synonyms: Methylcellulose; methylcellulose propylene glycol ether of methylcellulose; methylcellulose propylene glycol ether.

Chemical names and cas registery number:

Cellulose, 2-Hydroxypropylmethylether

Cellulose Hydroxypropylmethylether (9004-65-3)

Empirical Formula: $C_8H_{15}O_6\text{-}(C_{10}H_{18}O_6)N\text{-}C_8H_{15}O_5$

molecular weight: Approx-86,000.

Description: AN odorless, tasteless, white or creamy-white fibrous or granular powder.

Typical Properties

Apparent Density: 0.25-0.70 g/cm^3

Browning temperature: 190-200°C (374-392°F)

Charring temperature: 225-230°C (437-446°F)

Enzyme resistance: Comparatively enzyme-resistant, providing excellent viscosity-stability during long-term storage.

Gel formation: Undergoes a reversible transformation from sol-to-sac upon heating and cooling respectively.

Gel point: 50°C-90°C, depending upon the grade.

Ionic charge: No ionic charge (i.e., not a polyelectrolyte). Will not complex with metallic salts and ionic organic to from insoluble precipitates, thus presenting less compatibility problems.

Ash: 1.5%-3.0%, depending upon the grade.

Specific gravity: Approximately 1.3.

Specific activity: Provide some surfactancy in solution. Surface tensions: For such solutions range from 42 to 56 dynes per cm. (typical surfactant has a surface tension of 3.0 dynes per cm)

Stability and storage Conditions: Very stable in dry conditions, solution are stable at pH to 11.0 . Aqueous solutions are liable to be affected by macro-organisms. When used as viscosity-increasing agent ophthalmic solutions, an anti-microbial agent, such as benzalkonium chloride should be incorporated store in air tight container, in a cool place.

Incompatibilities: Extreme pH conditions: oxidizing materials. Safety: Human and animal feeding studies have shown hydroxyproply methylcellulose to be safe.

Table: 2: Research work on ophthalmic drug delivery system

S.No.	Drug	Dosage Form	Category of Drug	Polymers/base	References
1.	Pilocarpine	Ointment	Mitotic agent	Petrolatcum bases	[17]
2.	Pilocarpine	Emulsion	Mitotic agent	-	[18]
3.	Pilocarpine	Sol to gel System		Cellulose acetate Phthalate	[19]

4.	Pilocarpine	Hydrogel		Polyacrylic acid & poly acrylamide	[20]
5.	Pilocarpine	Gel		Polyacrylic acid	[21]
6.	Timolol	Sol-to-gel System	Anti-glaucoma Agent	Gelrite	[22]
7.	Flurlsiprofen	Gels	Anti-inflammatory	Pluronic F 127	[23]
8.	Timolol	In-situ Forming gel	Anti-glaucoma Agent	Hydroxy propyl Methyl cellulose And polyacrylic Acid	[24]
9.	Pilocarpine Hydrochloride	Gels	Mitotic agent	Pluronic F 127 Methyl cellulose Hydroxypropyl Methyl cellulose	[25]
10.	Tropicamide	liposome	Mydriatic agent	Poly carbophil	[26]

Table 3: Conventional and advanced ocular drug

S. No.	Drug	Dosage form	Polymer/Bases	References
1.	Erythromycin Estolate	Hydrogel Inserts	Corpolymer of Polyvinyl Pyrrolidione, Vinyl acetate, Glycidly Methacrylate Ethyl acrylate	[27]
2.	Pilocarpine	Ocular inserts	Poly (2-hydroxy ethyl methacrylate)	[28]
3.	Ciprofloxacin Hydrochloride	In-situ gelling System	Poloxamer/ Hyaluronic Acid	[29]
4.	Timolol Maleate		gelrite	[30]

TYPES OF *in-situ* GEL SYSTEM

In vitro properties of in situ forming gels for the parentrals:

The purpose of this research was to

Formulation a solution of a water – insoluble interpolymeric complex (IPC) containing poly (methacrylic acid) (PMA), 15 kDa, and poly Poly (ethylene glycol) (PEG), 20 kDa, in a biocompatible cosolvent system; [31]

Demonstrate that the IPC solution can transform into a gel, in situ at physiological pH; and

Determine the ability of the gel to entrap, protect, and control the release of macromolecular drugs such as proteins and oligonucleotides. Tenary phase diagram were prepared to identify cosolvant composition containing N-methylpyrrolidone (NMP), ethanol, and water that dissolve the IPC. IPC solutions (40, 50 or 60% w/v) each containing 1 mg of either model proteins, fluorescein isothiocyanate (FITC)- insulin and FITC-albumin, or 24-mer phosphorothioate oligonucleotides, were placed in container that were immersed in buffer, pH 7.4 . Aliquots of the buffer were sampled periodically and analysis for the macromolecular content. In addition, in vitro bioactivity of another model protein, α-amylase, contained in the IPC solution was also determined. The studies demonstrated that a cosolvent containing 1:1:2 ratio of NMP/ethanol/water was most suitable for dissolving the IPC. Concentrate>30% w/v IPC were required to form the gel, however, those mixture containing >60% w/v IPC could not be easily injected via 18-22 gauge needle. The gel can entrap and control the release of the model macromolecules for up to 6 days, in vitro. In addition, the gel can maintain the bioactivity of the protein, α-amylase, for 6-days. Therefore an IPC gel can entrap, protect, and control the release of macromolecular drugs over a period of 6-days, in vitro, and therefore can be considered for in vivo investigation. [32]

Development of dry powder inhalers

Development of dry powder inhalers involves powder recrystallization, formulation, dispersion, delivery and deposition of the therapeutic agent different regions of the airways in prophylaxis/ treatment/ diagnosis of pulmonary and systematic disorder.

Conventional powder production by crystallization and milling has many limitations resulting into development of alternative techniques to overcome the problems. In the last decade many patents have been filed claiming improvement in aerosol performance of dry powder inhalers through the use of

Incorporation of fines of carrier to particles to occupy active sites on the surface and use of hydrophobic carriers to facilitate deaggregation through reduced surface energy and particles interaction [33]

Reducing aerodynamic diameters through particle engineering and incorporating drug into porous or low particles density, and/or Preparing less cohesive and adhesive particle through corrugated surfaces, low bulk density, reduced surface energy and particle interaction and hydrophobic additives. Moisture within dry powder inhaler (DPI) products has also been shown to influence aerosol performance via capillary force and electrostatic interaction. [34]

Innovations in Transdermal Drug Delivery: Formulations and Technique

The transdermal route of drug delivery has attached researches due too many biomedical advantage associated with it. However, excellent impervious nature of skin is the greatest challenge that has to be overcome for successfully delivering drug molecules to the systematic circulation by this route. Various formulation approaches used to systematically deliver drug molecules include use of prodrugs/lipophilic analogs, permeation enhancers, sub saturated systems and entrapment into vesicular systems. Further, the adhesive mixture, physical systems of the delivery system and release liner influence drug release and its permeation across the skin. In addition, great strides in designing delivery systems for maximizing percutaneous drug permeation without comprising with ease of therapy cannot be neglected in improving functionality of transdermal drug delivery systems. [35]

Modified-release solid formulations for colonic delivery

The transdermal route of drug delivery has attracted researchers due to many biomedical advantages associated with it. However, excellent impervious nature of skin is the greatest challenge that has to be overcome for successfully delivering drug molecules to the systematic circulation by this route. Various formulations approaches used to systematically deliver drug molecules include use of prodrugs/lipophilic analogs, permeation enhancers, sub saturated systems and entrapment into vesicular systems. Further, the adhesive mixture, physical system of the delivery systems and release liner influence drug release and it's permeation across the skin. In addition, great strides in designing delivery systems for maximizing percutaneous drug permeation without comparing with ease of therapy cannot be neglected in improving functionally of transdermal drug delivery systems. [36]

Modified-Release solid Formulations for Colonic Delivery

Solid formulation intended for targeted drug release into the lower gastrointestinal (GI) tract are beneficial for localized treatment of several disease and conditions, mainly inflammatory bowel diseases, irritable bowel syndrome and colon cancer. Also, because of their inherent potential to delay or avoid systematic drug absorption from the small intestine, colonic formulations can be utilized for chronotherapy of diseases which are affected by circadian biorthythms (e.g., asthma, hypertension and arthritis), and to achieve clinically relevant bioavailability of drugs that are poorly

absorbed from the upper parts of the GI tract because of their polar nature and/or susceptibility to chemical and enzymatic degradation in the small intestine (e.g., proteins and peptides). Modified-release (MR) formulation technologies both utilize a single or a combination of two or more physiological characteristics of the colon, which includes pH, micro flora (enterobacteria), and transit time and luminal pressure. Accordingly, these technologies may be grouped under four distinct classes; pH-controlled (or delayed-release) system, time-controlled (or time-dependent) system, microbially-controlled system, and pressure-controlled systems. Among these, formulations that release drugs in response to colonic pH, enterobacteria, or both are most common and promising. [37]

An *IN SITU* gelling systems for parenteral delivery

Polymer complexes formed by electrostatic interactions or hydrogen bonds between polymer strands can be utilized as a drug delivery systems, as its ability to undergo a sol-gel transformation in response to changes in temperature, pH, and solvent concentration can lead to an in situ forming delivery system. A polymer complex of polyacrylic or polymethacrylic acid and polyethylene glycol, previously reported to be formed primarily by hydrogen bonds, is being investigated as such a system. Stable below pH≥5.7, the complex is soluble in water but dissolves in a hydroalcoholic solvent to yield a clear viscous solution. Upon injection, the diffusion of ethanol from the liquid transforms the system into a gel upon contact with physiological conditions. The gel disappears from the site with time due to dissociation of the complex. Water-soluble and low molecular weight, the dissociated components can be eliminated by glomerular filtration. Using a concentration of 50% ethanol as the co-solvent, the system can be injected by syringe. Thus, an interpolymer complex of polymethacrylic acid and polyethylene glycol may be utilized as a parenteral controlled- release drug delivery system. [38]

FUTURE APPLICATIONS

Time-controlled Pulsatile Delivery System for Bioactive Compounds

In the body under physiological conditions, many vital functions are regulated by pulsed or transient release of bioactive substances at a specified time and site. Thus, to mimic the function of living systems, it is important to develop new drug delivery devices to achieve pulsed delivery of a certain amount of a bioactive compound at predetermined time intervals. The ability to deliver bioactive compounds and/or therapeutic agent to a patient in a pulsatile or staggered release profile has been a major goal in drug delivery research over the last two decades. The plasma peak is obtained at an optimal time by timing drug administration. The number of doses per day can be reduced. Based on the relevance of potential therapeutic applications, a variety of design strategies have been formulated in the pursuit of pulsatile release. Overall, these systems can be categorized into reservoir, capsular and osmotic devices. [39]

A novel *in situ* gel for sustained drug delivery and targeting:

The objective of this study was to develop a novel chitosan-glyceryl monooleate (GMO) *in situ* gel system for sustained drug delivery and training. The delivery system consisted of 3% (w/v) chitosan and 3% (w/v) GMO in 0.33 M critric acid. *In situ* gel was formed at a biological pH. *In vitro* release studies were conducted in Sorensen's phosphate buffer (pH 7.4) and drug were analyzed either by HPLC or spectrophotometry. Characterization of the gel included the effect of cross- linker, determination of diffusion coefficient and water uptake by thermo gravimetric analysis (TGA). Mucoadhesive property of the gel was evaluated *in vitro* using an EZ-Tester. Incorporation of a cross-linker (glutaraldehyde) retarded the rate and extent of drug with drug-encapsulation microsphere. Drug release from the gel followed a matrix diffusion controlled mechanism. Inclusion of GMO enhanced the mucoadhesive property of chitosan by three-to sevenfold. This novel *in situ* system can be useful in the sustained delivery of drug via oral as well as parenteral routes. [40]

Sustained ophthalmic delivery of ofloxacin from a pH triggered *in situ* gelling system

The poor bioavailability and therapeutic response exhibited by conventional ophthalmic on solutions due to rapid precorneal elimination of the drug may be overcome by the use of *in situ* gel forming systems that instilled as drops into the eye and undergo a sol-gel transition in the cul-de-sac. The present work describes the formulation and evaluation of an ophthalmic delivery system of an antibacterial agent, ofloxacin, based on the concept of triggered *in situ* gelation. Polyacrylic acid (Carbopol (R) 940) was used as the gelling agent in combination with hydroxyprpylmethylcelluose (Methocal E50LV) which acted as a viscosity enhancing agent. The developed formulation was therapeutically efficacious stable, non-irritant and provided sustained release of the drug over an 8-h period. The developed system is thus a viable alternative to conventional eye drops. [41]

SUMMARY

Current research and development technique are based on the development of drugs which can have the following proportion:

- Better patient compliance
- Easy administrator
- More bioavailability
- Less frequency of dosing
- Better permeability
- Immediate results

Development of an ophthalmic drug delivery system is most complex of all because of the fact that eye is the most sensitive to outer environment. On the more ocular drugs have less bioavailability owing to the fact that eye can accommodate only 7.0 µl of the drug instilled and the rest is lost with the lachrymal secretion. So to obtain required therapeutic effect, it requires frequent instillation which is again not considered a good practice by the patient. Various drug delivery systems have been the back point of blurred vision and lack of patient compliance. An ideal ophthalmic drug delivery system should have the property of sustaining drug release and remain in contact with the cornea of eye for extended period of time. The answer to this entire problem can be given by the in situ gelling systems which provide [42]

- Improved local bioavailability
- Reduce dose concentration
- Improvement patient acceptability
- Reduce dosage frequency

- In situ gel systems are basically liquid preparation which form gel in contact with the cornea in the cul-de-sac of the eye
  - Change in pH
  - Change in temperature
  - Ion activation
- The aqueous polyacrylic acid solution (carbopol solution) containing a viscosity enhancing agent hydroxyl methyl cellulose can be used as in-situ gelling ophthalmic delivery system. The system offers an effective alternate to system based on using carbopol alone. [43]
- The in-situ gel forming system will have good patient acceptance because it is easy to instilled into the eye and gradually erodes by dissolution of the gel, obviating the need for removal. [44]
- The long residence time of gel formed in situ along with its ability to release drug in a sustained manner will assist in enhancing ocular bioavailability. [45]
- Change in the concentration of the polymers affect the rheological behavior and release profile of incorporated drug from the gels. This offers flexibility in design of in situ gel formulated system with desirable rheological properties and drug release rate. [45]

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