INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com ISSN 2230 – 8407
Review Article

AN INSIGHT TO OPHTHALMIC IN-SITU GEL: AN OVERVIEW

Thakur Reeta Rani*, Sharma Mohit
Department of pharmaceutics, M. M. College of Pharmacy, M. M. University, Mullana, Ambala, Haryana, India

Article Received on: 11/01/12 Revised on: 20/02/12 Approved for publication: 10/03/12

*Email: reetabit@gmail.com

ABSTRACT
Ocular drug delivery has been a major challenging and interesting field for the pharmaceutical scientists due to unique anatomy and physiology of the eye. The major problem encountered in ocular drug delivery is the rapid loss of the drug through lachrymal drainage which results in poor bioavailability and therapeutic response of the drug. There are some static (different layers of the eye i.e. cornea, sclera, retina) and dynamic (blood aqueous and blood retinal barrier) barriers which also affect the bioavailability of the drug. In-situ gels are the liquid preparations which upon instillation undergoes the phase transition in cul-de sac in the eyes to form a viscous gel and this occurs due to environmental changes in the eye (due to change in pH, change in temperature and ion-induced). This review is to specify the different phase transition process and polymers used in forming in-situ gelling system.

Keywords – lachrymal drainage, cul-de sac, in-situ gel, phase transition.

INTRODUCTION

Today in the pharmaceutical industry the ophthalmic drug delivery is one of the most interesting and challenging area. In past few years there have been tremendous increase in the research and development in this area. The anatomy and physiology of the eye makes difficult to achieve proper drug concentration after the instillation of the desired form[1]. The conventional dosage form i.e. eye drops have major problem that they cannot provide the desired concentration of drug into the eye due to loss in naso lachrymal drainage[2]. Therefore it remains a big challenge for the formulator to deliver the drug at target tissue without causing much loss of the drug or increase the systemic side effects[1]. Various different preparations like ocular inserts, hydrogel etc have been developed to prolong the contact time on ocular surface. The main problem with these preparations is patient compliance and blurred vision[3], so the liquid dosage forms are more preferable

An ideal ocular preparation must be

1) That on instillation does not cause any irritation to the eye and blurred vision.
2) Should and be able to withstand lachrymal fluid dilution without being rapidly eliminated after the instillation by precorneal elimination.
3) Should have retaining power so that the drug remain in the precorneal area for longer period of time and increase the bioavailability of the drug in the eye[4].

To overcome the problems of conventional dosage forms i.e. rapid drug loss, blurred vision and patient compliance in-situ gels can be prepared.

Reasons For Poor Ocular Bioavailability

Application of eye drops to the cul-de-sac is most common method of administration of the drug molecule in the treatment of ocular diseases. The major problem that is encountered in ophthalmic preparations is the rapid elimination of the drug from the eye due to the lachrymal drainage system. This causes undesirable effects. The residence time of the ocular preparations is limited as the volume that retain in the cu-de-sac is 7-9µL and most of the instilled volume of the preparation is cleared within few minutes. Thus the bioavailability of the ocular preparations is limited to 1-10 %[5].

Nasolacrimal Drainage System

This system major factor which contribute to precorneal drug loss which results in poor ocular bioavailability[6]. The nasolachrymal drainage system consists of three parts the secretory system, distributive system and the excretory system[7]. The secretory system is comprise of secretors which secretes tear fluid which spreads over the corneal surface during blinking of eyes through eye lids and tear meniscus around the lid edge of the open eyes which is distributive system. The excretory system consists of upper and lower puncta, canaliculi and nasolachrymal duct[5].The cul-de sac normally holds 7-9µl of tear fluid and normal tear flow rate is 1.2-1.5µL/ minutes[8].

Overview Of Eye

For research and to develop an effective ophthalmic delivery system a good knowledge of the structure and physiology of the eye is necessary.

The eye is an organ of vision. The eye ball is a spherical organ of about 25mm in diameter consists of a lens and two fluid filled chambers which are enclosed by three layers:

Cornea and sclera.

Uveal tract (consist of iris, cilliary body and choroid)

The retina

Sclera[5, 7, 9, 10]

The sclera is made up of collagen fibres and proteoglycans which made it tough in nature. It protects the inner layers of the eye. It constitutes the posterior one-sixth of the eye ball and also providing integrity to it which helps in defining the shape and length of the eye. The ocular preparations cross the sclera through perivascular spaces or through empty spaces within the collagen network.

Cornea[11, 12, 13]

It is composed of five layers the superficial layer is epithelium, bowman's membrane, stroma, descemet's membrane and the endothelium

The epithelium: it consists of 5 to 6 layers of cells. It makes up about 10% of the total corneal thickness in man. The thickness of the membrane is about 5-100µm and the number of layer increases up to 10 in the thicker cornea. The layer is

hydrophobic in nature and make it barrier for the hydrophilic drugs.

The bowman's membrane: it occurs as a thin uniform sheet with a thickness of 8-14µm and not a true elastic membrane. It is not considered as a barrier to drug permeation through the cornea.

The stroma: this covers the 90% of the thickness of the cornea and made up of modified connective tissue. The 70-80% wet weight of the stroma is water and the 20-25 % dry weight is collagen, some proteins and mucopolysaccharides. The stroma is main barrier for the lipophilic drugs.

Descemet's membrane: it lies between the stroma and endothelium is very strong, homogeneous and resistant membrane. It has an approximate thickness of 6µm and regenerates if getting damaged.

The endothelium: this is single layer of flat epithelial like cells and covers the most of the posterior surface of the cornea and responsible for maintaining the corneal hydration. The permeability of the endothelium is 200 times more than that of epithelium. It consist of Na^+/k^+-ATPase pump which depends on the concentration of bicarbonate ion maintains the balance between passive movement of water into the stroma and the active movement of fluid out of it which is responsible for maintaining corneal transparency and thickness. The absorption of the drug is affected by the thickness of the cornea by increase in path length.

Conjunctiva[7, 14, 15, 16]

It is transparent membrane and lines the inner surface of the eyelids and reflected onto the globe. It is a highly vascularized mucus membrane which forma a continuous surface area of 18cm^2. It is involved in the formation and maintenance of the precorneal tear film and in protection of eye. It is divided into three distinct parts (1) bulbar conjunctival epithelium which is contagious with that of the cornea (2) fornix epithelium and (3) palpebral epithelium which is contiguous with epidermis of the eyelids. The globlet cells are an important anatomical element of the conjunctiva. There are about 1.5 million globlet cells. The globlet cells synthesize secretory mucins and TFF-peptides. The TFF peptides contribute to the rheological properties of the tear film by specific non-covalent interactions with mucins forming an entangled network.

Tear Film [6, 7, 8]

The exposed part of the eye is covered by a thin fluid layer which is called as precorneal tear film. This film maintains corneal transparency and good visuals functions of the eye. The thickness of the film varies from 3-10µm and is the first structure encountered by the topically applied application. The resident volume is about 10µl. There are three layers of the tear film which consists of following:

Superficial layer: it is a multimolecular film and 100nm thick and derived from meibomian glands embedded in the tarsal plate of the eyelid and accessory sebaceous glands of zeiss. It consists of sterols esters, triacylglycerols and phospholipids and spreads over the aqueous layer during blinking. The lipids help to reduce the evaporation of the tear fluid and helps in maintaining the osmolality of the tears.

Aqueous layer: the lachrymal gland and the accessory gland contribute to the formation of the aqueous layer. It consists of water, inorganic salts, glucose and urea as well as retinol, ascorbic acid, various proteins. This middle layer constitute of 98% of the tear film.

Mucous layer: it is attached to glycocalix of the corneal/conjunctival surface and consists of glycoprotiens. The layer is produced by the conjunctival globlet cells and lachrymals gland. The layer is very sensitive to hydration and forms a gel-layer with viscoelastic rheological properties. It plays an important role in the stability of the tear film as well as in the wetting of the corneal and conjunctival epithelium.

Drug Delivery System For The Eye

The most common route for the treatment of ocular diseases is topical medication. The application of drug via this route is preferred due to ease of administration and its low cost. Topical route of application is used for the treatment of the disorder affecting the anterior segment of the eye. The various anatomical and physiological barriers are there which hinders the drug absorption to the posterior part of the eye. A major fraction of the applied drug formulation is loss due to the nasolachrymal drainage and high ratio of tear turnover which cause lower bioavailability of the drug to the posterior part of the eye.

The route of administration mainly depends on corneal permeability of the drug molecule. Other routes are also there for the treatment of diseases which includes systemic route and intra-ocular. Systemic route is mainly used for the treatment diseases affecting the posterior part of the eye. The main drawback of the systemic route is the availability of the drug is 1-2 percent which reaches to the vitreous humour. The main barrier in this route is blood retinal barrier which governs the entry of the drug to the posterior part of the eye. The intra-ocular route of administration includes the intravitreal delivery of drug to the posterior part of the eye. Intravitreal injections remain the main route of delivery in order to avoid systemic drug loss[17, 18]

Mechanism Of Ocular Absorption[5, 6, 8]

The drug from the eye is absorbed by 2 routes i.e. by corneal route and by non corneal route

Corneal route

The corneal absorption is the major pathway of drug absorption for the topically applied formulation. The drug absorption is occurring by two mechanism transcellular and paracellular diffusion. Most of the lipophilic drugs are absorbed by transcellular diffusion and the hydrophilic drugs are absorbed by parracellular diffusion. In general, corneal penetration is mainly governed by the lipophilicity of the drug but it is also affected by other factors including solubility, molecular size and shape, charge and degree of ionization.

Non corneal route

The absorption is occurring through conjunctiva and sclera. There are three routes by which drugs can permeate through sclera.

a) Through the perivascular spaces.
b) Through the aqueous media of gel-like mucopolysaccharides.
c) Through the empty spaces within collagen network.

This route is considered to be non productive route as the most of the drug reaches to the systemic circulation before it reaches to the intraocular tissues. This route may be important for the hydrophilic compounds with large molecular weights such as timolol maleate and gentamicin.

Barrier In Ocular Drug Delivery

In the ocular drug delivery there are three main barriers for the drug molecule to pass and penetrate to the intraocular tissues i.e. a) cornea b) conjunctiva c) sclera

Cornea[19, 20]

It is the main pathway for the topically applied drug to penetrate to the intraocular tissues. It consists of five layer 1) epithelium 2) bowman's membrane 3) stroma 4) descemet's membrane 5) endothelium. The penetration of the drug is depending on their n-octanol – water coefficient. The drugs which have a partition coefficient between 10-100 can easily pass through the cornea as they contain both lipophilic and hydrophilic properties.

Conjunctiva[20, 21]

It is a thin and vascular mucous membrane have two to three layers of epithelial cells which is over lying to a highly vascular connective tissue. There are tight junctions on the apical surface of the epithelium which act as a main barrier to drug penetration across the tissue. The drug molecule (less than 20,000 da) can easily penetrate through the conjunctiva.

Sclera[9, 10]

It is the outermost layer of the eye which acts as a protective barrier to the inner parts of eye. It is made up of hydrated collagen fibril and arranged in an irregular manner which makes it opaque.

There is another barrier which is blood ocular barrier. The blood ocular barrier is consisting of blood-aqueous barrier and blood-retinal barrier.

Blood-ocular barrier[8, 17]

It is composed of endothelial cells and it is located in anterior part of the eye. It regulates the exchange of the solutes between blood and intraocular fluid and also preventing the passage of unspecific solutes.

Blood-retinal barrier

It prevents the entry of toxic substance, plasma components and water into the retina of eye.

Conventional Ocular Delivery Systems[22]

The conventional delivery system includes solutions, suspensions, and ointments. These constitute almost 90% of current ophthalmic preparations and offers some advantages like ease of administration by the patient, ease of production and low cost of manufacturing. However there are some disadvantages are there for these conventional dosage forms like very short contact time with ocular surface and fast nasolachrymal drainage which is responsible for the poor bioavailability of the drug.

Solutions[22, 23]

The solutions are most preferred delivery system for ophthalmic drug delivery system offering advantages like low cost of production, simplicity and low cost of formulation, however there are disadvantages like poor bioavailability, fast nasolachrymal drainage which leads to systemic side effects also and needs frequent dosage as there is more loss of drug from precorneal system.

Suspensions[24, 25, 26]

These are formulations in which drug molecule is suitably suspended in the aqueous vehicle. The particle size of the drug molecule plays important role in the suspension. The suspensions have more limitations as compared to the solutions. They need to be adequately shaken before use to ensure correct dosing. They are more expensive than solutions and drug required to achieve marginally improved bioavailability is high and if the drug particle size is get more than 10 µm then the eye take them as foreign material and due to reflex action the drug loss is more.

Ointments[27, 28, 29]

They generally consist of dissolved or dispersed drug into a suitable base. They are semisolid preparations and well tolerated by the patient. The bioavailability also get increased as these preparation are viscous in nature and resist to nasolachrymal drainage and the contact time of the preparation also get increased, however these also have some disadvantage like as they are oily preparations can cause blurred vision and matting of the eyelids, causes discomfort to the patient.

Colloidal Drug Delivery Systems[30, 31, 40]

Colloidal drug delivery systems include liposomes, niosomes and micro and nanoparticles. These delivery systems have been studied over many years in order to achieve drug targeting, increasing bioavailability of drug molecules and protection of drug molecule from enzymatic degradations. Colloidal carriers are small particulates systems ranging in size from 100-400nm.

Nanoparticles

They are defined as sub micrometer-sized polymeric particles ranging from 10-1000nm. In this the drug molecule can be dissolved, entrapped or adsorbed and depending on the process by which they are made they can be called as nanospheres or nanocapsules. Nanospheres have matrix like structure in which the drug molecule is dispersed or dissolved in the matrix or drug molecule is adsorbed at the surface of the particle, whereas nanocapsules consist of polymer shell and a core, where drug can either dissolved or adsorbed on the surface. The most common polymers used for the preparation of nanoparticulate system for ocular drug delivery system are poly-alkylcynoacrylates, caprolactone and polylactic-co-glycolic acid copolymers. The major limiting issue in making nanoparticles is of maintaining the particles size of the drug molecules, drug release rate and stability of the formulation.

Liposomes

Liposomes are vesicles which consist of concentric spheres of lipid bilayers separated by water compartments. The diameter of the liposomes ranging from 80 nm to 100 nm. They are amphiphillic in nature and accommodate themselves into both lipophilic and hydrophilic drugs. According to their sizes they are classified as small unilamellar vesicles (SUVs) 10-100nm and large unilamellar vesicles (LUVs) 100-300nm and if there is more than one bilayers they are known as multilamellar vesicles (MLVs). Liposomes are valuable for ocular drug delivery system as they are simple to prepare but the main problem associated with liposomes is there stability (due to hydrolysis of phospholipids), there limited drug loading capacity, blurred vision due to large size makes there use limited.

Niosomes

The limitations of liposomes like their stability; drug loading capacity niosomes has been developed. Niosomes are the nonionic surfactant vesicles which also consist of same bilayered structure as liposomes. They are more stable than liposomes moreover niosomes are biocompatible and biodegradable. They were also shown to increase ocular bioavailability of hydrophilic drugs because of the fact they contain surfactant which also acts like the permeation enhancer and also remove the mucous layer from the ocular surface.

Polymeric Delivery System

This Delivery System can be divided into three groups.

Viscosity enhancing polymers[32-35]

These polymers increase the viscosity of preparation and thus decreases lachrymal drainage and increase the bioavailability of drug to the eye. The different polymers that are used to increase the viscosity are some hydrophilic polymers include polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP), cellulose derivatives such as methyl cellulose and polyacrylic acids (Carbopols). Chrai and Robinson evaluated the use of an MC solution of pilocarpine in albino rabbits and found a decrease in the drainage rate with increasing viscosity.

Mucoadhesive polymers[36, 37]

Bioadhesion is the phenomena by which the drug molecule is attached to the specific biological tissue by means of interfacial forces and if the surface of the tissue contains mucin then this is known as mucoadhesion.The mucoadhesive polymers interact with ocular mucin and increases the contact time of the formulation with the ocular tissues. The most commonly used bioadhesive polymers are macromolecular hydrocolloids with numerous hydrophilic functional groups capable of forming hydrogen bonds.

In-situ gelling polymers[38, 39, 40]

These polymers are also viscous and undergo solution to gel phase transition when expose to the physiologic condition present in eye such as ionic strength, temperature, pH or solvent exchange. The principal advantage of in situ gelling system is easy, accurate and reproducible administration of a dose.

Hydrogels[31]

Increase in solution viscosity by using polymers improves the retention of the gels on the corneal surface. Currently there are two categories of hydrogels namely preformed gels and in-situ gels. Preformed gels may be defined as the viscous solution which does not undergo any modification after they instilled into the eyes. The polymers that are used to prepare preformed gels may include cellulose, polyvinyl alcohol (PVA), hyaluronic acid and carbomers, whereas in situ gels are viscous preparation which when administers into eyes goes into transition from solution phase to gel phase due to physicochemical changes.

Methods By Which Phase Transition Occurs

There are three methods which are used to triggers the phase change at ocular surface these are a) change in temperature i.e. thermosensitive, ph and electrolyte compositions

Transitions by change in temperature[5,7,41,42,43]

These in situ gels are liquid at room temperature (20-25 degree Celsius) and when they come in contact with fluids present in eye (35-37deg Celsius) they undergo phase transition as temperature increases. The polymers used for temperature induced gelation includes poloxamers, cellulose derivatives and xyloglucan.

Poloxomers (Pluronics): it is thermo reversible phase change polymers which consist of more than 30 different non-ionic surface active agents. These contain tri block of A-B-A type having polyethylene oxide (PEO) and polypropylene oxide (PPO). The PEO-PPO-PEO unit is commonly known as pluronics. It is available as liquid, paste and solid due to different molecular weights of PEO-PPO units. This ranges from 11000-14000. The Poloxomers are liquid below 25 deg and goes thrmogellation between 25 to 35 deg and thus increases the residence time of the drug and ocular surface. The process of gellation occurs through micellization which depend on critical micellization temperature (CMT) and critical micellization concentration (CMC).

Transition by change in pH[5, 41, 44]

In these gels the transition of phase is triggered by change in pH. The polymers used are cellulose acetate phthalate (CAP) latex and its derivatives like carbomers.

The polymer CAP is a free running solution at a ph 4.2 and becomes a gel at ph 7.2 for this property it is used in making ion activated in-situ gel.

Carbomer which is a cross linked poly (acrylic acid) and high molecular weight polymer commonly known as carbomer is widely used in ophthalmic preparations. It offers mucoadhesives properties to the formulation but as the concentration of carbomer increases its acidic nature causes stimulation of eye tissues. So to overcome this ocular drug delivery system which contains carbopol shows the phase transition into gel from the liquid solution at pka of about 5.5.

Ion- sensitive in-situ gels[44, 45]

In this the phase transition from sol to gel is triggered by change in ionic strength. The most common polymer used for ion sensitive in-situ gel is gellan gum i.e. gelrite which is a linear anionic heteropolysacchride secreted by microbe sphingomonas elodea. The gelrite consist of glucose, glucouronic acid and rhamnose in molar ratio 2:1:1. The gelrite when comes in contact with cations present in the tear fluid changes into viscous clear gel. This is caused due to cross linking of negatively charged helices by monovalent or divalent cations like Na^{+}, ca^{2+}, k^{+}. The mechanism of gelrite is like in ion free solution it forms double helices at room temperature and has low viscosity as that of water but when gel forming cations like calcium, magnesium are present then they form cation mediated cross linking in the polymer. The cations which are divalent like calcium or magnesium are more superior to the monovalent cations like sodium in the promotion of gellation of the polysaccharides.

CONCLUSION

The solutions and the aqueous suspension are most widely used for the treatment of ocular diseases. The main disadvantage of the above pharmaceutical dosage forms is the rapid drug loss from the surface of the eyes and there poor bioavailability and due to this there is requirement of frequent dosing which can lead to systemic side effects. The ophthalmic drug delivery which we have to be focused is to minimises the precorneal factors and prolong the activity of the active ingredient at the site of action and gives better effects. This can be achieved by approaching the novel in situ gels for the treatment of ocular diseases these gels are more stable and easy to administered into the eyes and do not cause any blurring into the eyes and patient compatible and improves the bioavailability of the drug , reducing the dosing frequency up to once daily as required than in case of the conventional dosage forms.

REFERENCES

1. Rupenthal ID, Green CR, Alany GR. Comparison of ion- activated in situ gelling systems for ocular drug delivery part 1: physicochemical characterization and in vitro release. Int. J. Pharm. 2011; 411: 69-77.
2. Gupta S, Vyas PS. Carbopol/chitosan based pH triggered in situ gelling system for ocular delivery of timolol maleate. Sci. Pharm. 2010; 78: 959-976.
3. Liu Y, Liu J, Zhang X, Zhang R, Huang Y, Wu C. In situ gelling gelrite/ alginate formulations as vehicle for ophthalmic drug delivery. AAPS Pharm. Sci. Tech. 2010; 2: 610-620.
4. Qi H, Chen W, Huang C, Li L, Chen C, Li W, Wu C. Development of a Poloxomers analogs/carbopol-based in situ gelling and mucoadhesive

ophthalmic delivery system for puerarin. Int. J. Pharm.2007; 337: 178-187.
5. Nanjwade BK, Manvi FV, Majappa AS. In situ-forming hydrogels for ophthalmic drug delivery. J. Cont. Rel.2007; 122: 119-134.
6. Hillery AM, Lioyd AW, Swarbrick J. Drug delivery and targeting for pharmacists and pharmaceutical scientist edited by Taylor and Francis 2001. 329-353.
7. Ludwig A. The use of mucoadhesive polymers in ocular drug delivery. Adv. drug del. rev., 2005;57: 1595-1639.
8. Shayne coxgad, Ph.D., D.A.B.T. Pharmaceutical manufacturing handbook Production and Processes, Gad Consulting Services Cary, North Carolina A John Wiley & Sons, Inc., Publication, 2008. p. 729-767.
9. Macha S, Hughes PM, Mitra AK. Overview of ocular drug delivery, Ed., Ophthalmic Drug Delivery Systems, 2nd ed., Marcel Dekker, New York: 2003. p. 1 – 11.
10. Rathore KS, Nema RK. An insight into ophthalmic drug delivery system. Int. J. Pharm. Sci. and drug Res.2009; 1: 1-5.
11. Sasaki H, Yamamura K, Mukai T, Nishida K , Nakamura J, Nakashima M , et al. Enhancement of ocular drug penetration. Crit. Rev. Ther. Drug Carrier Syst. 1999; 16 (1): 85-146.
12. Klyce SD, Crosson CE, Transport processes across the rabbit corneal epithelium: A review. Curr. Eye Res.1985; 4 (4): 323-331.
13. Ahmed I. The noncorneal route in ocular drug delivery, in Mitra, A K., Ed. Ophthalmic Drug Delivery Systems.2nd ed., Marcel Dekker. New York. 2003, pp. 335 -363.
14. Huang A J W, Tseng SCG, Kenyon KR. Paracellular permeability of corneal and conjunctival epithelia. Invest. Ophthalmol. Vis. Sci.1989; 30 (4): 684 -689.
15. Ahmed I, Patton TF. Importance of the noncorneal absorption route in topical ophthalmic drug delivery. Invest. Ophthalmol. Vis. Sci.1985; 26 (4): 584 - 587.
16. Jarvinen K, Jarvinen T, Urtti A. Ocular absorption following topical delivery. Adv. Drug Del. Rev.1995; 16: 3-19.
17. Pandya TP, Modasiya MK, Patel VM. Ophthalmic in-situ gelling system. Int. J. of pharm. and life Sci. 2011; 2: 730-738.
18. Gaudana R, Jwala J, Boddu SHS, Mitra AK. Recent perspective in ocular drug delivery. Expert review pharmaceutical research. 2008; 26(5): 1197-1216.
19. Maurice DM, Mishima S. Ocular pharmacokinetics In: M.C. Sears (Ed.) handbook of experimental pharmacology, vol 69, pharmacology of the eye. Springer-verlag, berlin-heidelberg. P.19-166.
20. Newell FW, ophthalmology. Principles and concepts, 6th edition C.V Mosby co. St.louis, MO 1986
21. Watsky MA, Jablonski MM, Edelhauser HF. Comparison of conjunctival and corneal surface areas in rabbit and human. Curr.Eye. Res 7, 483-46.
22. Lang JC. Ocular drug delivery conventional ocular formulations, Adv. Drug. Deliv. Rev.1995; 16 (1): 39 – 43.
23. Fitzgerald P, Wilson CG. Polymeric systems for ophthalmic drug delivery, Polymeric Biomaterials, Marcel Dekker, New York: 1994. p. 373 – 398.
24. Wilson CG, Olejnik O, Hardy JG. Precorneal drainage of polyvinyl alcohol solutions in the rabbit assessed by gamma scintigraphy. J. Pharm. Pharmacol. 1983; 35(7): 451- 454.
25. Olejnik O, Weisbecker CA. Ocular bioavailability of topical prednisolone preparations. Clin. Ther.1999; 12 (1): 2-11.
26. Davies NM, Wang G, Tucker IG. Evaluation of a hydrocortisone/ hydroxypropyl - [beta] - cyclodextrin solution for ocular drug delivery. Int. J. Pharm. 1997; 156 (2): 201- 209.
27. MacKeen DL. Aqueous formulations and ointments. Int. Ophthalmol. Clin. 1980; 20 (3): 79 -92.
28. Sieg JW, Robinson JR. Vehicle effects on ocular drug bioavailability II: Evaluation of pilocarpine, J. Pharm. Sci. 1977; 66 (9): 1222 – 1228.
29. Greaves J L, Wilson CG, Birmingham AT. Assessment of the precorneal residence of an ophthalmic ointment in healthy subjects. Br. J. Clin. Pharmacol. 1993; 35 (2):188 -192.
30. Mayol L, Quaglia F, Borzacchiello A, Ambrosia L. A novel Poloxomers/hyaluronic acid in situ forming hydrogel for drug delivery: rheological, mucoadhesive and in vitro release properties. Eur. J. Pharm. and Biopharm. 2008; 70:199-206.
31. Eaga CM, Mohan J, Kandukuri, Allenki V, VamsaniMR. In-situ gels- a novel approach for ocular drug delivery. Der. Pharmacia letter. 2009; 1 (1): 21-33.
32. Chrai SS, Robinson JR. Ocular evaluation of methyl cellulose vehicle in albino rabbits. J. Pharm. Sci.1974; 63 (8): 1218-1223.
33. Saettone MF, Giannaccini B, Ravecca S, La MF, Tota G. Polymer effects on ocular bioavailability- the influence of different liquid vehicle on the mydriatic response of tropicamide in humans and in rabbits. Int.J. Pharm. 1984; 1:187-202.
34. Lee VH, Robinson JR. Topical ocular drug delivery: recent developments and future challenges. J. Ocul. Pharmacol. 1986; 2 (1): 67- 108.
35. Park H, Robinson JR. Mechanisms of mucoadhesion of poly (acrylic acid) hydrogel. Pharm. Res. 1987; 4 (6): 457- 464.
36. Robinson JR, Mlynek GM. Bioadhesive and phase - change polymers for ocular delivery. Adv. Drug. Del. Rev. 1995; 16 (1): 45 -50.
37. Zignani M, Tabatabay C, Gurny R. Topical semi - solid drug delivery: Kinetics and tolerance of ophthalmic hydrogels. Adv. Drug Deliv. Rev. 1995; 16 (1): 51 –60.
38. Krauland AH, Leitner VM, Bernkop - Schnurch A. Improvement in the in situ gelling properties of deacetylated gellan gum by the immobilization of thiol groups. J. pharm. Sci.2003; 92 (6): 1234 -1241.
39. ssGurny R, Ibrahim H, Buri P. The development and use of in situ formed gels, triggered by pH. Biopharmaceutics of Ocular drug Delivery, CRC press, Boca raton, 1983. p. 81-90.
40. Gaudana R, Ananthula HR, Parenky A, Mitra AK. Ocular drug delivery, the AAPS journal.2010; 12 (3): 348-360.
41. Rajas NJ, Kavitha K, Gounder T, Mani T. In situ ophthalmic gels: a developing trend. Int. J.Pharm. Sci. Rev. and Res.2011;7 (1): 8-14.
42. Gariepy ER, Leroux JC. In situ-forming hydrogel-review of temperature sensitive systems. Eur. J. Pharm. and Biopharm. 2004;58: 409-426.
43. Jeong B, Kim SW, Bae YH. Thermosensitive sol-gel reversible hydrogels. Adv. Drug. Del. Rev. 2002; 54: 37-51.
44. Ding S. Recent developments in ophthalmic drug delivery. Reviews / Research. 1998; 1: 328-335.
45. Rupenthal ID, Green CR, Alany RG. Comparison of ion-activated in situ gelling systems for ocular drug delivery. Part 2. Precorneal retention and in vivo pharmacodynamics study. Int. J. pharm. 2011; 411: 78-85.
46. Ma WD, Xu H, Wang C, Nie SF, Pan W. Pluronic F127-g-poly(acrylic acid) copolymers as in-situ gelling vehicle for ophthalmic drug delivery system. Int. j. Pharm. 2008; 350: 247-256.
47. Liu Z, Li J, Nie J, Liu H, Ding P, Pan W. Study of an alginate/HPMC-based in situ gelling ophthalmic delivery system for gatifloxacin. Int. J. Pharm. 2006; 315: 12-17.
48. Wu H, Liu Z, Peng J, Li L, Li N, Li J.et-al. Design and evaluation of baicalin-containing in situ pH-triggered gelling system for sustained ophthalmic drug delivery. Int. J. Pharm. 2011; 410: 31-40.
49. Kumar MT, Bharathi D, Balasubramaniam J, Kant S, Pandit JK. pH-induced in-situ gelling systems of indomethacin for sustained ocular delivery. Indian. J. Pharm. Sci.2005; 67: 327-333.
50. Mohan EC, Kandukuri JM, Allenki V. Preparation and evaluation of in situ gel for ocular drug delivery, J. Pharm. Res. 2009; 2: 1089-1094.
51. Pandit JK, Bharathi D, Srinatha A, Ridhurkar DN, Singh S. Long acting ophthalmic formulation of indomethacin: evaluation of alginate gel system. Indian. J. Pharm. Sci. 2007, 37-40.
52. Cohen S, Lobel E, Trevgoda A, Peled Y. A novel in situ forming ophthalmic drug delivery system from alginates undergoing gelation in the eye. J. Cont. Rel. 1997; 44: 201-208.

TABLE -1 DRUGS WITH THERE MECHANISM OF GELLATION

Drug used	Mechanism of gelation	Polymer used	Reference
Gatifloxacin	Ion activated	Alginate and HPMC	47
Gatifloxacin	Thermosensitive	Pluronic f127-g-poly(acrylic acid) copolymer	46
Timolol maleate	Thermosensitive and ph triggered	Pluronic f 127, chitosan	12
Ciprofloxacin HCL	Ion sensitive	Gelrite gellan gum and sodium alginate	12
Ciprofloxacin	Thermosensitive, ion activated, pH- triggerd	Pluronic f-127, gellan gum, carbopol 940	50
Indomethacin	Ion activated	Sodium alginate	51
Indomethacin	pH triggered	Carbopol 974 P, HPMC K15	49
Pefloxacin mesylate	Ion sensitive	Gelrite gellan gum	12
Puerarin	Ph triggered	Carbopol/HPMC based gel	12
Puerarin	Ph triggered	Poloxamers analogs/carbopol	12
Pilocarpine	Ion activated	Sodium alginate	52
Biacalin	pH Triggered	Carbopol	48