International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 2 Mar-Apr 2022, pp: 789-797 www.ijprajournal.com ISSN: 2456-4494

A Review On-Ain-Situ Ocular Gel Delivery System

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Submitted: 01-04-2022 Accepted: 09-04-2022

ABSTRACT: In-situ forming gels process. The formulation is liquid when instilled into the eye which undergoes gel formation rapidly in cul-de-sac of the eye in response to environmental changes such as pH, temperature and ion; finally release the drug slowly under physiological conditions. Blindness and vision impairment are the mostdevastating global health problems resulting in a substantial economic and social burden. Delivery of drug to particular parts of the anterior or posterior segment of eye has been a major challenge due to various protective barriers and elimination mechanisms associated with the unique anatomical and physiological nature of the ocular system. Drug administration to the eye by conventional delivery systems results in poor ocular bioavailability (<5%). The designing of a novel approach for a safe, simple and effective ocular drug delivery is a major concern and requires innovative strategies to combat the problem. Over the past decades, several novel approaches involving different strategies have been developed to improve the ocular delivery system. Among these, the ophthalmic in-situ gel has attained a great attention over the past few years. This review discussed and summarized the recent and the promising research progress of in-situ gelling in ocular drug delivery system.

KEYWORDS: In-situ ocular gel, polymers, Drug delivery, pH sensitive gels, temperature sensitive gels, ion sensitive gels.

I. INTRODUCTION

[1]The eye is a complex and unique part of the human organs that has been considered as the window to the human soul.

Broadly, the human eye is divided into two segments that are anterior and posterior segments.

The specific disease conditions of the eye are associated with each of these broad segments. For instance, conjunctivitis, glaucoma, blepharitis, and cataract are some of the diseases that affect the anterior segment of the eye, while diabetic retinopathy and age-related macular degeneration are known to affect the posterior segment.

Ocular drug delivery has reminded as one of the most challenging tasks for pharmaceutical scientists. The unique structure of eye restrict the entry of drug molecule at required site of action. Anatomically , ocular drug delivery either target the anterior segment or posterior segment of the eye.

In situ ocular gel is one of the recent advancement in ocular drug delivery system. **In situ ocular gel** system comprise delivery vehicle composed of polymers (natural, semi synthetic or synthetic) which has a special property of sol-gel conversion when influenced by some biological stimulus such as pH, temperatureand ions.

To overcome the problems of attainment and retention of optimum drug concentration at the site of action within the eye, various approaches of novel ocular drug delivery were studied. In situ ocular gel is considered to be one of the novel ocular drug delivery system. In situ gel system comprise delivery vehicle composed of polymers (natural, semi synthetic or synthetic) which has a special property of sol-gel conversion when influenced by some biological stimulus.

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Characteristics Of An Ideal Ocular Drug Delivery System[2]

- It should be able to provide therapeutic concentration of the drug at the target tissues by overcoming the blood ocular barriers.
- It should provide targeted delivery to the ocular tissues with minimal systemic effect. It should be safe and non-irritating to the tissues.
- It should provide prolonged drug delivery , thereby reducing the dosing frequency.

ADVANTAGES OF IN SITU GELS[2]

1. Ease of aministration
2. Improved local bioavailability
3. Reduced dose concentration
4. Reduced dosing frequency
5.Improved patient compliance and comfort
6. Sustained and controlled drug release
7. Drug effect is prolonged hence frequent instillation Is not required.

DISADVANTAGES OF IN SITU GELS[2]

1. Hydrogel may result in blurred vision as well as foreign body sensation to patients.
2. Only small fraction of the drug being ocularly absorbed.
3. These preparations have no bioavailability.
4. only 10 percent drug concentration is available at site of action.

APPLICATIONS

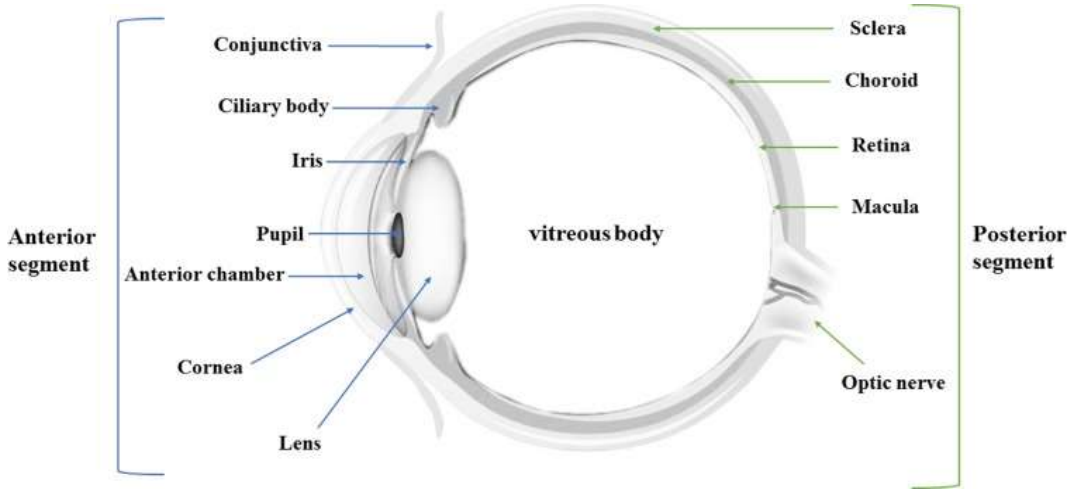
1. levofloxacin, is an antibacterial agent , is made in the form of in situ gel with additional encapsulation techniques by chitosan nanoparticles. Effective carrier for treating eye infections.

2. Brimonidine tartrate along with carbopol composition polymer and hydroxyl propyl methyl cellulose gives sustained release of drug and decreasing intraocular pressure to treat glaucoma.

THE ANATOMY OF OCULAR SYSTEM[1]

The eye is a highly specialized organ of photoreception for processing light energy from the environment to produce action potentials in specialized nerve cells, which subsequently relayed to the optic nerve and to the brain where the information is processed and consciously appreciated as vision. The eye is small and complex organ that is separated from rest of the body by multiple layers of biological barriers.The anterior segment involves conjunctiva, ciliary body, iris, pupil, anterior chamber, cornea and lens. The posterior segment consists of sclera, choroid, retina, macula and optic nerve.

FIGURE – 1 OF ANATOMY OF EYE



The conjunctiva plays many roles including protection of ocular surface, producing of tear films and a conduit for drug clearance into systemic circulation and also for drug delivery indeeper tissues. It is transparent membrane present over the inner area of the eyelids know as palpebral conjunctiva and also cover 1/3rd part of eyelid known as bulbar conjunctiva. This membrane is moistened by the tear films.

IN SITU GELLING SYSTEM [3]

1. In situ gel system is formulated as liquid preparation suitable to be instilled into eyes which upon exposure to the physiologic environment changes to gel, thus increasing the precorneal

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residence time of the delivery system, and enhances the ocular bioavailability of the drug

2. The formation of gels depends on factors like change in a specific physico-chemical parameter (pH, temperature, ion-sensitive) by which the drug gets released in a sustained and controlled manner.

3. Topical application of drugs to the eye is the well established route of administration for the treatment of various ocular diseases like dryness, conjunctivitis, keratitis, eye flu etc.

4. Development of ocular drug delivery systems has always been challenging because of the drawbacks with ocular route like nonproductive absorption, impermeability of drugs to cornea, drainage, induced lachrymation and tear turn over.

5. New approaches have been investigated for delivery of drugs to the eye by making use of polymers that pays a key role in delivery of drugs to the pre and intra ocular tissues.

6. Resulted into achieving the increase in bioavailability and extending the duration of therapeutic action of ocular drug. Smart polymeric systems have proved to be promising means of delivering the drugs. These polymers undergo sol-gel transition after administered. They are in solution phase before administration, but gels under physiological condition.

7. In situ gel-forming systems can be described as low viscosity solutions that undergo phase transition in the conjunctival cul-de-sac to form viscoelastic gels due to conformational changes of polymers in response to the physiological environment. The rate of in situ gel formation is important because between instillation in the eye and before a strong gel is formed, the solution or weak gel is produced by the fluid mechanism of the eye .Both natural as well as synthetic polymers can be used for the fabrication of in situ gels.

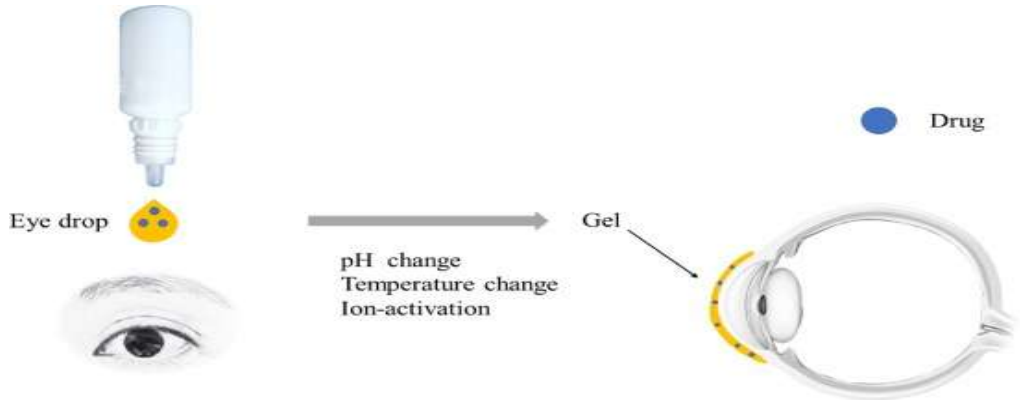
PROCESS[4]

Ophthalmic in-situ gelling is comprising of environmentally sensitive polymers that will be altered structurally with the small changes in specific conditions like pH, temperature and ionic strength in the environment.

In-situ forming gels are liquids during instillation into the eye and then undergoes rapid gelation in the cul-de-sac of the eye to form viscoelastic gels in response to environmental changes. lastly release the drug slowly under physiological conditions.

Consequently, the residence time of the gel formed in-situ will be extended and the drug is released in a sustained manner which leads to enhanced bioavailability, minimized systemic absorption and reduced frequent dosing regimen resulting to improved patient compliance.

Furthermore, some other potential advantages such as simple manufacturing process, ease of administration, and deliverance of accurate dose have been exhibited by in-situ gelling systems



solution

Mechanisms of gelling system

In-situ gel formation may be achieved by a number of mechanisms including temperature , pH- and ion-activated systems.

Temperature triggered in-situ gel system

which utilizes the temperature sensitive polymers that exist as a liquid form below its low critical temperature (LCST) and undergoes gelation when the environmental temperature reaches or is above the LCST.

Examples of polymers used –Xyloglucan , Chitosan.

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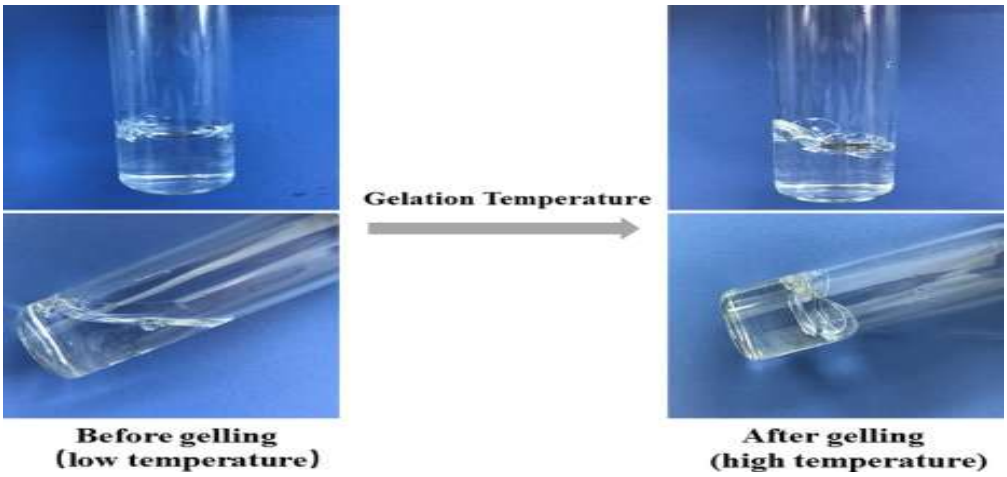

FIGURE- 4 OF TEMPERATURE TRIGGERED IN SITU GELLING

The pH induced in-situ gel

Contains polymers which possess acidic or alkaline functional groups within the chain molecule and undergoes a sol-gel phase transition on change from a low pH to high pH environment.

Examples - Polyacrylic acid (PAA, Carbopol 940), polycarbophil, and cellulose acetate phthalate.

Ion-activated systems

are also known as osmotically triggered in-situ gel systems wherein the polymer undergoes a sol-gel transition due to changes of ionic concentration, which is typically triggered by mono or divalent cations in tear fluid particularly Na^{+}, $Mg^{2+}$and Ca^{2+} [25]. In addition, sol-gel phase transition has known to be induced by enzymatic cross linking and photon polymerization.

Examples - Gellangum , alginate , pectin.

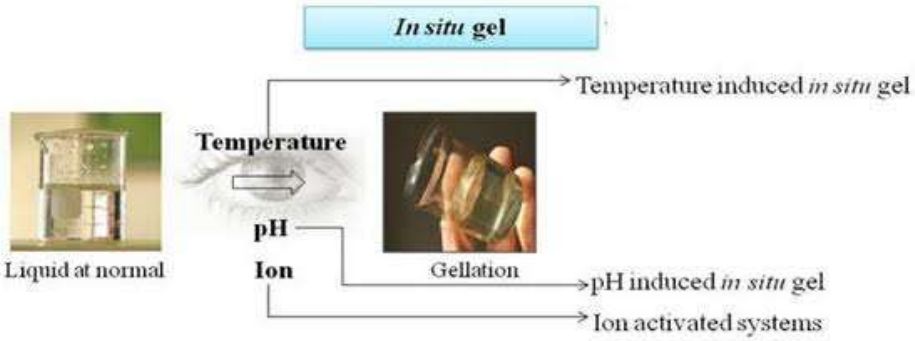

FIGURE-5 OF ION ACTIVATED SYSTEM

INSTRUMENTS HANDLED

1. Brook Field viscometer

2. Spectrophotometer

BROOK FIELD VISCOMETER

• Principle

Classical Brookfield viscometers employ the principle of rotational

viscometry - the torque required to turn an object, such as a spindle, in a

fluid indicates the viscosity of the fluid.

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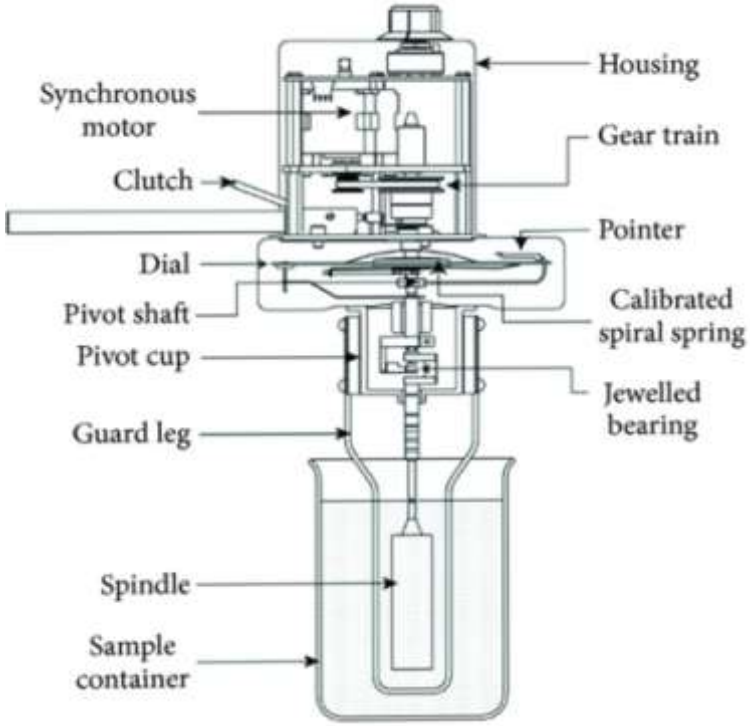

FIGURE-6 OF BROOK FIELD VISCOMETER

Working

The Brookfield Viscometerrotates a conical spindle at a precise speed and measures the torque needed to overcome the viscous resistance to the induced movement caused by the presence of sample fluid between the spindle and sample container. This allows the dynamic viscosity to be measured.

Use

1. Measures fluid viscosity and flow properpties.
2. Measurement of friction

SPECTROPHOTOMETER

Principle

Spectrophotometry is a method to measure how much a chemical substance absorbs light by measuring the intensity of light as a beam of light passes through sample solution. The basic principleis that each compound absorbs or transmits light over a certain range of wavelength.

• A spectrophotometer is an instrument that measuresthe amount of light absorbed by a sample.

• Spectrophotometer techniques are mostly usedto measure the concentration of solutes in solution bymeasuring the amount of the light that is absorbed by the solution in a cuvette placed in the spectrophotometer.

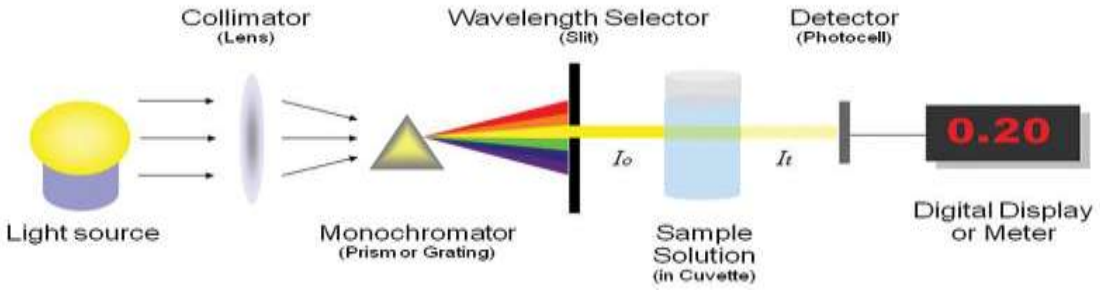

FIGURE-7 OF SPECTROPHOTOMETER

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WORKING

• White light radiation source that passes through a monochromator (a prism or a diffractiongrating that separates the white light into all colors of visible spectrum)

• After separation of light it passes through a filter(to block out unwanted light, sometimes light of different color) and a slit (to narrow the beam of light).

• The beam of light passes through the sample that is in the sample holder.

• The light passes through the sample and the unabsorbed portion (reflected)strikes a photodetector and produces electrical signals which is proportional to intensity of the light.

• The signal converted to readable output (absorbance) that is used in analysis of sample.

Uses

1. Measurement of uvlight , infrared light and visible light.
2. Measurement of intensity.

SELECTION OF PREPARATION METHOD[9]

In situ gel is prepared by COLD METHOD

Preparation of in situ gel formulations

Poloxameranalogs were used as the gelling agents, and the in situ gels were prepared by using a cold method (17). The polymeric solutions were prepared by dispersing required quantity of Poloxamer 407 and Poloxamer 188 in cold water (5 ^{0} C) using a magnetic stirrer until the poloxamer completely dissolve (approximately 2 hours). The dispersion was kept in a refrigerator for 48 hours to get clear solution.

20 g of cold sample solution were put into a beaker and placed in a temperature-controlled stirrer. A thermometer was immersed into the sample solution for constant monitoring. The solution wsas heated at the rate of 2 ^{0} C/min with the continuous with stirring at 200 rpm. The temperature at which the magnetic bar stopped moving due to gelation was reported as the gelation temperature. The maximum limit for gelation was checked up to 60 ^{0} C. Optimum poloxamer ratios were determined and selected with sol-gel temperature as 32-34 ^{0} C which is the eye surface temperature.

In situ gels were selected according to pH values and gelling temperatures of formulations. F11 (ratio of P407 and P188 were 20% and 5%, respectively) was selected as optimum formulation for preparation an ocular formulation. After detection of the optimum in situ gel compositions sodium alginate of different concentrations (0.1%, 0.3%, and 0.5%) and for each formulations same concentration of VCZ were added in poloxamer solutions with continuous stirring until completely dissolved. Benzalkonium chloride (0.02% w/w) was added as a preservative to the solutions. Sufficient amount of sodium chloride (0.9% w/w) was added to the mixture to maintain the isotonicity. The effect of drug and the other compositions of formulations on gel temperature were also evaluated.

The prepared ocular formulations were characterized such as clarity, gelling capacity, pH, viscosity and drug content. In addition gelling temperature of formulations was determined and statistical analysis was performed using t-test. Data were considered statistically significant at $p<0.05$. The experiments were repeated four times.

DRUG AND EXCIPIENTS[3]

Drugs -For ophthalmics in-situ gel suitable candidatesare moxifloxacinhydrochloride, Linezolid ,Gatifloxacin.

1. Polymers - They are responsible for providing gelling properties.
2. HPMC E 50 LV HPMC K 4M Xanthan gum , Hydroxy ethyl cellulose,carbapol
3. Preservatives:- -These include Benzalkonium chloride chlorhexidine acetate
4. Solvents:- -Distilled water.

Sodium alginate – ophthalmic gel forming mucoadhesivepolymer .

Hydroxypolymethylcellulose – is a viscosity enhancer in order to achieve the desired consistency to facilitate sustained drug release.

Other excipients used are chelating agents, surfactants, and cyclodextrins, which, along with active ingredients, form inclusion complexes. This increases solubility, permeability, and bioavailability of poorly soluble drugs.

PREFORMULATION STUDIES[3]

1. Description : Transparent / opaque preparation , proper labelling , imprinted Rx.
2. Assay : determines the strength or content of the API in ophthalmic preparation.
3. Identification: this is done to verify the identity of active pharmaceuticals ingredients.
4. Impurities : this test determines the presence of any compound which is not an API or excipient of ophthalmic preparation.

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CLINICAL APPLICATION OF IN-SITU GELLING[3]

To date, some of in-situ gel formulations have been commercially available for ocular drug delivery (Table 6). For instance, Timoptic-XE®, containing timolol maleate (0.25% and 0.5%) in gellan gum has been available on market since 1994, which is applied topically on the eye to treat glaucoma.

PREPARATION OF IN SITU OPHTHALMIC GEL [FLURBIPROFEN][7]

MATERIALS REQUIRED:

Flurbiprofen
Carbopol (934, 940 and 971)
HPMC (E15, K4M, K100)
Ethanol-0.5
Distilled water – q/s

PREPARATION OF INSITU GEL OF FLURBIPROFEN

- Aqueous solutions of varying concentrations of different polymers and drug were prepared and evaluated for gelling capacity and viscosity in order to identify the compositions suitable for use as in situ gelling systems.
- All ingredients were weighed accurately and the formulations were prepared by dispersing different grades of polymers carbopol (934, 940 and 971) solutions in different concentrations (0.1% w/v, 0.3% w/v, and 0.5% w/v) and HPMC (E15, K4M and K100) solutions in different concentrations (1% w/v and 1.5% w/v) in distilledwater with continuous stirring until completely dispersed and allowed to hydrate overnight. Flurbiprofen (0.03%) was dissolved in 0.5 ml of ethanol and then added to the above polymeric solutions under constant stirring to obtain a uniform solution.
- The pH of the solution was adjusted to 7.4 using 0.1N NaOH solution. Benzalkonium chloride (BKC) was then added to the above solution and mixing was confirmed until uniform and clear obtained. Final volume was made up by adding required amount of distilled water. All the formulations were terminally sterilized by auto-claving at 121 °C and 15 lb for 15 min.

EVALUATION TESTS FOR IN SITU FORMING GELS[7]

Sol-gel transition temperature and gelling time

Sol-gel transition temperature is the temperature at which the formation of gel takes place. To determine this temperature the prepared formulation which is in the sol form is kept in a test tube and heated by increasing the temperature and the final temperature at which gel formation takes place is noted. The time required for the generation of gel is noted as gelling time.

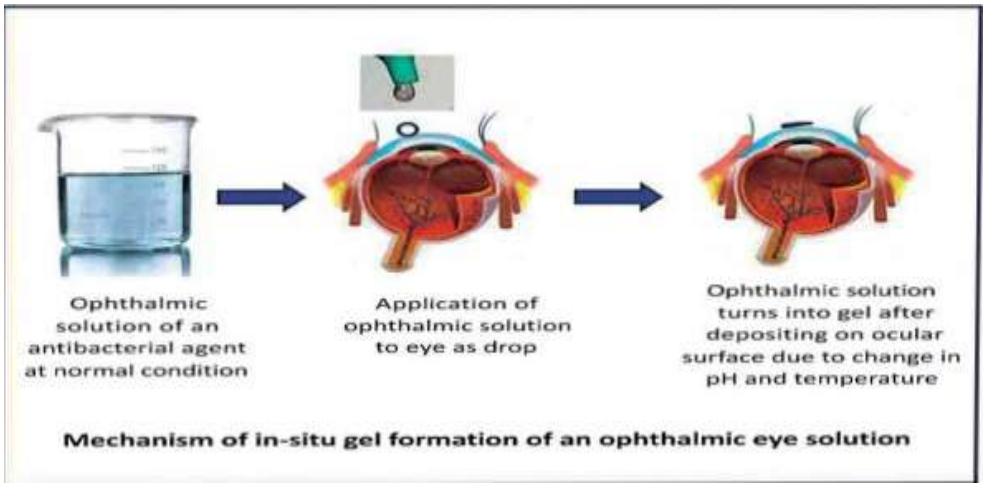

Fig.8

Clarity:

Clarity of the prepared formulation can be estimated by visual observation. The prepared formulation is kept under light alternatively against black and white backgrounds for the particles. When HPMC is used as a polymer, at high temperatures it will get precipitated so after autoclaving of HPMC containing formulation it

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forms a cloudy mass. It can be disappeared and retains original clarity after standing it for overnight and then the clarity of the formulation is visualized. And also, UV-visible spectro-photometer can also be used for the measurement of percentage transmission of the light through the formulation under the visible region at 490nm wavelength by using reference standard most preferably water.

Isotonicity:

Isotonicity is the important parameter which should be measured properly especially for the ophthalmic preparations as the difference in isotonicity will lead to the damage of the tissue and it causes irritation to the eye. Hence, all the ophthalmic formulations should be tested for isotonicitymeasurement. Isotonicity of the ophthalmic preparation can be measured by mixing the small amount of the formulation in few drops of blood and it is observed under microscope at 45x magnification and compared with the standard ophthalmic marketed formulation.

Ocular irritancy test:

Ocular irritancy test should be done before marketing the product and the test used for knowing about the ocular irritancy is Draize irritancy test.

For conducting this test healthy rabbits (male) three in number are chosen. Each rabbit weight is around 1.5 to 22 kilo gram. Then the dosage form is instilled into the eyes of the rabbit and the formulation should be in a sterilized form. The administration of the dose should be continued for one week by giving the dose in alternate days. Generally cross-over design is taken into practice. And the rabbits used for this design should be washed with saline for three days before the test is carried out. And the results can be evaluated by testing the rabbit eye or by visual inspection of the rabbit eye for the appearance of redness, swelling, inflammation and also can be checked for the excess secretions from the eye.

Sterility studies:

For ophthalmic products the sterility testing is compulsory it is done in order to know about any viable bacteria is present in the final sterilized formulation. If it is found that any organism is present it can be again send back for sterilization or the batch should be cancelled.

LIST OCULAR IN-SITU GELS APPROVED FOR MARKET.[8]

Name of the product	Polymer	The type of in-situ gelling system	Company	Ref.
Timoptic-XE® (Timolol maleate ophthalmic gel forming solution)	Gellan gum	Ion-induced	Merck Pharmaceuticals, USA	[99]
Pilopine HS® (pilocarpine hydrochloride ophthalmic gel)	Carbopol 940	pH-triggered	Alcon laboratories, inc. USA	[26]
Akten® (Lidocaine hydrochloride)	HPMC	Temperature-triggered	Akorn Inc., Lake Forest, IL	[100]
AzaSite (azithromycin ophthalmic solution)	Poloxamer 407	Temperature-triggered	InSite Vision	[101]
Timoptol-LA (Timolol maleate)	Gellan gum	Ion-activated	Laboratories Merck Sharp and Dohme	

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II. CONCLUSION

The in-situ gelling system is one the promising and extensively studied strategies that could prolong precorneal resident time and offer the sustained release drug delivery, thus improve ocular bioavailability and therapeutic efficacy and reduce systemic absorption and toxicity.

Due to its drug release sustaining ability and decrease the frequency of administration, in-situ gel could improve patient compliance.

As the eye is the most essential and sensitive part of the body, the safety issues of ophthalmic formulations is critically important.

the increased viscosity of in-situ gel may cause some limitations like blurred vision and discomfort to patient resulting in a faster elimination due to reflex tears and blinks. Therefore, critical control of the viscosity should be taken into consideration during designing and optimization of in-situ gel formulation in order to reduce the limitations to the tolerable level.

At present, most of the ophthalmic in-situ gels were designed only for the formulations containing of single active ingredient. In the future, some more suitable strategies should be developed for the formula consisting of multiple ingredients such as Traditional Chinese Medicine in particular, which involves a multi-target approach to produce their action. Lastly, in the future, we expect the innovation of new and more reliable in-situ forming polymers which may be responsive to some biochemical markers associated with the disease conditions of the eye.

REFERENCES

[1]. Majeed A, Khan NA. Ocular in situ gel: An overview. Journal of Drug Delivery and Therapeutics. 2019 Jan 15;9(1):337-47

[2]. Agrawal, A.K., Das, M. and Jain, S., 2012. In situ gel systems as 'smart'carriers for sustained ocular drug delivery. Expert opinion on drug delivery, 9(4), pp.383-402.

[3]. Chowhan A, Giri TK. Polysaccharide as renewable responsive biopolymer for in situ gel in the delivery of drug through ocular route. International journal of biological macromolecules. 2020 May 1;150:559-72.

[4]. Gupta H, Jain S, Mathur R, Mishra P, Mishra AK, Velpandian T. Sustained ocular drug delivery from a temperature and pH triggered novel in situ gel system. Drug delivery. 2007 Jan 1;14(8):507-15.

[5]. Cao Y, Zhang C, Shen W, Cheng Z, Yu LL, Ping Q. Poly (N-isopropylacrylamide)–chitosan as thermosensitive in situ gel-forming system for ocular drug delivery. Journal of controlled release. 2007 Jul 31;120(3):186-94.

[6]. Mohan EC, Kandukuri JM, Allenki V. Preparation and evaluation of in-situ-gels for ocular drug delivery. J Pharm Res. 2009 Jun;2(6):1089-94.

[7]. Mohan, E. C., Kandukuri, J. M., &Allenki, V. (2009). Preparation and evaluation of in-situ-gels for ocular drug delivery. J Pharm Res, 2(6), 1089-94.

[8]. Morsi N, Ibrahim M, Refai H, El Sorogy H. Nanoemulsion-based electrolyte triggered in situ gel for ocular delivery of acetazolamide. European journal of pharmaceutical sciences. 2017 Jun 15;104:302-14.

[9]. Gupta H, Aqil M, Khar RK, Ali A, Bhatnagar A, Mittal G. An alternative in situ gel-formulation of levofloxacin eye drops for prolong ocular retention. Journal of pharmacy &bioallied sciences. 2015 Jan;7(1):9.

[10]. Laddha UD, Mahajan HS. An insight to ocular in situ gelling systems. Int. J. Adv. Pharm. 2017;6(02):31-40.