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pH Sensitive *in Situ* Ocular Gel: A Review

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ABSTRACT:

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientists, the major problem encountered to pharmaceutical scientist is rapid pre-corneal elimination of the drug, resulting in poor bioavailability and therapeutic response, because of high tear fluid turnover and dynamics. In situ-forming gels are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form visco-elastic gel and this gel provides a response to environmental changes. *In-situ* gelling systems are viscous polymer based liquids that exhibit sol-to-gel phase transition on the ocular surface due to change in a specific physico-chemical parameter like temperature, ionic strength, or pH. A major problem in ocular therapeutics is the attainment of optimal drug concentration at the site of action, which is compromised mainly due to pre corneal loss resulting in only a small fraction of the drug being ocularly absorbed. The effective dose administered can be altered by increasing the retention time of medication into the eye by using *in situ* gel forming systems, thereby preventing the tear drainage.

KEYWORDS: *in situ*, pH sensitive, carbopol, precorneal residence time, pH triggered.

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INTRODUCTION

1.1. Ocular drug delivery

Eye is unique and vital organ. It is considered as window of the soul. We can enjoy and view the whole world only with this organ. There are many eye ailments which affect this organ and one even can loss the eye sight. Therefore many ophthalmic drug delivery systems are available. These are classified as conventional and newer drug delivery systems. Eye drops that are conventional ophthalmic delivery systems often result in poor bioavailability and therapeutic response, because high tear fluid turnover and dynamics cause rapid precorneal elimination of the drug. A high frequency of eye drop instillation is associated with patient non-compliance. Inclusion of excess drug in the formulation is an attempt to overcome bioavailability problem, is potentially dangerous if the drug solution drained from the eye is systemically absorbed from the nasolacrimal duct. Various ophthalmic vehicles such as inserts, ointments, suspensions and aqueous gels have been developed in order to lengthen the residence time of instilled dose and enhance the ophthalmic bioavailability. These ocular drug delivery systems however have not been used extensively because of some drawbacks such as blurred vision from ointments or low patient compliance from inserts.

Several *in situ* gelling system have been developed to prolong the precorneal residence time of a drug and improve ocular bioavailability. These systems consist of polymers that exhibit sol to gel phase transitions due to change in specific physicochemical parameter (pH, temperature) in their environment, the cul de sac in this case. Depending on the method employed to cause sol-to-gel phase transition on the eye surface the following three types of systems are recognized, pH triggered system, temperature dependent system and ion activated system. Using these three methods above *in situ* gelling ophthalmic delivery system is developed.[1] Topical anti-infectives are commonly used to treat fungal conjunctivitis and infection of cornea caused by susceptible strains of bacteria such as *Staphylococcus aureus, Staphylococcusepidermidis, Streptococcuspneumoniae, Enterobacter cloacae, Haemophilusinfluenzae, Proteus mirabilis and Pseudomonas aeruginosa*. They are also indicated for the treatment of fungal corneal ulcers caused by susceptible strains of the following bacteria: *Staphylococcusaureus,Staphylococcusepidermidis, Streptococcus pneumoniae, Pseudomonasaeruginosa, Serratiamarcescens and Propionibacterium* acnes etc.[2]

1.1.1. Advantages of Ocular Drug Delivery Systems:

- Easy convenience and needle free drug application without the need of trained personnel assistance for the application, self-medication, thus improving patient compliances compared to parenteral routes.

- Good penetration of hydrophilic, low molecular weight drugs can be obtained through the eye.
- Rapid absorption and fast onset of action because of large absorption surface area and high vascularisation. Ocular administration of suitable drug would therefore be effective in emergency therapy as an alternative to other administration routes.
- Avoidance of hepatic first pass metabolism and thus potential for dose reduction compared to oral delivery.[3]

1.1.2. Disadvantages of Ocular Drug Delivery Systems:

- The physiological restriction is the limited permeability of cornea resulting into low absorption of ophthalmic drugs.
- A major portion of the administered dose drains into the lachrymal duct and thus can cause unwanted systemic side effects.
- The rapid elimination of the drug through the eye blinking and tear flow results in a short duration of the therapeutic effect resulting in a frequent dosing regimen.

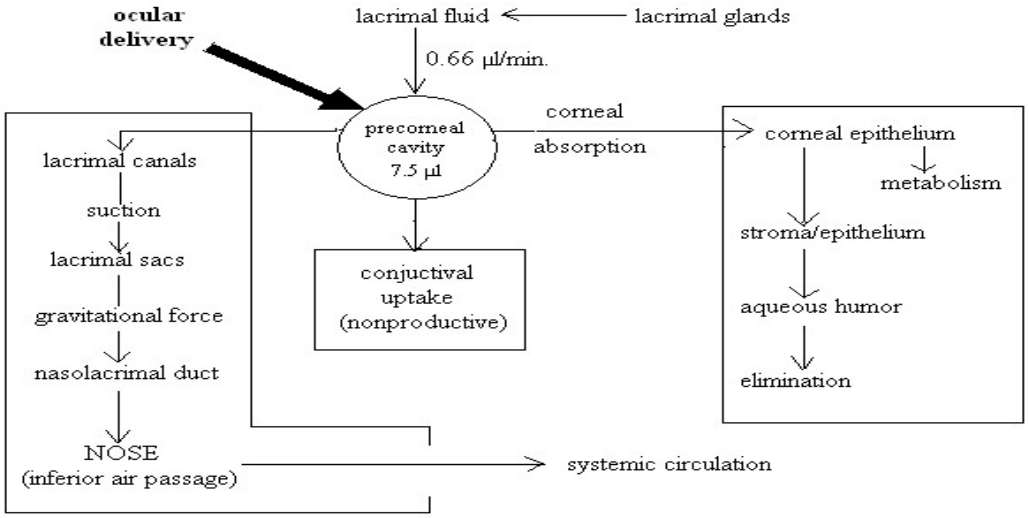

Fig. 1 Routes of ocular absorption of drugs.

1.2. Absorption and bioavailability of the drugs from the eye

The drug solution instilled as eye drops into the ocular cavity may disappear from the precorneal area of the eye by any or a composite of the following routes, shown in Fig.1

- Nasolacrimal drainage,
- Tear turnover,

- Productive corneal absorption,
- Nonproductive Conjuctival uptake.

Drug administered by instillation must penetrate the eyes and do so primarily through the cornea. Corneal absorption is much more effective than scleral or conjuctival absorption, in which removal by blood vessels into the general circulation occurs. [3] Many ophthalmic drugs are weak bases and are applied to the eye as aqueous solution of their salts. The free base and the salts will be in an equilibrium that will depend on the pH and the individual characteristics of the drug molecule. To aid in maintaining storage stability and solubility, the medication may be acidic at the moment of instillation but usually, the neutralizing action of the lacrimal fluid will convert it rapidly to the physiological pH range (pH 7.4) at which there will be enough free base present to begin penetration of the corneal epithelium. Once inside the epithelium (lipid rich) the undissociated free base dissociates immediately to a degree that the dissociated moiety then will tend to penetrate the stroma because it is water-soluble. At the junction of the stroma (lipid poor) and endothelium (lipid rich), the same process that took place at the outer surface of the epithelium must occur again. Finally, the dissociated drug leaves the endothelium for the aqueous humor.

Here it can readily diffuse to the iris and the ciliary body, the site of its pharmacological action. The topical application of ophthalmically active drugs to the eye is the most prescribed route of administration for the treatment of various ocular diseases. It is generally agreed that the intraocular bioavailability of topically applied drugs is extremely poor. Upon instillation of an ophthalmic solution; most of the instilled volume is eliminated from the pre corneal area. This loss is mainly due to drainage of the excess fluid by the nasolacrimal duct or elimination of the solution by tear turnover, which will results in poor ocular bioavailability. [4]

1.3. General fungal infections of eye and its medications

Fungal infections of the eye are important amongst the clinical conditions responsible for ocular morbidity and blindness. In tropical countries, including India, keratitis is the most frequently encountered fungal infection, although the orbit, lids, lacrimal apparatus, sclera, conjunctiva and intra-ocular structures may also be involved.

1.3.1. Keratomycosis: -

Mycotic keratitis in the tropical and subtropical zones is largely due to filamentous fungi, although yeasts, particularly *Candida* may also be responsible in a small percentage of cases. The most common predisposing factor is trauma to the eye with vegetative matter.

1.3.2. Orbital cellulitis: -

Orbital cellulitis is an infection of the soft tissue surrounding the orbit. Orbital cellulitis of fungal origins the most serious ocular infection with significant potential morbidity, including loss of vision, cavernous sinus thrombosis, intracranial spread of infection and occasionally death.

1.3.3. Endophthalmitis:-

Endophthalmitis is an inflammatory reaction of intraocular fluid or tissues. It can be both infectious and noninfectious. Infectious (post-operative, post-traumatic or endogenous) endophthalmitis is one of the most serious and vision threatening complications of ophthalmic surgery. [5]

Table 1 Principal antifungal drugs used to treat fungal infections of the cornea.

1.Fluconazole
a. Synthetic bistriazole.
b. Oral (200 mg/day), Topical 1–2% solution, Intravenous preparation at 2 mg/ml (dose is 100 mg/day).
c. Excellent safety profile and good intraocular penetration.
d. Increasingly available worldwide; available as topical ophthalmic preparation in some countries.
e. Excellent results in natamycin-resistant and miconazole-resistant *Candida* keratitis with deep lesions.
f. Intravenous fluconazole with oral itraconazole and penetrating keratoplasty reported useful for *Acremonium* keratitis.
2.Natamycin (Pimaricin)
a. Polyene.
b. Commercially available as topical 5% suspension for ophthalmic use in some countries, where it constitutes first-line therapy for mycotic keratitis.
c. Broad spectrum activity against filamentous fungi and yeast-like fungi causing corneal infections.
d. Ophthalmic preparation is well tolerated, stable and can be sterilized by heat.
e. Relatively high levels achieved in cornea after topical application.
f. Treatment of keratitis due to species of *Fusarium, Aspergillus, Curvularia,* and *Candida* generally yields good results.
3.Amphotericin B
a. Macrocyclic polyene, which is variably fungistatic or fungicidal.
b. Active against*Aspergillus* species and *Candida* species; emergence of resistant mutants is rare.
c. Commonly administered as a topical 0.15–0.30% solution; intracameral administration (20-30 mg/ml) also reported. Intravenous route may be used in desperate cases.
d. Considered as first-line treatment of keratitis due to *Candida* species in many countries, and mycotic keratitis in regions where natamycin is not available.
e. Penetrates deep corneal stroma after topical application.
f. In addition to direct fungicidal effect, also shows immunadjuvant properties.
g. Topical preparation (0.15%) is well-tolerated. Experimental and clinical data suggest that collagen shields soaked in this drug (0.5%) are useful and convenient to treat mycotic keratitis (especially that caused by *Candida albicans*).

4.Flucytosine (5-fluorocytosine)

a. A synthetic fluorinated pyrimidine.

b. Topical (1%) solution well tolerated; can be given orally (150 mg/kg/day) or intravenously.

c. Active against *Candida, Cryptococcus*and related fungi; effective against some strains of *aspergillus*.

d. Most useful as adjunctive therapy for yeast keratitis.

5.Clotrimazole

a. Imidazole.

b. Used topically as 1% solution or cream; oral route not used now.

c. Broad spectrum of activity against *Aspergillusin vitro* and in vivo; hence was suggested (years ago) as treatment of choice for *Aspergillus* keratitis.

6.Miconazole

a. Synthetic phenyl ethyl imidazole.

b. Reported routes of administration in mycotic keratitis: topical (1%), subconjunctival (10 mg), intravenous (600–1200 mg/day); topical and subconjunctival administration generally well tolerated.

c. Broad spectrum of activity against many ocular pathogenic fungi, including *Aspergillus, Candida* and *Scedosporium.*

d. Once advocated as second-line treatment for keratitis unresponsive to natamycin.

e. Concomitant administration of oral ketoconazole and topical miconazole found useful in clinical mycotic keratitis.

7. Econazole

a. Imidazole.

b. Topical (1%).

c. Broad spectrum of activity against filamentous fungi.

d. Good results obtained in treating clinical *Fusarium* keratitis.

8. Ketoconazole

a. Synthetic dioxolane imidazole.

b. Oral (200-600 mg/day) Topical 1–2%.

c. Good *in vitro* activity against *Aspergillus flavus*, *Candida* species, *Curvularia*species and some other ocular fungal pathogens.

d. Reported useful in treatment of nonseveremycotic keratitis following oral administration.

e. Concomitant administration of oral ketoconazole and topical miconazole reported to be useful for clinical mycotic keratitis.

9. Itraconazole

a. Synthetic dioxolane triazole.

b. Oral capsule (200–400 mg/day); well-absorbed and excellent safety profile after oral administration. A 1–2% topical suspension in artificial tears. Oral solution and intravenous formulation recently developed, but no reports about use of these for therapy of fungal infections of the cornea.

c. Good *in vitro* activity against all *Aspergillus species, Candida*, and many dematiaceous fungi.

d. No interactions with oral antidiabetic drugs.

e. Reported to be very useful for treatment of *Aspergillus* and *Curvularia* keratitis and in non-severe *Fusarium* keratitis.

1.4. Ocular drug delivery systems

1.4.1 Solutions and suspensions

Solutions are the pharmaceutical dosage 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. Solutions also have disadvantages:

a) The solution stays for a short time on eye surface,
b) It has poor bioavailability,
c) The instability of the dissolved drug and the necessity of using preservatives.

1.4.2. Sprays

Although not commonly used, some practitioners use Mydriatics or Cycloplegics alone or in combination in the form of eye spray. These sprays are used in the eye for dilating the pupil or for Cycloplegics examination.

1.4.3. Contact lenses

Contact lenses can absorb water soluble drugs when soaked in drug solutions. These drug saturated contact lenses are placed in the eye for releasing the drug for a long period of time. The hydrophilic contact lenses can be used to prolong the ocular residence time of the drugs.

1.4.4. Artificial tear inserts

A rod shaped pellet of hydroxy propyl cellulose, without preservative is commercially available (Lacrisert). This device is designed as a sustained release artificial tear for the treatment of dry eye disorder.

1.4.5. Filter paper strips

Sodium fluorescein and bengal dyes are commercially available as drug-impregnated filter paper strips. These dyes are used diagnostically to disclose corneal injuries and infections such as herpes simplex and dry eye disorders.

1.4.6. Micro emulsion

Due to their intrinsic properties and specific structures, microemulsions are a promising dosage form for the natural defense of the eye. Indeed, because they are prepared by inexpensive processes through auto emulsification or supply of energy and can be easily sterilized, they are stable and have a high capacity of dissolving the drugs.

1.4.7. Ocular Inserts

Ocular inserts, one of the new classes of drug delivery systems, which are gaining worldwide praise, release drugs at a pre-programmed rate for a longer period by increasing the precorneal residence time.[6] The goal of this delivery system is to provide a therapeutic amount of drug to the ocular tissues to achieve promptly and then maintain the desired drug concentration by increasing the contact time between the preparation and the Conjuctival tissue.[7] To achieve this goal particularly for chronic diseases such as glaucoma, it would be advantageous and more convenient to maintain a dosing frequency to once, or at most, twice a week regimen.An appropriately designed extended release ocular insert can be a major advance in this direction compared to conventional immediate release dosage forms. [8]

1.4.8. Collagen Shield

Collagen is regarded as one of the most useful biomaterials. The excellent biocompatibility and safety is due to its biological characteristics, such as biodegradability and weak antigenicity, these properties made collagen the primary resource in medical applications. Collasomes show promise among drug delivery systems to the human eye. They are first fabricated from procine scleral tissue, which bears a collagen composition similar to that of the human cornea. The shields are hydrated before they are placed on the eye. Shields are not individually fit for each patient, as are soft contact lenses and therefore, comfort may be problematic and expulsion of the shield may occur.

1.4.9. Ocular Iontophoresis

Iontophoresis is the process in which direct current drives ions into cells or tissues. When Iontophoresis is used for drug delivery, the ions of importance are charged molecule of the drug. Ocular Iontophoresis offers a drug delivery system that is fast, painless and safe; and in most cases; it results in the delivery of a high concentration of the drug to a specific site. But the role of Iontophoresis in clinical ophthalmology remains to be identified.

1.4.10. Liposomes

Liposomes are phospholipid lipid vesicles for targeting drugs to the specific sites in the body; provide the controlled and selective drug delivery and improved bioavailability. Liposomes offer the advantages of being completely biodegradable and relatively non-toxic but are less stable than particulate polymeric drug delivery systems.

1.4.11. Niosomes

In order to circumvent the limitations of liposomes, such as chemical instability, Oxidative degradation of phospholipids, cost and purity of natural phospholipids, niosomes have been

developed as they are chemically stable compared to liposomes and can entrap both hydrophilic and hydrophobic drugs. They are non-toxic and do not require special handling techniques.

1.4.12. Mucoadhesive Dosage Forms

The successful development of fewer mucoadhesive dosage forms for ocular delivery still poses numerable challenges. This approach relies on vehicles containing polymers, which will attach via noncovalent bonds to conjuctivalmucin.

1.4.13. Nanoparticles and Microparticles

Particulate polymeric drug delivery systems include micro and nanoparticles. The upper size limit for microparticles for ocular delivery is about 5-10 mm, above this size; a scratching feeling in the eye can result after ocular application. After optimal drug binding to microspheres or nanoparticles, the drug absorption in the eye enhanced significantly in comparison to eye drops.[9]

1.4.14. Hydrogels

The most common way to improve drug retention on the corneal surface is undoubtedly by using polymers to increase solution viscosity.Hydrogels are polymers endowed with inability to swell in water or aqueous solvents and induce a liquid–gel transition. Currently, two groups of hydrogels are distinguished, namely preformed and *in situ* forming gels. Preformed hydrogels can be defined as simple viscous solutions which do not undergo any modifications after administration. *In situ* forming gels are formulations applied as solutions, sols or suspensions that undergo gelation after instillation due to physicochemical changes inherent to the eye .[10]

1.4.15. *In situ* gel

Distinguishing from preformed hydrogels, *in situ* forming gels are formulations, applied as a solution, which undergoes gelation after instillation due to physicochemical changes inherent to the biological fluids. In this way, the polymers which show sol-gel phase transition and thus trigger drug release in response to external stimuli are the most investigated. *In situ*gels are providing such “sensor” properties and can undergo reversible sol-gel phase transitions upon changes in the environmental condition. These “intelligent” or “smart” polymers play important role in drug delivery since they may dictate not only where a drug is delivered, but also when and with which interval it is released.[11]A polymer used to prepare *in situ* gels should have following characteristics:-

1. It should be biocompatible.
2. It should be capable of adherence to mucus.
3. It should have pseudo plastic behavior.
4. It should have good tolerance and optical clarity.

5. It should influence the tear behavior.

The polymer should be capable of decreasing the viscosity with increasing shear rate there by offering lowered viscosity during blinking and stability of the tear film during fixation.[12]

1.5. In situ gelling systems

In situ gelling systems are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. *In situ* gel forming drug delivery is a type of mucoadhesive drug delivery system. The formation of gel 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. Many natural, biodegradable, biocompatible and synthetic polymers like alginic acid, pluronic F127, xyloglucan, gellan gum, carbopol, pectin, chitosan, poly (DL lactic acid), poly (DL-lactide-coglycolide) and poly-caprolactone etc. are used in the preparation of *in situ* gelling system. Mainly *in situ* gels are administered by oral, ocular, rectal, vaginal, injectable and intraperitoneal routes. *In situ* gelling system becomes very popular nowadays because of their several advantages over conventional drug delivery systems like sustained and prolonged release of drug, reduced frequency of administration, improved patient compliance and comfort.[13, 14]

Approaches for *in situ* gelling system:

1.5.1. Stimuli-responsive *in situ* gel systems:-

1.5.1.1. Temperature induced *in situ* gel systems.

1.5.1.2. pH induced *in situ* gel systems.

1.5.2. Osmotically induced *in situ* gel systems (Ion-activated systems)

1.5.3. Chemically induced *in situ* gel systems:-

1.5.3.1.Ionic crosses linking.

1.5.3.2. Enzymatic cross linking.

1.5.3.3. Photo-polymerization.

1.5.1. Stimuli-responsive *in situ* gel systems:

Stimuli-responsive polymers are defined as polymers that undergo relatively large and abrupt, physical or chemical changes in response to small external changes in the environmental conditions.[15]

1.5.1.1. Temperature induced *in situ* gel systems:

Temperature is the most widely used stimulus in environmentally responsive polymer systems. The change of temperature is not only relatively easy to control, but also easily applicable both *in vitro* and *in vivo*. In this system, gelling of the solution is triggered by changein temperature, thus sustaining the drug release. These hydrogels are liquid at room temperature(20–25 °C) and undergo gelation when in contact with body fluids (35– 37 °C), due to an increase in temperature. The use of biomaterial whose transitions from sol-gel is triggered byincrease in temperature is an attractive way to approach in-situ formation. The polymers whichshow temperature induced gelation are poloxamers or pluronics, cellulose derivatives (methylcellulose, HPMC, ethyl (hydroxyl ethyl) cellulose (EHEC) and xyloglucan etc.[6]

1.5.1.2. pH induced *in situ* gel systems:

Polymers containing acidic or alkaline functional groups that respond to changes in pH are called pH sensitive polymer. Gelling of the solution is triggered by a change in pH. At pH 4.4 the formulation is a free-running solution which undergoes coagulation when the pH is raised by the tear fluid to pH 7.4. The pH change of about 2.8 units after instillation of the formulation (pH4.4) into the tear film leads to an almost instantaneous transformation of the highly fluid latex into a viscous gel. The polymers with a large number of ionisable groups are known as polyelectrolytes. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups. The polymers which show pH induced gelation are cellulose acetate phthalate (CAP) latex, carbomer and polymethacrilic acid (PMMA), polyethylene glycol (PEG). [7]

1.5.2. Osmotically induced *in situ* gel systems (Ion-activated systems):

In this method, gelling of the solution instilled is triggered by change in the ionic strength. The rate of gelation depends on the osmotic gradient across the surface of the gel. The aqueous polymer solution forms a clear gel in the presence of the mono or divalent cations typically found in the tear fluids. The electrolyte of the tear fluid and especially Na+, Ca2+ and Mg2+ cations are particularly suited to initiate gelation of the polymer when instilled as a liquid solution in the conjuctival cul-de-sac. The polymers which shows osmotically induced gelation are gelrite, gellan gum, hyaluronic acid and alginates etc.[8]

Some of the polymers used as *in situ* gelling agents are:

- Gellan gum
- Alginic acid
- Carbomer
- Pluronic F127
- Xyloglucan
- Pectin
- Xanthum gum
- Chitosan

1.5.4. Carbomer

Cross-linked poly (acrylic acid) of high molecular weight, commercially availableas CarbopolR, is widely used in ophthalmology to enhance precorneal retention to the eye. Carbopol R934 is a synthetic polymer composed of 62% of carboxyl groups with a high molecular weight formed by repeating units of acrylic acid, cross-linked with either allyl sucrose or allylethers of pentaerythritol. Carbopol offers the advantage of exhibiting excellent mucoadhesive properties when compared with other polymers (e.g. cellulose derivatives, and polyvinyl alcohol). Concentration of Carbopol increases in the vehicle, its acidic nature may cause stimulation to the eye tissues. In order to reduce the total polymer content and improve the gelling properties, an ocular drug delivery system based on a combination of Carbopol and methylcellulose has been developed. Carbopol is a polyacrylic acid (PAA) polymer, which shows a sol to gel transition in aqueous solution as the pH is raised above its pKa of about 5.5. Carbopol are in compatible with cationic polymers, strong acids, high level of electrolytes and they swell in water 1000 times when exposed to water to form gelation pH of 4-6 do not dissolve in water.[16, 17]

1.5.5. Advantages of *in situ* gelling system

1. In situ gels are the most advanced formulation available for ocular drug delivery.
2. Avoiding systemic side effects as conventional ophthalmic formulations drained out from eye and goes to systemic circulation through oesophageal route.
3. Eye drops and other similar formulations need a large amount of drug as these formulations having poor ocular residence time and corneal absorption.
4. pH sensitive gels having excellent property of transforming from sol form to gel form instantly when coming in contact to ocular fluid and exhibiting better therapeutic level.

1.6. *In situ pH sensitive ocular gel*-

Method of preparation (pH triggered method):-

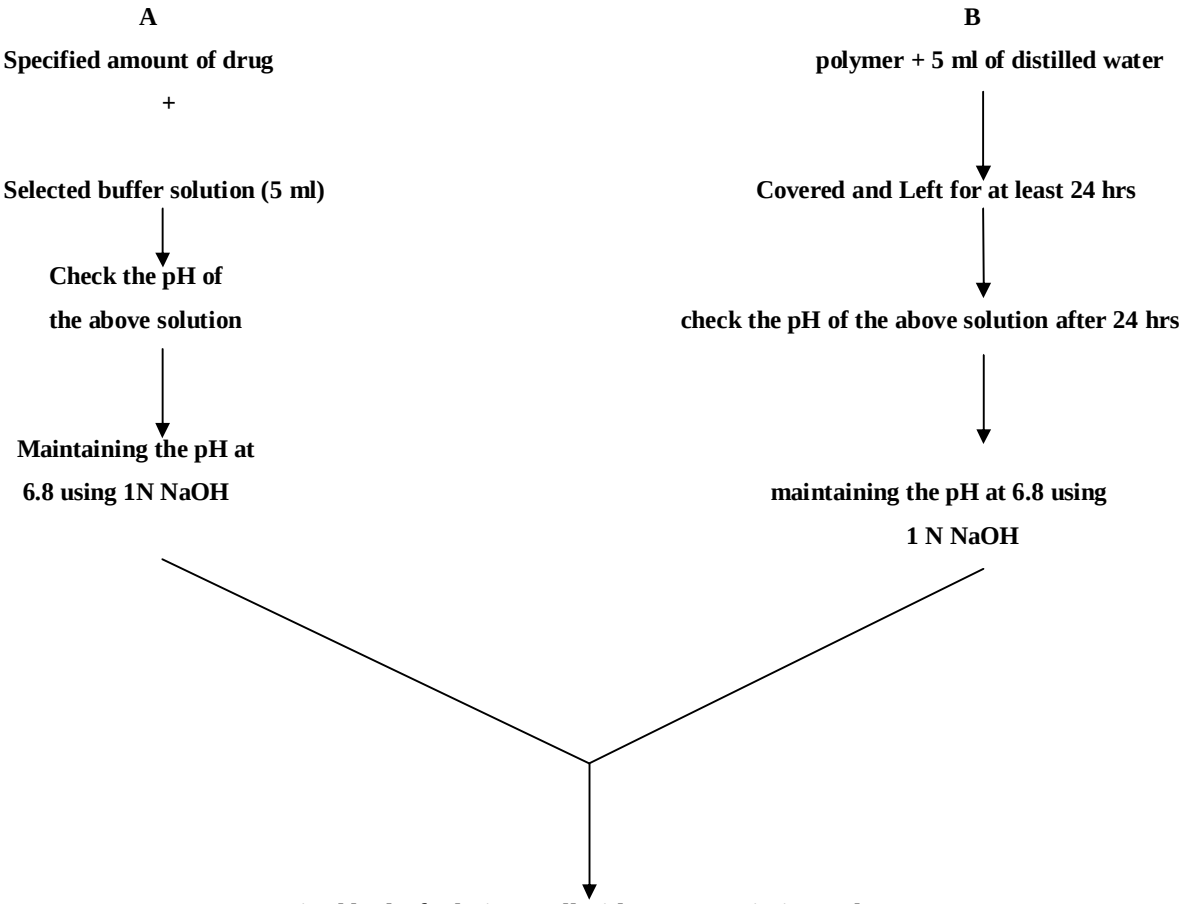

Fig. 2 method of preparation

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