In-situ gels -a novel approach for ocular drug delivery

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Abstract

To achieve effective ophthalmic therapy, an adequate amount of ingredients must be delivered and maintain at the site of action with in the eye. The anatomical structure and the protective physiological process of the eye exert a formidable defense against ophthalmic drug delivery. The most frequently used dosage forms i.e. ophthalmic solutions and suspensions are compromised in their effectiveness by several limitations, leading poor ocular bioavailability. This review deals with topical ophthalmic drug delivery systems as a means to localize and prolong drug activity at its site of action by use of a novel in-situ gel approach. These gels are instilled as drops into the eye and undergoes a sol to gel transition in the cul-de-sac, improved ocular bioavailability by increasing the duration of contact with corneal tissue, there by reducing the frequency of administration required in case of conventional ophthalmic solutions, thus optimizing ocular therapy.

Keywords: In situ gels, Polaxomer, Gellan gum, Hydroxy propyl cellulose, Hydroxy propyl methyl cellulose.

Introduction

The field of Ocular drug delivery is one of the interesting and challenging endeavors facing the pharmaceutical scientist. As an isolated organ the eye is very difficult to study from a drug delivery point of view. It is very difficult to obtain specimen of eye tissues containing drugs from humans, consequently one is compelled to use animal models as guide. As a result, unfortunately the human ocular disposition characteristics of virtually every important drug are incomplete or unknown.

Despite these severe limitations significant improvement in Ocular drug delivery have been made. The improvements have been with objective of maintaining the drug in the biophase for an extended period. The anatomy, physiology and biochemistry of the eye render this organ impervious to foreign substances. It is a challenging to the formulator to

circumvent the protective barriers of eye so that the drug reaches the biophase in sufficient concentration.

Physiological barriers to diffusion and productive absorption of topically applied drug exist in the precorneal and corneal spaces. The precorneal constrains responsible for poor ocular bioavailability of conventional ophthalmic dosage forms are solution drainage, lacrimation, tear dilution, tear turnover and conjunctival absorption [Fig.I]. Drug solution drainage away from the precorneal area has been shown to be the most significant factor in reducing the contact time of the drug with the cornea and consequently ocular bioavailability of topical dosage forms. The instilled dose leaves the precorneal area within 2 minutes of instillation in humans. In rabbits the process of drainage, generally takes 5-10 minutes [1]. However, most of the drugs are rapidly lost through nasolacrimal drainage immediately following dosing. Both the conjunctival and nasal mucosa has been indicated as the main potential sites for systematic absorption of topically applied drugs. Tears dilute the drug remaining in the cul-de-sac, which reduces the transcorneal flux of the drug. The drug entity, pH, tonicity of the dosage forms as well as formulation adjuvants can stimulate tear production [2].

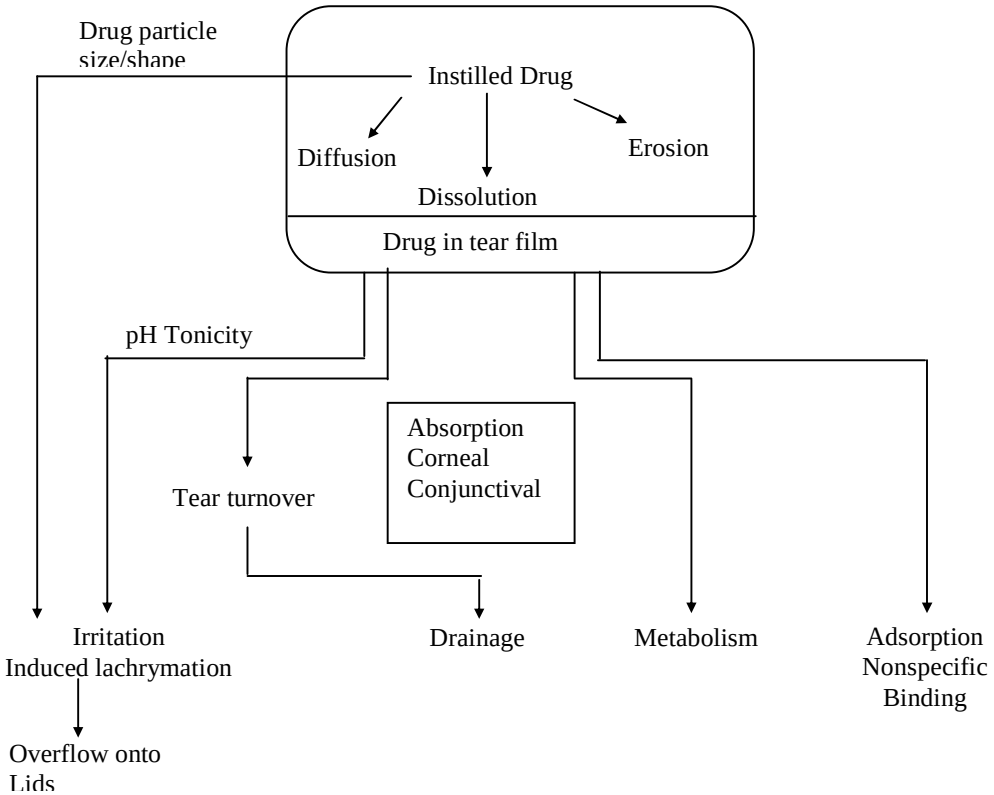

Fig I: Absorption mechanism of conventional eye drops

Topical application of ophthalmic drugs is further made inefficient by tear turnover, which is about 16% in human. Due to these factors typically less than 1% of the drug reaches the aqueous humor [3]. Metabolism in the precorneal area has been shown to account for further loss of the drug. The low fraction of the applied dose further

undergoes rapid elimination from the intraocular tissues and loss through the canal of schlemn (or) via absorption through the ciliary body (or) suprachoroid into episcleral space [4]. Binding of drug to protein also contributes to the loss of drugs through the precorneal parallel elimination loss pathway.

Anatomically cornea consists of five distinct layers, which anteriorly to posteriorly be the epithelium, Bowman's membrane, stroma, Descmet's membrane and endothelium. The epithelium and endothelium are cellular and lipophilic. The stroma contains 76-80% of water while the remainder consists of collagen fibrils. Each of the three barriers was found to contribute significantly to diffusional resistance of drugs of intermediate lipophilicity. However, the epithelium is the predominant rate limiting barrier for hydrophilic drugs where as stroma is rate limiting for most of the lipophilic drugs. Recent studies suggest that the noncorneal route of absorption involving penetration across the sclera and conjunctiva may be significant for drug molecules with poor corneal permeability. Studies with inulin [5], timolol maleate [6], gentamicin [7] and PGF2 [8].suggest that these drugs gain access through the non-corneal route. However, the corneal absorption represents the major mechanism of absorption for the most therapeutic entities.

The physiological barriers to topical corneal absorption force the clinician to recommend frequent doses of drug at extremely high concentrations. This pulsed type of dosing [Fig II] is represented with many side effects. It has been noted that the administration of topical timolol in the treatment of open angle glaucoma has resulted in therapeutic concentration of timolol in systemic circulation. Frequent local instillations of antiglucoma agents, antibiotics, antivirals and sulfonamides provide an unusually high drug and preservative concentrations at the epithelial surface resulting in ocular cytopathologies.

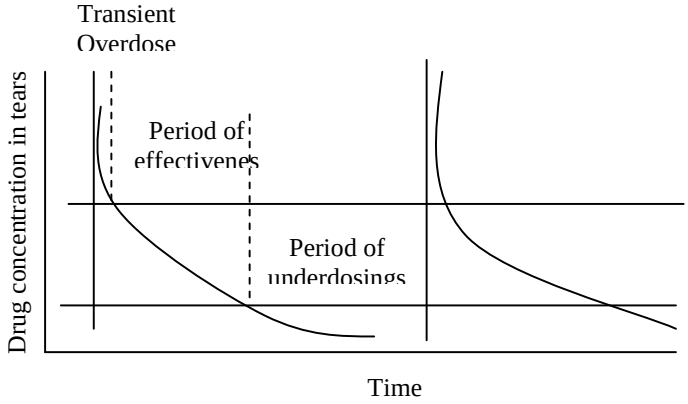

Fig. II

The existing ocular drug delivery systems are thus fairly primitive and inefficient. However, the design of ocular system is undergoing gradual transition from an empirical to rational basis. Interest in the broad areas of ocular drug delivery has increased in recent years due to an increased understanding of a number of ocular physiological process and pathological condition. The focus of this review is the approaches made towards optimization of ocular delivery systems. Attempts have been made towards to increase ocular contact time, to enhance the corneal permeability and site specificity.

Conventional ocular drug delivery system:-

The conventional ocular delivery systems are used ubiquitously in today's ocular disease management are solutions, suspensions, these are sterile, contain a preservatives, is isotonic, has a pH of cirla 7.4 for patient comfort and has limited shelf life after opening. Eye drops provide a pulse entry of the drug, followed by a rapid decline in drug concentration, the kinetics, of which approximately to the first order. To overcome these problems, it is the consensus of most clinicians that a solution or suspension form of a drug delivery system is preferred by the patient provided that extended duration can be accomplished with these forms. [9]

Role of Polymer(s) in drug delivery

The first approach made towards research in the field of improving the ocular contact time of solutions utilizes the incorporation of polymers into an aqueous medium such as polyvinyl alcohol (PVA), polyvinyl pyrolidine (PVP), methylcellulose (MC), carboxymethyl cellulose (CMC), and hydroxypropyl cellulose (HPC). The increased solution viscosity reduced the solution drainage. Increasing the solution viscosity of pilocarpine solution from 1 to 100 cps through the incorporation of methylcellulose reduced the solution drainage rate constant 10 times while only a 2-fold increase in pilocarpine concentration in the aqueous humor was obtained [10]. An optimal viscosity of 12-15 cps has been suggested for ocular drug absorption by Paton and Robinson [11]. Natural polymers namely sodium haluronate and chondroition sulfate are being investigated as viscosity inducing agents. Prolonged residence time with an extended duration of action for 1% pilocarpine has been observed with 0.2-0.3% sodium hyaluronate solutions [12]. In considering approach of increasing solution viscosity to enhance ocular drug absorption the lipophilicity of the drug should be taken into account. The results to date suggest that increasing solution viscosity has limited utility in causing marked improvement in the amount of drug absorbed.

Colloidal Systems

Colloidal system, encompassing liposomes and micro and nanoparticles, have been studied as drug carriers in ophthalmic drug delivery over many years. Colloidal particles are subjected to the same clearance mechanisms as other foreign bodies that may come into contact with the ocular surface, and tend to be washed away by reflex tearing. Larger particles are more likely to be entrapped under the eyelids or in the inner canthus and so remain in contact with the corneal and conjunctival epithelia for extended periods. For patient comfort, it is considered that solid particles intended for ophthalmic use should not exceed 5-10 μm diameter. The use of a bioadhesive polymer (e.g. polyacryclic acid, chitosan, hyaluronic acid) that prolongs the residence time in the precorneal region may confer an advantage [13]. One interesting approach involves the use of lectins to selectively bind particulates to the required area of the precorneal region for extended periods.

Liposomes[14] are membrane like vesicles, consisting of phospholipid by-layers surrounding an aqueous compartment. Their stability and limited drug loading capability restricts the potential of liposomes as a topical ophthalmic drug delivery system. In addition, large-scale manufacture of liposomes is expensive and technically challenging.

Microparticles have an average particles size grater than 1μm and may be microcapsules or microspheres. Microspheres are monolithic particles of insoluble drug dispersed in a polymer matrix, whereas microcapsules consist of a polymeric membrane surrounding a solid or liquid drug reservoir. Upon topical instillation, the particles reside in the ocular cul-de-sac, and the drug is released from the particles through diffusion or polymer degradation.

Nanoparticles are solid colloidal drug carriers ranging from 10 to 1000 nm. These may also be made from the insoluble drug, or the drug may be entrapped within the particle or adsorbed onto its surface. The payload (the dose of drug delivered) is comparatively small and represents a limiting factor for the use of nanoparticles in drug delivery. A wide range of polymers has been used in the manufacture of micro and nanoparticles for ophthalmic drug delivery including poly (alkyl) cyanoacrylate, polylactic acid and albumin.

Eye Ointments

Ointments are semisolid preparations intended for external application. They are usually formulated using mixtures of semisolid and solid hydrocarbons (paraffins), which have a melting or softening point close to body temperature and are non-irritating to the eye. The medicinal agent is added to the base either as a solution or as a finely micronized powder. Upon instillation in the eye, ointments break up into small droplets and remain as a depot of drug in the cul-de-sac for extended periods. Ointments are therefore useful in improving drug bioavailability and in sustaining drug release. Although safe and well tolerated by the eye, ointments suffer with relatively poor patient compliance due to blurring of vision and occasional irritation.

Solid matrices and devices

A number of solid polymeric inserts and discs have been developed as ophthalmic drug delivery systems. Inserts allow for accurate dosing, reduced systemic absorption and in some cases, better patient compliance resulting from a reduced frequency of administration and a lower incidence of visual and systemic side effects. Inserts are affected to a lesser extent by nasolacrimal drainage and tear flow than the more conventional dosage forms, and are associated with reliable drug release and longer residence times in the conjunctival cul-de-se. However, patient resistance to placing a solid object in the precorneal region is an issue to some significance. These inserts have been classified as degradable or non-degradable (i.e. those that have to be removed on completion of therapy). Various materials have been utilized in the development of degradable inserts, including polyvinyl alcohol, hydroxypropylcellulose, polvinylpyrrolidone and hyaluronic acid. Non-degradable inserts have been shown to provide more predictable release rates than soluble inserts and are prepared from insoluble materials such as ethylene vinyl acetate copolymers and styrene-isoprene-styrene block copolymers.

Preformed Hydrogels

Preformed hydrogels for topical administration in the eye can be based on natural, synthetic or semi synthetic polymers. Some characteristics of the more commonly used polymers are listed [Table1].

Polymer	**Origin**	**Characteristics**
Cellulosic derivatives	Semisynthetic	Good tolerance Optical clarity Newtonian behavior Similar refractive index as the cornea
Poly (vinyl alcohol)	Synthetic	Newtonian behavior Wetting agent
Sodium hyaluronate	Skin, connective tissues, muscles, tendon, vitreous body, aqueous humor	Biocompatible Mucoadhesive Pseudoplastic behavior Viscoelastic behavior
Carbomer	Synthetic	Good tolerance Bioadhesion Possibility to be neutralized by the active compound in its basic form

Table I: Characteristics of polymers used to prepare preformed hydrogels for ophthalmic applications

Hydrogels

Increase in solution viscosity by using polymers improves retention of product on the corneal surface. More recently, the approach to improve precorneal retention is based on the use of mucoadhesive polymers. The principle for use of bioadhesive vehicles relies on their ability to interact with the mucin-coating layer present at the eye surface.

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 modification after administration. Those may be Cellulose, Poly vinyl alcohol, Hyaluronic acid and Carbomer. In situ forming gels are formulations, applied as Solutions, or suspensions that undergo gelation after instillation due to physico-chemical changes inherent to the eye. Those may be Gellan gum, Poloxamer, CAP latex.

The polymers chosen to prepare ophthalmic hydrogels should meet some specific rheological characteristics. It is generally well accepted that the instillation of a formulation should influence tear behavior as little as possible. Because tears gave a pseudoplastic behavior, pseudoplastic vehicles would be more suitable as Newtonian formulations, which have a constant viscosity independent of the shear rate, whereas pseudoplastic solution exhibit decreased viscosity with increasing shear rate, thereby

offering lowered viscosity during blinking and stability of the tear film during fixation [15].

Cellulose Derivatives

Because pure cellulose in not water soluble due to its relatively high crystallinity, cellulosic derivatives have been used for a long time as viscosifiers in eollyria. Methylcellulose (MC) was first introduced in ophthalmic formulations in the 1940s as a mean of decreasing their fluidity same years later, Mueller and Deardorff [16] showed in man that solutions of homatropine hydro bromide exhibited enhanced cycloplegic and mydriatic activity in the presence of MC. Further promising results were obtained in 1962 by Haas and Merrill[17], who reported a lowered intraocular pressure in man after administration of pilocarpine incorporated in an MC vehicle. Currently, a large number of commercial formulations contain cellulosic viscosifiers, including Adsorbotear (Alcon, fort worth, Texas) and Tears Naturale (Alcone, Fort Worth, Texas). The cellulosic derivatives most commonly used in ophthalmology are Methylcellulose (MC), Hydroxyethylcellulose (HEC), Hydroxypropylcellulose (HPC), Hydroxypropyl methylcellulose (HPMC), Sodium carboxymethylcellulose (CMC Na).

The boundary between viscous solutions and gels for cellulosic derivatives is particularly difficult to define because data regarding the hydrocolloid concentration or the viscosity of the final formulation are not always available. Comparing the performance of three different cellulosic derivatives, namely HEC, HPC, and HPMC, [18] reported that HEC solutions were the most effective in reducing the elimination rate of sodium fluorescein from the cornea, probably due to a better tolerance. In fact, the volunteers rated HEC as the most comfortable, whereas HPC and HPMC gave rise to complaints of irritation and blurred vision. Several studies have clearly demonstrated the efficacy of cellulosic polymers in increasing ocular availability of numerous drugs when compared with simple saline solutions by decreasing the drainage rate from the eye[19,20]. For example, Chrai and Robinson[21] found a 100-fold change in viscosity by using MC as the viscosity-inducing polymer.

However, they reported that increasing the viscosity above 15-20 cps, which appeared as the optimum viscosity, did not lead to proportional improvement. Subsequent advances in the polymers field with respect to ocular drug delivery has led to the use of poly (vinylalcohol) (PVA); sodium hyaluronate and carbomer, which often give better results [22, 23] than celluloses.

Poly (vinyl alcohol)

PVA is a synthetic polymer commercially obtained by polymerization of vinylacetate to poly (vinyl acetate) and subsequent hydrolysis to PVA. Conflicting results were obtained by Linn and Jones[24] who found that PVA exhibited a significantly shorter elimination time than another cellulosic derivative, namely HPMC Numerous authors[25, 26] reported quite similar results in favor of 0.5% MC over 1.4% of PVA rabbits of humans. These last findings seemed more reasonable than those of Krishna and Brow because 0.5% MC solutions exhibit significantly greater viscosity compared with 1.4% solutions based on PVA. Patton and Robinson[27] highlighted those presuming contradictory results. By testing solutions based on MC and PVA, the authors concluded that two vehicles exhibiting or at least approximating to Newtonian behavior in the same viscosity

range could not have significantly different effects on ocular drug bioavailability. Moreover, they established that as demonstrated for MC [28].

Lachrymal drainage evaluations of PVA formulations by γ scintigraphy have demonstrated a significant delay of the drainage in man and rabbits when compared with a saline solution. Some commercial products, particularly for the treatment of dry eye are based on PVA including Hypo Tears (IOLAB CORP., Claremont, California) and Liquifilm (Allergan, Irvine, and California.).

Sodium Hyaluronate

The sodium salt of hyaluronic acid (SH) is a high molecular weight biological polymer composed of repeating disaccharide units of glucuronic acid and N-acetylglucosamine, a specific ultra pure fraction being patented as Healon (Kabi Pharmacia, Sweden) by Balazs[29] in 1979. Bernatchoz et.al.[30] have extensively reviewed its use as a vehicle in ocular drug delivery.

γ Scintigraphic data of Snibson et.al.,[31] pointed out a very interesting phenomenon. They demonstrated that the residency times of 0.2% and 0.3% SH solutions on the cornea were significantly longer for patients having dry eye syndrome than in healthy subjects. The rationale for such a result was that the alteration of tear mucin in dry eyes might have modified the interaction of SH with the ocular surface.

An extended residence time is one of the factors used to select artificial tears for the therapy of KCS. At present the therapeutic schedule in the treatment of dry eye implies frequent instillations, which lead to two major short comings, patient discomfort and side effects due to preservatives used in multiple dosage forms such as benzalkonium chloride, it has been frequently proposed as a vehicle of choice in tear substitutes and all the studies reported improvement of several symptoms associated with KCS, such as blurred vision, pain, photophobia, with this kind of treatment. A further advantage of SH in this application is its pseudoplastic behavior.

The ability of SH to prolong drug release by increasing precorneal drug residence time has been studied (mostly in animals) for several ophthalmic compounds such as pilocarpine[31, 32, 33] or, more recently gentamicin[34]. Residence time of gentamicin in humans was found to be 2.23 fold superior when instilled in 0.25% SH formulation in an isotonic phosphate buffer solution and drug bioavailability was significantly improved for at least 10 minutes.

Carbomer

Cross-linked poly (acrylic acid) of high molecular weight commercially available as Carbopol (B.F Goodrich Chemical Company, Ohio) is widely used in ophthalmology to enhance precorneal retention to the eye. Preparation of Carbopol hydrogels is simply based on the dispersion of the polymer in water at room temperature followed by neutralization process with agents such as sodium hydroxide; triethanolamine, or directly with active basic compounds. The maximal viscosity is obtained at neutral pH. Carbopol offers the advantage of exhibiting excellent mucoadhesive properties when compared with other polymers. (e.g., cellulose derivatives, PVA and SH) The mechanisms involved in the mucoadhesion ability of Carbopol have been investigated previously. Four mechanisms of interaction between mucin and poly (acrylic acid) have been described are electrostatic interaction, hydrogen bonding, hydrophobic interaction and interdiffusion.

These mechanisms can be explained by the similar features of the mucus network and the cross-linked poly (acrylic acid) are macromolecular expanded network, negative charges, and significant hydration in aqueous media and significant number of carboxyl groups.
The efficacy of Carbopol in enhancing precorneal residence time has been extensively studies by incorporating tracers such as sodium fluorescein or active compounds such as pilocarpine or prednisolon.
Comparing different types of poly (acrylic acid) (Carbopol 940-934-941and 910) unlu et. al.,[35] concluded that Carbopol 940 showed superior appearance and clarity. The results reported in these studies showed the superiority of poly (acrylic acid) as a sustained release agent over reference solutions [36] or over some hydrogels. However the majority of authors avoided tolerance evaluations. Only Ludwig et.al.[37] noted some differences in acceptability of Carbopol formulations (0.1 and 0.2%) from one patient to another. A large number of commercial ophthalmic preparations contain Carbopol including tear substitutes such as Lacrigel (Europhta, Monaco), Lacrinorm (Chauvin Montpellier, France) or formulations containing active compounds such as Iduviran (Chauvin, Montpellier, France) and Pilopine (Alcon Fort Worth Texas).
Other natural or synthetic polymers have also been evaluated as potential vehicles to prolong the residence time of drugs at the surface of the eye but are currently being further investigated. Therefore, they are not extensively discussed in this article but are principally mentioned here for reference, chondroitin sulfate [38]xanthan gum [39] poly (vinylpyrrolidone) [40] and chitosan. Briefly, xanthan gum and chitosan are both polysaccharides of natural origin being respectively obtained by an aerobic fermentation of a carbohydrate with Xanthomonas compestris and by deacetylation of chitin. An important difference between the two polymers is the anionic character of xanthan gum, where as chitosan exhibits positive charges. The possible advantage of chitosan over xanthan gum is it has bioadhesive property. Therefore, chitosan has attracted attention for topical ophthalmic applications, for example to enhance tobramycin delivery to the eye [41].γ Scintigraphic evaluations have shown that the presence of chitosan was efficient to prolong precorneal residence time of formulations, when compared with a commercial solution [42].

In-situ forming gels

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. A new approach is to try to combine advantages of both solutions and gels, such as accuracy and facility of administration of the former and prolonged residence time of the later. Thus, in situ hydrogels can be instilled as eye drops and undergo an immediate gelation when in contact with eye. The liquid to semisolid phase change can be triggered by increased temperature, increased pH and ionic strength of the tear film.

Thermo reversible hydro gels

These hydro gels are liquid at room temperature (20-25^0 C) and undergo gelation when in contact with body fluids (35-37^0 C), due to an increase in temperature. Different thermal settings gels have been described in this Review. For example acrylic acid copolymers

and N-isopropylacrlamide derivatives ophthalmic administration such as tolerance have limited the choice of such polymers. Poloxamers, commercially available as pluronic (BASF–Wyandotte, USA), are the most commonly used thermal setting polymers in ophthalmology. They are formed by a central hydrophobic part (poly oxy propylene) surrounded by hydrophilic part (ethylene oxide).

Depending on the ratio and distribution along the chain of the hydrophobic and hydrophilic sub units, several molecules weights are available, leading to different gelation properties. Pluronic F-127, which gives colorless and transparent gels, is the most commonly prepared by solubilization of the polymer in cold water (5-10^0 C) followed by gelation up on warming to ambient temperature[43].

Three principal mechanisms have been proposed to explain the liq-gel phase transition after an increase in temperature, including the gradual desolvation of the polymer, increased entanglement of polymeric network and also intra molecular hydrogen bonds might promote gelation. The importance of the entanglement process in the gelation phenomenon of poloxamers has been confirmed by using of fluorescent probe technique to evaluate the hydration and diffusion processes in pluronic F-127 solutions. The mucomimetic property of poloxamers is supposed to be due to their hydrophobic and hydrophilic sequences simulating mucin action by adsorption of the aqueous layer of tears on the hydrophobic epithelium. Owing to their protective and mucomimetic action poloxamers have also been evaluated for the treatment of dry eye. For examples flow base containing 18% of poloxamer 407, sodium chloride, and potassium chloride has been shown to possess clinically advantageous of this product is the formation of solid residues on the eye lids after instillation of 50 micro liter of solution this problem being overcome by instillation of smaller volumes.

A recent γ scintigraphic study on a semi inter penetrating network based on poloxamer have been shown to remain significantly longer at the surface of the eye than a reference solution (t 50% about 25-fold higher). Some applications of thermo reversible hydro gels in ophthalmology refer to the use of other polymers like polaxamines, which are copolymers of poly (ethylene oxide) and poly (propylene oxide) obtained from a precursor, commercialized as tetronic[38].

P^H induced gelation

Pseudolatexes can be defined as artificial latexes prepared by the dispersion of a preexisting polymer in aqueous medium in situ gelling pseudo latexes for ophthalmic use can be described as aqueous colloidal dispersions of polymer, which become viscous gels after instillation in the conjunctival cul-de-sac due to modification of the pH.

Pseudo latexes are obtained by dispersion of an organic solution of a preformed polymer in an aqueous medium, leading to an o/w emulsion. Solvents from the internal phase are then evaporated to obtain a fluid dispersion of polymeric particles with a size generally smaller than 1 μm. Two principal methods are commonly used to prepare ophthalmic pseudo latexes, the solvent evaporation process and the salting out process. Both methods allow the production of a lyophilized and easily re dispersible power. Thus, pseudo latexes have the advantage of the latex as well as the stability of active compounds such as pilocarpine, which is sensitive to aqueous media. In addition, such systems represent an interesting technological alternative that avoids the use of organic solvents, which can cause problems such as toxicity. Bioactive materials can be added in to these systems at

various times of the preparation, in aqueous or in the organic phase during preparation or by adsorption on the final latex. Ibrahim has listed some pre requisites necessary for an optimal formulation of ophthalmic pseudo latex.

- Solubility of the polymer selected in organic solvents as well as insolubility in water.
- Existence on the macromolecule of ionizable groups, which can react with the electrolytes of the lachrymal fluid.
- Use of a high molecule weight polymer.
- Rapid coagulation process after instillation to avoid pre corneal drainage of the formulation.
- Compatibility of the different components of the colloidal dispersion with pre corneal tissues.

First preliminary investigations of pH-sensitive nano particulate (latex) for ophthalmic administration began in the early 1980 s and have been extensively studied and developed the preparation of latexes containing pilocarpine with cellulose acetate phthalate (CAP). The choice of this polymer was determined by the compatibility of the polymer with the active compound, the ability of the CAP latex to be a free-running solution at pH 4.2 and gel at gel at 7.4 and finally latex stability at relatively low pH which is a pre requisite to ensuring the stability of pilocarpine.
Finally, it is important to note that irritation tests on rabbits including examination of the corneal, the iris and the conjunctiva have demonstrated that the investigated pseudo latexes did not induce visible irritation. However a sensation of discomfort seems to be unavoidable after the coagulation of the solution in the conjunctival cul-de-sac as is the case for any semisolid preparation.

Ionically induced gelation

Gellan gum is an anionic exocellular polysaccharide by the bacterium pseudomonas elodea, having the characteristic property of cation-induced gelation. The acetylated form is commercially available as gelrite (Kelco division of Merck and Co, USA). The sol-gel transition process is induced by the presence of monovalent or divalent ions such as Na^{+} and $Ca^{+\cdot}$ Some other parameters influence the phase transition. e.g.: The concentration of polysaccharide, the temp of the preparation, and the nature and the concentration of cations. It was determined that divalent ions such as magnesium or calcium were superior to monovalent cations in promoting the gelation of the polysaccharide. However the concentration of sodium tears (2-6g/l) is quite sufficient to induce the gelation. Because the presence of lachrymal fluid is required to induce gel formation, accidental gelation during storage does not occur as with thermo reversible gels.
The gelling mechanism is based on a modification of the conformation of the polysaccharide. It corresponds to the formation of double helical junction zones in the presence of cations followed by aggregation of double–helical segments, leading to a three dimensional net work.
Efficacy of Gellan gum has been evaluated by measuring Pharmacokinetics parameters and pharmacological response was found an increased ocular bioavailability of timolol maleate when incorporated in gelrite formulations versus the commercial timpotic

solution. This result was confirmed by Vogel et al., who observed a two fold decrease of the intra ocular pressure of patients after administration of gelrite containing timolol[16].

Conclusion

Solutions and aqueous suspensions 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 conjunctiva. A considerable disadvantage of using eye drops is the rapid elimination of the solution and their poor bioavailability. The ophthalmic drug delivery discusses, minimize the precorneal factors and prolong drug activity at its site of action. This can be achieved by adopting the novel in situ gel approach. These gels are easy to instill at the same time improved ocular bioavailability by increasing the duration of contact with corneal tissue, there by reducing the frequency of administration required incase of conventional ophthalmic solutions, thus optimizing ocular therapy.

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