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ADVANCEMENTS IN OPHTHALMIC IN SITU GEL DRUG DELIVERY SYSTEMS: DEVELOPMENT, EVALUATION, AND CHARACTERISTICS

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ABSTRACT

Eyes are delicate and vulnerable to trauma and infections. The placement of medications or adding Drug delivery into the eye is extremely challenging because of the precorneal zone's removal mechanisms which decreases the precision. The cornea's rapid absorption and depletion, along with diminishing pharmacological effects, are some of the shortcomings associated with the conventional ocular delivery system, which uses sperms, lotions, and emulsions, which are somewhat effective. Conversely, in situ polymeric systems are able to maintain the desired concentration of the drug at the site of action such that maximum therapeutic action can be achieved. New formulated ocular drug delivery systems include in-situ gels, dendrimers, niosomes, and Ocusert as well as others. In situ gelling systems begins as a liquid before application but transforms into a gel following application, when there's a change in temperature, pH, or ions. Many efforts for the formulation of long acting in-situ gels have been undertaken. Recent works in ocular drug delivery have been directed towards the use of a variety of drug delivery technologies to design a system that enhances the residence time of the drug at the eye surface while at the same time diminishes the rate of clearance. The review highlights the features, strategies and assessment of methodologies.

KEYWORDS: Ophthalmic, In-situ gel, Eyes, Drug delivery system, development.

1. INTRODUCTION

The system for delivering drugs to the eyes is highly important but also very difficult to use. This is due to the fact that the eye of the human is regarded as an organ that is quite self-contained and has little to no direct access to drug delivery. There are also other problems that come with the conventional methods. They have a low pre corneal retention time and very low bio availability. This problem is attributed to the rapid and high troth turnover of the drugs within the pre-corneal tear film. Other factors such as tear drainage, tears and non-diseased absorption of the conjunctiva also aggravate the problem.[1] In an attempt to address the limitations left in the conventional formulations, many researchers have come up with novel stable and sustained release in situ gels. There are some deficiencies in the area of research particularly in the ocular medication administration, new drug delivery technologies are being implemented, and efforts have been made in this area. One of the main goals is to create systems that reduce the rate of drug elimination while simultaneously increasing the drug carrier's contact time at the surface of the eye. Gel systems in-situ are defined as liquid preparations for administration. These formulations are initiated for use in the eye where upon contact with the bio environment, they become gellified. The system's pre-corneal retention time is extended by this modification. Consequently, effective concentration of the medication within ocular tissues is greatly increased.[2] When specific physio-chemical parameters, such as pH, temperature, or ion sensitivity, alter, gel formation might be considered coherent. These changes enable the drug's controlled and prolonged release. These types of systems are also characterized for a number of parameters, such as drug content, clarity, pH, gelling capacity, viscosity, in vitro drug release studies, texture analysis, sterility testing, isotonicity, accelerated stability studies, and irritancy tests. FT-IR spectroscopy is interfaced in order to observe polyvinyl polymers and the drug's potential incompatibilities.[3] Some of the novel forms of dosage developed include in-situ gels, collagen shields, minidiscs, eye films, ocuserts, nanosuspensions, nanoparticulate systems, liposomes, niosomes, dendrimers, and Iontophoresis of the eyes. New smart systems of polymers have shown potential in drug delivery. After administration, these polymers may experience a sol-gel transition. They exist in a liquid state before administration and become gels after

administration. This transition helps in the improvement of ocular drug's bioavailability by raising its retention period in the augmenting corneal permeability.[4]

Different physical and chemical factors are able to trigger in situ gel formation for example; temperature, the level of acidity, light, a magnetic field, and an electric field. These for their part, responsive polymers, mimic biological systems in an extremely simplified way, by providing pH and temperature as the only external changes which permits change in formulation properties. The in-situ gels may be manufactured with the use of naturally occurring or artificial polymers. These gels may be delivered via several routes including intraperitoneal, injectable, vaginal, rectal, oral, and ocular routes.[5]

This article outlines basic principles of in situ gels and describes the different methods used for in situ gelling. The article also explores various classifications of smart polymers and how such polymers gel from a sol state, as well as in situ gelling polymers assessments.

Achieving the desired medication concentration in the eye is the primary goal of an in-situ gelling device. This has been an issue that is common to conventional dosage forms, but which has improved with the use of innovations.

A few of the problems that are linked with the low bioavailability of eye medication administration is the drainage of the injected solution, lacrimal protein binding, tear production, corneal surface area restriction, poor corneal metabolism, and ineffective absorption.

In order to resolve these issues, scientists have developed new drug delivery systems for use in ocular pharmacotherapy. Primarily, the objective of these improvements is enhancement of ocular dwell time of drug therapy. Collagen shields and inserts have been used with great success particularly in elderly patients. Nevertheless, such techniques are associated with problems of low acceptability to the patients and losing the device with the patient being unaware of its position.

There are six basic requirements for preparation of dosage forms for eye application: sterility and preservation, particle size restrains, pH level, stability and comfort of the eye. Of these, sterility can be regarded as the most important. Medications that are used onto the eyes must be free from infection. There may be opportunities for bacteria to invade the body through damaged skin of the eye. For example, Pseudomonas aeruginosa infection might get worse within 2-3 days and might lead to complete vision loss.

Thermal injections are generally required for some autoclaving methods, while membrane filtration with a pore size of 0.22 micrometres is adequate for other drugs. This procedure also has a great advantage in that it frees the solution from turbidity and sterilises it.

Because Tear fluid is isotonic with blood and other tissues, it is necessary to raise the level of bioavailability of drug.

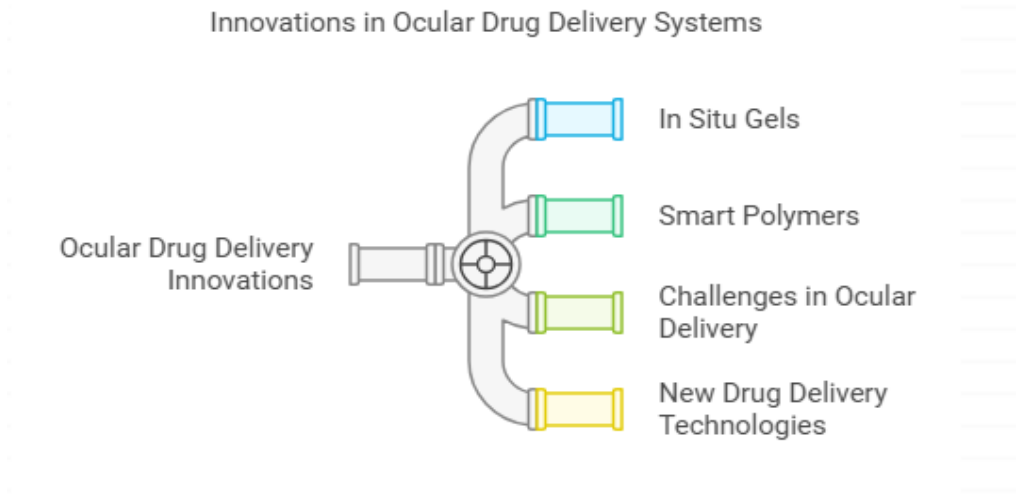

Figure 1: Innovations in Ophthalmic medication delivery system.

2. ADVANTAGES OF DELIVERY OF OPHTHALMIC DRUG SYSTEM

It offers a stable and regulated way for administering drugs. The formulation increases ocular drug bioavailability through increased the amount of time the cornea makes contact. The extended duration of drug action decreases the frequency of instillations to be done in a day. It eases the compliance of the patient administering the drug and increases the effective usage. In terms of patient comfort, it is relatively less irritating than insoluble and soluble insertions. The system avoids complicated procedures; therefore, it is easy to use.[6]

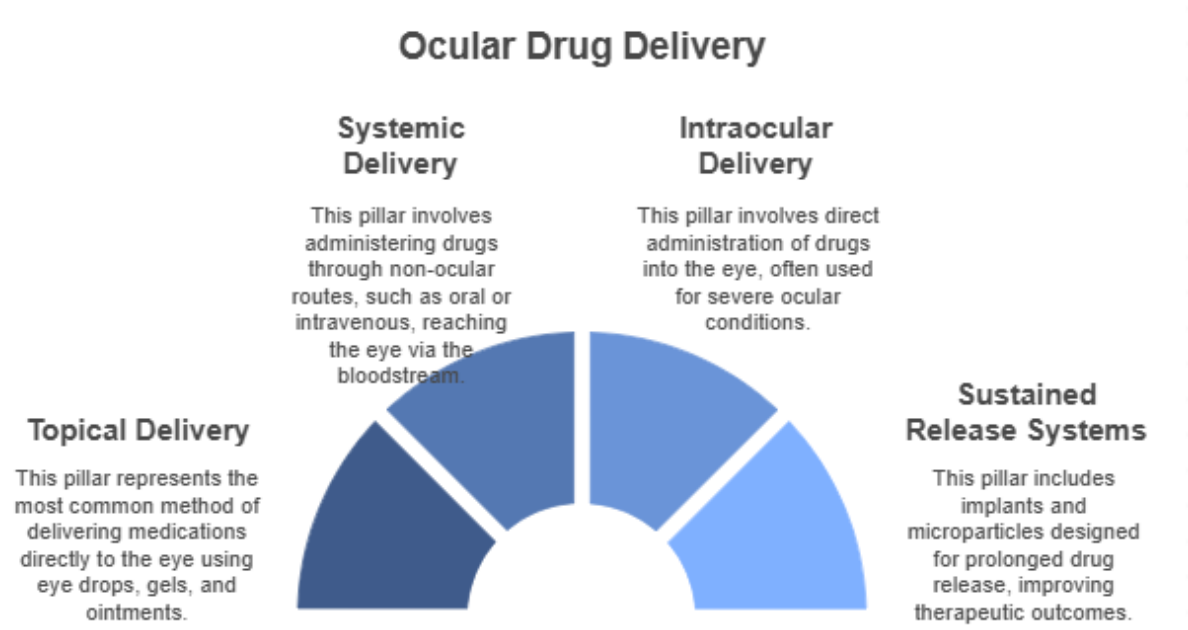

Figure: 2 Different routes of ophthalmic medication delivery system.

3. POLYMER CHARACTERISTICS FOR IN SITU OPHTHALMIC PREPARATION

In situ ophthalmic gels are a promising dosage form to enhance drug delivery for ocular conditions and diseases. These gels can be administered as a liquid and gel at the eye surface which increases retention of drugs and bioavailability. Polymers that can result in efficient in situ ophthalmic formulations are important precursors. This document highlights the essential properties of the above polymers which would need to be taken into account during the preparation of in-situ ophthalmic gels.

Gel

The biocompatibility of the material is necessary. It has to have adhesive properties toward the mucus membrane. A polymer that shows apparent viscosity decrease with increasing shear stress should be used. Tolerance should be good, whereas optical transparency is more apprehended. The material's properties should influence tear characteristics.

Such polymer must characteristically decrease in viscosity as shear rate is increased.[7]

4. ANATOMY OF THE EYE

Structure of eye simplifies into a sphere that has walls that form three layers. The outermost layer is known as the scleral extending into the middle layer which includes the choroid layer, the ciliary body, and the iris, and the innermost layer is known as the retina which is made of nervous tissue. The osseous layer that is called the tissue. The sclera cites the inside tissues of the eye. It has white colour apart from the transparent region that is present at the front of the eyeball referred to as the cornea, which serves the purpose of letting the light to the eyeball.

The choroidal layer is present in the internal part of the sclera and has many vascular structures. In the anterior part it transforms to the pigmented coloured part called the iris (black, blue, green or hazel) of the eye. What can be seen in the mirror includes the eyeball's (iris, pupil, sclera, conjunctiva, and cornea). The lens is found right behind the iris and the pupil, working as a focusing light onto the rear of the eye. The vitreous body, commonly referred to as the vitreous humor constitutes about 80% of the eye and is composed of clear gel. The pupil and house enclosed waist structures such as lens facilitate light to focus at the inner side of the eye. There are special cells sensitive to light rays in the internal wall of the globe and they all are called the retina. The retina contains photoreceptors that convert light energy into electrical energy and sends these signals to the brain through nerve pathways at the rear of the eye is the extension of the optic nerve. On other hand, the macula is small region of the retina. Which is the central area of optic vision that is special and sensitive. And its located-on top of a small pit, called the fovea, the fovea is the whole centre of the macular area.[8-11]

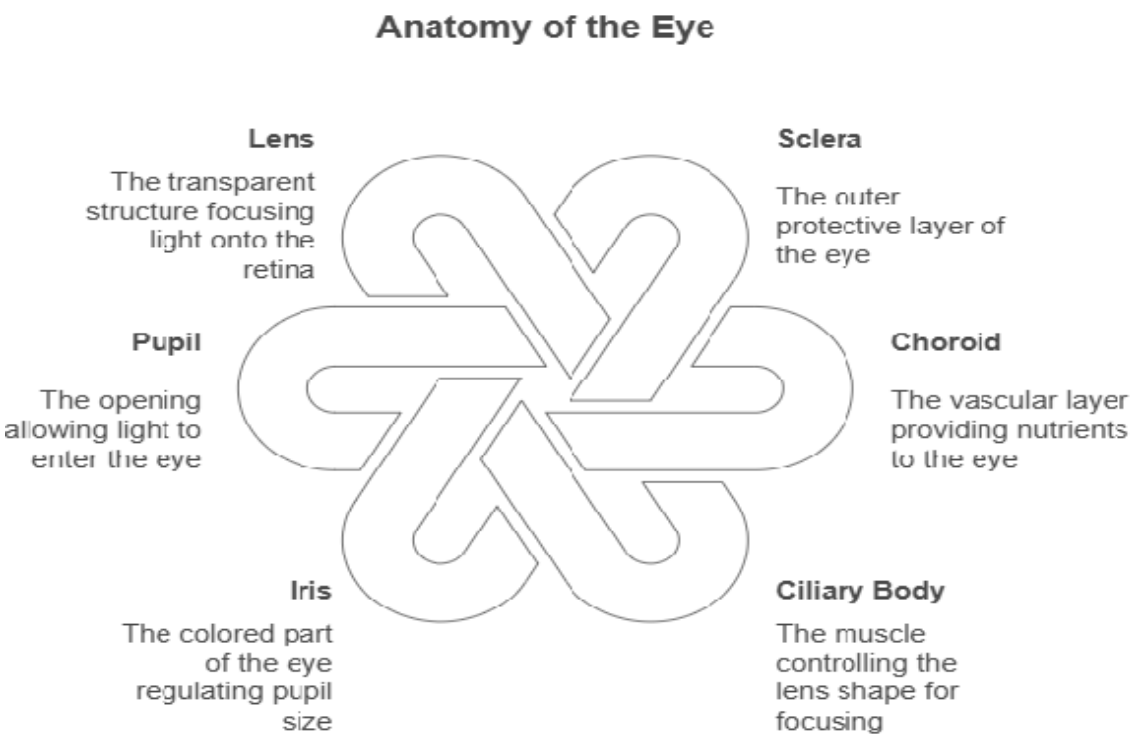

Figure 3: Anatomy of the Eye.

5. EYE CONDITIONS

Amblyopia (lazy eye)

One eye is said to be a "lazy eye" when it does not function as well as its counterpart. Consequently, the patient's lazy eye is typically referred to as the weaker eye. In childhood, this eye's use is quite limited which hinders its ability to be brought as close as possible, resulting in only one eye outshining the other in terms of vision quality. A strabismic eye may also just remain straight or it is possible that the weaker strabismic eye may wander.

Astigmatism

Astigmatism manifests itself in a distortion in the curvature of the eye which leads to blurry images. Most of the time, this condition may be treated successfully with sunglasses, contact lenses, or in rare cases, surgical methods.

Cataract

Cataract is a pathological condition of the lens of the eye that is a natural body organ which get become cloudy and leads to blurring of vision. This stratus clouding will continue to disorientate eyesight with time

Black eye

A black eye is characterized by swelling and bruising around the region of the eye after blunt trauma to the face. The area is mostly discoloured due to some form of injury.

Chalazion

A chalazion arises as a result of the blockage of an oil-producing gland in the eyelid, rendering it swollen and bump-like.

Conjunctivitis

Conjunctivitis, or pink eye, as many people call it, refers to the inflammation of the conjunctiva membrane of the eye. This condition is usually the result of infectious diseases, allergies or irritants.

Diabetic retinopathy

Diabetic retinopathy refers to the condition resulting from diabetes in which the high blood sugar levels damage the blood vessels of the eyes. With time, such diseased vessels might develop edema or atypically grow leading to a compromise on vision.[12, 13]

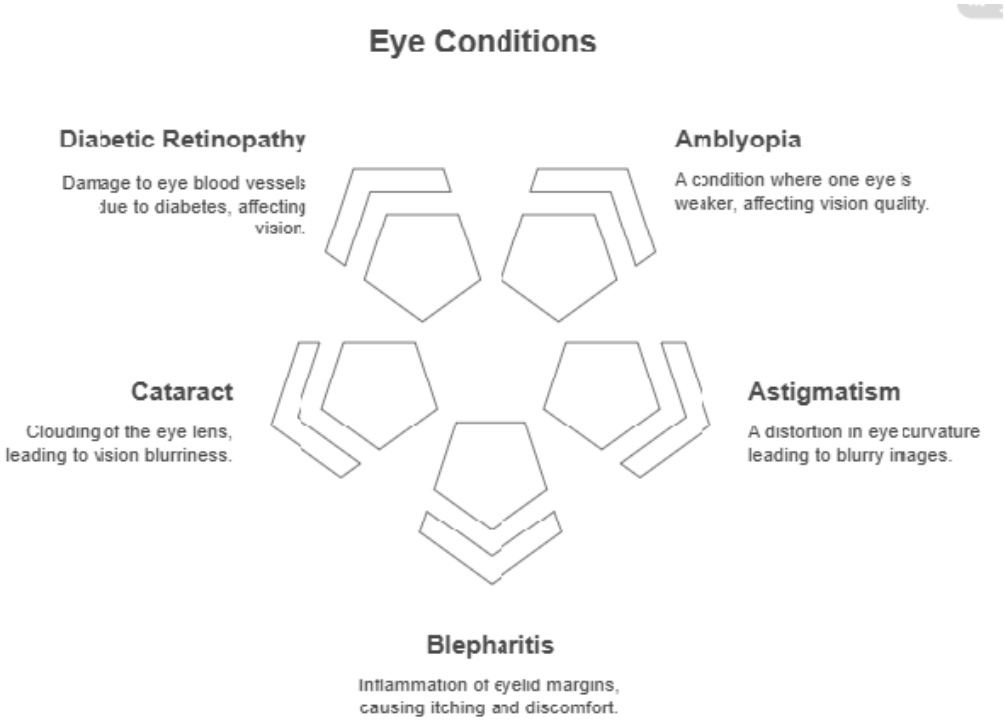

Figure 4: Eye Conditions.

6. TYPES OF TRADITIONAL DOSAGE FORMS

Ophthalmic Solutions: Eye Drops and Ophthalmic Inserts

Ophthalmic solutions are sterile and isotonic preparations in aqueous or oily, emulsion or suspension dosage forms that contain one or more active components. These doses are intended for instillation into the eye, where the medicine is absorbed and has the desired effect. Formulators may add excipients to change the osmotic pressure, pH, and viscosity, whereas some solutions are preservative-free.

Ointments

Ointments are semisolid dosage forms for the eye which are mainly based on schedules made of solid or semi-solid hydrocarbons which become liquid or soft at body temperature when applied. When placed in the eye, the ointment becomes little drops which can be retained in the conjunctival sac for a long time and improving drug availability. Never the less they are said to cause blurred vision and irritation making it important to apply them at night. In spite of the disorders related to their use, they are considered relatively safe and well tolerated.

Gels

In the case of gels, the relative composition of the components or the other components which do not cross link but enhance bonding, increases the viscosity. Dosing intervals of gels are longer than those of solutions due to their formulation. Drug activity in the eye has been improved using viscous systems such as cellulose acetate phthalate or Poloxamer 407 especially in delivery of pilocarpine. However, gel formulation has long been shunned due blurred vision and irritations of the eye making patient acceptance low. Furthermore, the high viscosity may also make large scale sterilization operation cumbersome where gels have not been popular.[14, 15]

7. IN-SITU OPHTHALMIC GEL SYSTEM

In-situ ophthalmic gels systems can be described as formulations which appear to be solutions but develop into gels when they are placed inside the eye. This gel formation has several mechanisms are follows.

IN-SITU GEL SYNTHESIS VIA A PHYSICAL MECHANISM

Swelling

hygroscopic swelling in which the material takes in moisture from the surrounding medium and increases in volume to fill the space that is required.

Swelling can be described as a dimensional change of the material, whereby the material incorporates moisture into itself so that it increases its volume to fill the required space. Substances such as glycerol that are polar and polymerizable can easily be photopolymerized by a photo initiator if the substance is readily available.

This procedure typically uses visible light and long wavelength ultraviolet (UV) radiation, as short wavelength UV light is rarely employed because to its limited penetration and is potentially harmful to biological tissue. With regards to ultraviolet photo polymerization, 2,2-dimethoxy-2-phenyl acetophenone is one of the most frequently used ketonic initiators followed by camphor quinone and ethyl eosin which are in volumes exposed to visible light.

On the other hand, these in situ formulations can also be created to degrade by chemical or enzymatic means or improve the in situ compounds field applications. When injected at the target site, the formulation is able to undergo photocuring in-situ with the help of fiber optic cables resulting in a prolonged drug release. The photo-reactions allow a rapid polymerization to occur at physiological temperature conditions.

The result is the capacity to fabricate these systems into complex geometries to make an implant. The photopolymerizable and biodegradable hydrogel functions as a tissue contact material and provides a controlled release.

Diffusion

As with the diffusion process, N-methyl pyrrolidone (NMP) is leached from the polymer solution into the surrounding medium, causing the polymer matrix to precipitate or gel. NMP has proven to be an effective solvent for these systems.[16, 17]

FORMATION OCCURS IMMEDIATELY WITHIN A SPECIFIED REGION VIA CHEMICAL REACTION.

Cross-Linking Facilitated By Ionic Interactions

In-situ formation via chemical reactions involves the precipitation of inorganic solids from a supersaturated ionic solution, as well as enzymatic and photo-initiated chemical reactions. Ion crosslinking cannot occur unless a polymer undergoes a phase transition in the presence of foreign ions which eventually leads to gel formation. Ion crosslinking is particularly important to polysaccharides; for instance, i-carrageenan can physically cross link to become elastic, only when exposed to calcium ions (Ca2+), whereas K-carrageenan would become hard and brittle at low concentration of potassium ions (K+).

The more aggressive gelling agent, Gellan, also known as Gelrite, is commonly used in IV Sullivan in-situ gel systems. It, like most gelling agents, is activated when exposed to monovalent and divalent cations such K+, Ca2+, Na+, and Mg2+. Furthermore, low-methoxylated pectins produce gels in the presence of divalent cations, preferentially Ca2+.

Alginic acid, like pectin, can form gels in the presence of divalent or polyvalent cations, such as Ca2+, due to the interaction between the glucuronic acid blocks of the alginate chains.[18, 19]

Cross-linking driven by enzymatic processes

Enzymatic as well as photochemical and chemical processes can be employed for gel formation which can also be done via catalytic processes. However, Natural enzymes triggered in-situ formation has not been extensively studied. Nevertheless, it appears to be advantageous compared to its chemical and photochemical counterparts.

Enzymatic approaches for example can be said to be more efficient since they operate at physiological temperature and pressure and do not have to deal with potentially toxic chemicals such as monomers and initiators. Hydrogel-based intelligent stimuli-responsive release systems have been developed to deliver insulin. Other factors can also be altered such as the amount of enzyme in order to enable the acceleration of the gel formation process. This allows mixtures to be injected before the gel solidifies.[20, 21]

8. APPROACHES IN IN-SITU GEL DRUG DELIVERY

The increasing use of in-situ gels is remarkable in the field of pharmacological sciences. This is owing to their ability to deliver drugs in a specific area and over a longer time. In this paper, the formulations and methods of how these systems are developed and applied are presented. Mechanisms of action, merits and possible drawbacks are discussed. Knowing these strategies allows one to design more improved systems for drug delivery. Such systems aim to enhance the therapeutic benefits to a great extent.

Thermo-reversible Gels

These gels can be achieved by the use of substances such as gelatin or poloxamers and their formation is brought about by a shift in temperature. The solution holds on to a liquid form when kept at low temperatures but changes to a gel when warmed to body temperature, achieving drug sustain release.

pH-sensitive Gels

These systems rely on polymers that react to pH changes. For example, polyacrylic acid swells and forms a gel in acidic environments. This property makes it ideal for drug delivery in areas with fluctuating pH levels, such as the gastrointestinal tract.

Under this system, gelation is caused mostly when the pH increases from 5 to roughly 7.4 which results in a change in pH. At a higher pH, the polymer interacts with mucin through hydrogen bonding. An interaction such as this leads to the formation of hydrogel.

Ion-sensitive Gels

They are a type of gels with ionic controllable electrospun fiber membranes incorporating chitosan or more often alginate. Diphasic and ionic discharge of certain ions causes the gelling state of the polymers through which the localized drugs can be delivered.

Enzyme-sensitive Gels: Such gels degrade in the presence of certain enzymes and thus can release or sustain target delivery of drugs for example in tumors over-expressive to certain enzymes.[22, 23, and 24]

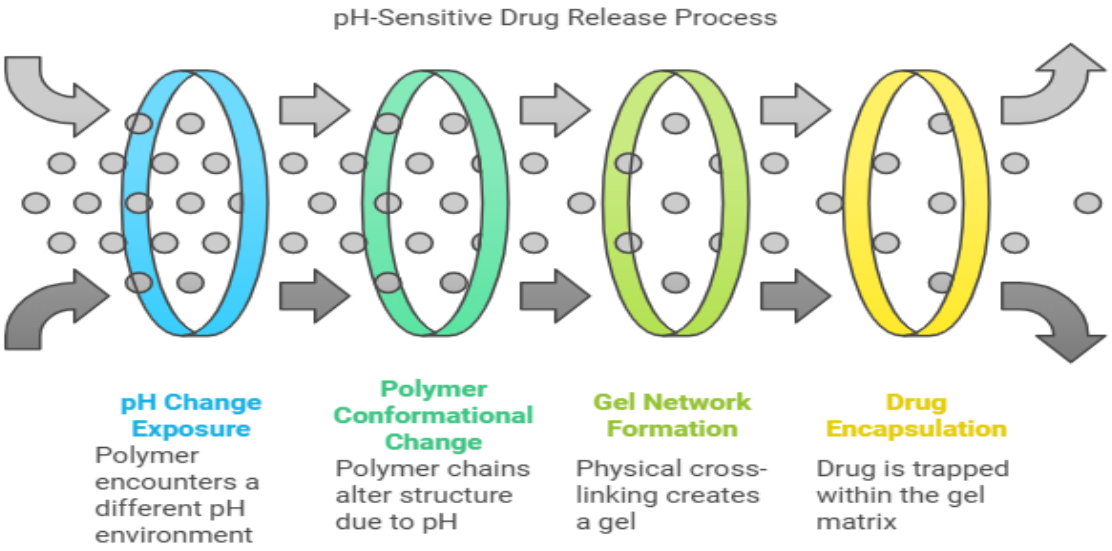

Figure: 5 PH Sensitive Drug Release Process.

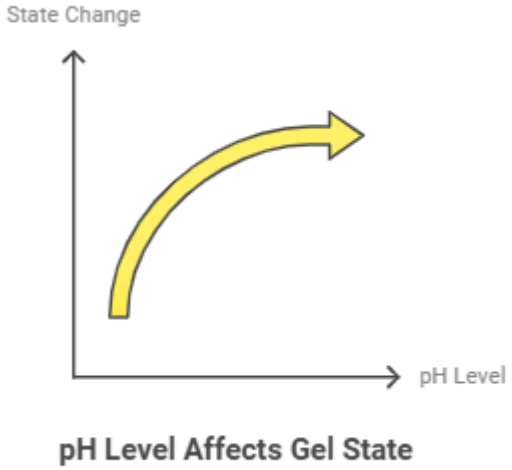

Fig. 6: Graphical representation of PH sensitive in-situ gel system.

9. EVALUATIONS OF IN-SITU GEL SYSTEM

All formulated solutions had a pH of 7.4 when tested for spread ability, pH measurement, gelling capacity, drug content, rheology, in-vitro diffusion studies, in-situ isotonicity, antibacterial assay, ocular testing in vivo in rabbits, and accelerated stability tests.

A formulation that is instilled in the eye as liquid drops should have the right viscosity that makes it possible for the liquid drops to be easily instilled. Once instilled it, the formulation should easily change from sol to gel form upon the change in the pH of the solution, temperature or ion exchange.

Aspects of Physical Examination

In-situ gelling agents' formulation is assessed for its clarity, pH, gelling capacity, and drug concentration.

Gelling Criteria

To test the formulation's gelling capacity, a drop is inserted in 2.0 ml of freshly prepared simulated tear fluid in a vial. The formulation is visually monitored, and the time it takes for gel formation to occur is recorded.[25, 26]

10. RHEOLOGICAL STUDIES

The viscosity of in-situ gel compositions can be determined using the Brookfield viscometer, as well as the Cone and Plate viscometer. Pour the formulas into the sampling tube to begin the analysis.

Some literature sources reported that the viscosity of such formulations prior to gelling is between 5 and 1000 mPas. Once eyeball ion gelation occurs, the viscosity jumps from approximately 50 up to 50,000 mPas.

We utilize two temperatures for testing; 25 degrees Celsius and 37 degrees Celsius (0.5 degrees variance). The temperature is controlled using a circulating bath connected to the viscometer adapter before any measurement is made.

The spindle angular velocity was gradually increased from zero to 20, 30, 50, 60, 100, and 200 rpm, and the appropriate viscosities were measured. The formulations had Newtonian pregelation but showed pseudoplasticity after gelling in simulated tear fluid.[27, 28]

11. IN VITRO DRUG RELEASE STUDIES

The in vitro release of the prepared in-situ gel solution was assessed using a Franz diffusion cell. The formulation was placed in the donor compartment, while the receptor compartment was filled with freshly prepared simulated tear fluid. A 0.22 µm dialysis membrane separated the two compartments. The assembly was placed on a thermostatically controlled

magnetic stirrer, with the medium temperature maintained at 37°C ± 0.5°C. 1 ml samples were taken from the receptor compartment at specified intervals (1 for up to 6 hours). To keep sink conditions consistent, an equal volume of new medium was introduced.

The diluted collected samples were made up to 10 ml in volumetric flasks of appropriate solvent and the analyses were carried out using a UV spectrophotometer at the corresponding wavelength taking the reagent blank as reference. The drug content was calculated using a linear regression equation based on the standard calibration curve, and the cumulative drug release percentage (%CDR) was obtained.

The collected release data were curve fitted to produce the best-fit drug release model. Various models such as Korsmeyer-Peppas and Fickian diffusion mechanisms were used to assess the kinetics of drug release.[25, 29, and 30]

12. TEXTURE ANALYSIS

A texture profile analyzer assesses the in-situ gel for its consistency, firmness, and cohesiveness. This test mainly informs the researcher about the strength of the gel and the ease with which it can be administered in vivo. For the gel to be in such close contact with the mucus surface, high adhesiveness values are necessary.[31]

13. ISOTONICITY EVALUATION

Isotonicity is a mandatory quality feature for any ophthalmic preparation. This is because these medications should not lead to a collapse or irritation of any eye tissue. All medications meant for the eye are said to be subjected to tests on isotonicity. This medication is isotonic eye drops which are expected to be safe for the eye. All eye formulations that show good release, gelling and desired viscosity undergo isotonicity testing. On examining the isotonic eye drops by placing a few drops on a slide and adding some blood before the mix is injected and observed under the microscope at 45 X, the product is also compared with a benchmark eye medicament available.[32]

14. INVESTIGATION OF DRUG-POLYMER INTERACTIONS AND THERMAL ANALYSIS

Interactions can be studied using Fourier Transform Infrared (FTIR) spectroscopy. In this scenario, the KBr pellet method is commonly used to determine the type of forces engaging during gelation. Thermogravimetric Analysis (TGA) determines how much water is present in the hydrogel of in situ formed polymeric systems. Furthermore, during the study of gelation, Differential Scanning Calorimetry (DSC) is performed to observe the variations in thermograms of the gel compared to those of the active components.[31]

15. ACTIVITY AGAINST BACTERIAL GROWTH

Ability of bacteria to grow is evaluated in terms of concentration of antibiotics and then compared to the growth inhibition brought about by a specific standard antibiotic complex. To execute the microbiological assay, the serial dilution technique is employed.[33]

16. EYE IRRITANCY TEST

In this test, 100 µl of the Draize irritancy test is used first for evaluating eye irritation potential of any ophthalmic product before its marketing so as to protect them from being sold. A Dreized agent is applied to the lower cul-de-sac of one of the eyes, and various criteria of assessment are observed 1 hour, 24 hours, 48 hours, 72 hours and 1 week after the application. The study is done on three male rabbits of 1.5-2 Kilogram. The sterile formulation was instilled but twice daily for seven days, after a three-day washout period with saline, cross-over study was performed. Signs of redness, swelling and eye watering were observed in the rabbits during the study.[34, 35]

17. RAPID STABILITY ASSESSMENTS

According to guidelines set by ICH, formulations are packaged in ambient colored vials and are also blister packed in Al foil for a small scale accelerated stability test conducted at 40±2°C, 75±5% RH for a period for a period of not more than 3 months. Clear samples of the formulations are examined as monthly intervals to monitor clarity, pH, and gelling capacity, amount of drug, rheological properties and in vitro dissolution.[32]

CONCLUSION

In pharmaceutical technology, polymers are effective as drug delivery systems which provide a way matrix from which the active ingredient is released. According to the recent study polymeric in-situ gel system has showed a prolonged drug release when compared to the traditional methods. There are a lot of natural, synthetic and semi-synthetic polymers that have emerged for controlled drug delivery systems. Moving forward, in-situ gel formulations include such biodegradable and biocompatible polymers that provide suitable, controlled drug release systems. This has enhanced, among other things, an acceptable level of release given biocompatible requirements, making it self-evident that in-situ gel dosage forms are preferred. With respect to the evolving science of drug delivery systems, particularly mhydrates, acquity 21 particularly folds forward variants has shown a hearing improvement over the traditional methods but it still remains a difficult area. However, with the challenges at hand, increasing understanding of the principles governing ocular drug absorption and disposition has spurred survivalism in drug delivery systems for the eye. Another method that has attracted the attention of researchers is the use of in situ synthetic ocular gels. These gels are able to deliver drugs continuously for a prolonged period of time with great stability and remarkable biocompatibility.

In-situ gels are evaluated on the basis of gels ability to form as well as many in vitro drugs release that is subsequent to gelling status of the hydrogels, drug and

polymer compatibility, thermal characterization, anti-bacterial activity, and ocular irritancy. Biodegradable washes what more the other promise does it bear.

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