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A Review on In Situ Gelling System for Ophthalmic Drug Delivery

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ABSTRACT

Ophthalmic drug delivery systems are both fascinating and problematic due to the normal physiological properties of the eyes, which restrict ocular product bioavailability. The development of novel ocular dosage forms for current drugs in order to enhance efficacy and bioavailability, as well as patient compliance and convenience, has become a major focus in the pharmaceutical business. Ocular In-situ gelling systems are a novel type of eye drug delivery systems that begin as a solution but rapidly convert into a thick gel when implanted or inserted into an ocular cavity where active pharmaceuticals are continually delivered. This sol-to-gel phase conversion is influenced by a range of variables, including variations in pH, the presence of ions, and temperature fluctuations. Post-transplantation gel is chosen for its viscosity and bio adhesive qualities, which prolongs the gel's presence in the ocular area and also ensures that the medicine is released slowly and continuously, in contrast to typical eye drops and ointments. This article provides an overview of situ gels, their numerous techniques of gelling, the many types of polymers utilized in situ gels, their gel-based methodologies, and the polymeric testing of situ gels.

Key words: *Ophthalmic, In-situ gel, bioavailability, polymers, novel, sol-to-gel phase.*

1. INTRODUCTION

In recent years, much emphasis has been placed on the development of innovative drug delivery systems. The therapeutic efficacy and safety of drugs administered conventionally can be enhanced by more precise spatial and temporal placement within the body via controlled drug administration. Drug distribution can be classified into three types: targeted delivery, controlled delivery, and modulated delivery. [1]

The eye is often employed as a gateway for drug delivery rather than systemic therapy to prevent the possibility of ocular injury from high blood concentrations of the drug, which is not intended. Because of the eye's unique architecture, physiology, and biochemistry, it is immune to outside molecules, posing a continuing challenge to the formulator to surpass the protective barriers of the eye without causing irreversible tissue damage. Most ocular treatments, such as eye drops and suspensions, require the application of opthalmically active drugs to the tissues surrounding the ocular cavity. [2] The majority of the medication included in these dosage forms is promptly diluted in the tear film as soon as the eye drop solution is administered into the cul-de-sac and is rapidly drained away from the precorneal cavity by continual tear flow and lacrimo-nasal drainage. As a result, the targeted tissues absorb just a small portion of the injected dose. As a result, concentrated solutions and frequent dosage are required for the instillation to have an appropriate therapeutic effect4. Polymeric film ocular drug delivery systems/ocular inserts, which are receiving worldwide acclaim, release medications at a pre-programmed pace for a longer period of time by increasing the pre-corneal residence time. [3]

Traditional drug administration methods, including as suspension, ointment, and solution, have limitations such as increased pre-corneal drainage, impaired vision, limited bioavailability, and short residence time. Drug absorption in the eye is severely limited by some protective mechanisms that ensure proper eye function, as well as other concomitant factors such as drainage of instilled solutions, lachrymation and tear turnover, metabolism, tear evaporation, non-productive absorption/adsorption, limited corneal area and poor corneal permeability, and binding by lachrymal proteins. One of the primary goals of ocular therapies is to avoid anatomical impediments and defensive mechanisms of the eye in order to elicit the desired pharmacological response. [4]

The goal of developing a therapeutic system is to achieve an optimal concentration of a medicine at the active site for the right period. A medicinal agent's ocular disposition and elimination are determined by its physicochemical qualities as well as the related ocular anatomy and physiology. A successful design of a drug delivery system thus necessitates an integrated understanding of the drug molecule as well as the limits imposed by the ocular route of administration. [5] To develop ocular delivery systems with high therapeutic efficacy, better, more sensitive diagnostic procedures and novel therapeutic agents are required, as traditional systems have significant limitations that make them less successful. [6]

There are two types of techniques that have been tried to boost the bioavailability and duration of the therapeutic activity of ocular medicines. The first is based on the use of sustained drug delivery devices, which allow controlled and continuous ocular drug delivery. The second step entails increasing corneal drug absorption while decreasing precorneal drug loss.[7] The development of in situ gel systems has gotten a lot of attention in recent years because of the several benefits that this polymeric system provides, such as simplicity of administration and reduced frequency of administration, enhanced patient compliance, and comfort. In situ gel formation happens as a result of one or more stimuli such as pH change, temperature modulation, and solvent exchange.

2. ANATOMY AND PHYSIOLOGY OF THE EYE

The eye is the most remarkable of the sense organs since it alerts us to a variety of objects both close and far. The eye is essentially spherical in shape except for the front section, the clear cornea, which bulges forward somewhat. The eyelashes, eyelids, tears, and blinking all serve to protect the eye. The eyelashes trap foreign objects as the blink reflex protects the eyes by closing them; blinking occurs often throughout awake hours to keep the corneal surface clear of mucus and moisturised with lacrimal gland tears. Tears remove irritants and are antibacterial, so avoiding infections. The protective functions of the eye lids and lacrimal system ensure that material injected into the eye is rapidly removed unless it is sufficiently small in volume, chemically and physiologically compatible with surface tissues. The eye is one of the most sensitive yet vital sense organs, making it a difficult target for topical medication administration. [8]

Generally, the eye is divided into two important segments:-

(1) The anterior segment which involves the cornea, conjunctiva, iris, pupil, ciliary body, anterior chamber, aqueous humor, lens and trabecular meshwork.

(2) The posterior segment includes vitreous humor, sclera, retina, choroid, macula and optic nerve. [9]

2.1 Absorption of Drugs in Eye

Drugs injected into the eye are frequently considered to be swiftly and completely absorbed. Contrary to popular opinion, the instant a drug is placed in the lower cul-de-sac of the eye, a number of factors immediately begin to impact the drug's bioavailability. Drugs are absorbed via corneal or non-corneal pathways. The non-corneal pathway involves absorption into the intraocular tissues via the sclera and conjunctiva. This method, however, is ineffective because it prevents the medication from entering the aqueous humour. Thus, maximum absorption occurs through the cornea, which transports the medication into the aqueous fluid. Historically, the goal of ophthalmic drug delivery systems has been to optimise ocular drug absorption while minimising systemic absorption. Transcorneal drug penetration is influenced primarily by corneal barriers, the physiochemical characteristics of the medicines, and the active ion transport mechanisms present at the cornea.

2.2 Corneal barriers

The primary barrier to drug absorption into the eye is the corneal epithelium. The corneal epithelium serves as a protective barrier against foreign substances and also acts as an impediment to ion movement. The corneal epithelium is made up of a basal layer of columnar cells, squamous cells, and superficial cells with polygonal shapes. Although intracellular tight connections completely surround the most superficial cells in a healthy corneal epithelium, the intracellular gaps between wing cells and basal cells are larger. Certain allow big molecules to diffuse paracellularly exclusively through these cell layers. Tight junctions act as a selective barrier for small molecules and totally block macromolecules from diffusing along the paracellular pathway. Corneal stroma is a highly hydrophilic tissue that serves as a rate-limiting barrier for the ocular absorption of the majority of lipophilic drug. Maintaining proper corneal hydration is the responsibility of the corneal endothelium. [10]

2.3 Blood-ocular barriers

Blood-ocular barriers protect the eye from xenobiotics in the blood stream. These barriers are composed of two components: the blood-aqueous and the blood-retina. The anterior blood-eye barrier is made up of endothelial cells in the uvea (the eye's middle layer beneath the sclera). It is composed of three components: the iris, the ciliary body, and the choroid). This barrier inhibits plasma albumin from entering the aqueous humour and also restricts the entry of hydrophilic drugs into the aqueous humour from plasma. The posterior barrier between the bloodstream and the eye is made up of retinal pigment epithelium (RPE) and the constrictive walls of retinal capillaries.24 Unlike retinal capillaries, the choroid's vasculature is perfused with blood and has porous walls. While drugs readily enter the choroidal extravascular space, their distribution into the retina is constrained by the RPE and retinal endothelia. [11]

2.4 Physiochemical properties of drug

The transcellular or paracellular pathway is the primary method through which drugs cross the corneal epithelium. While hydrophilic drugs prefer the paracellular route, which involves passive or altered diffusion through intracellular gaps, lipophilic drugs prefer the transcellular route. Passive diffusion along concentration gradients, either transcellular or paracellular permeation, is the primary method of permeation for topically administered drugs. Additionally, lipophilicity, solubility, molecule size and shape, charge and degree of ionisation all influence the route and rate of penetration into the cornea. [12]

2.5 Mechanism of ocular drug absorption

Instillation-administered drugs must permeate the eye, primarily through the cornea, but also via non-corneal pathways. These non-corneal pathways, which entail drug diffusion over the conjunctiva and sclera, appear to be particularly significant for drugs with low corneal absorption.

Drugs permeate the corneal membrane from the precorneal region. As a result, the mixing and kinetic behaviour of drugs in tears have a direct effect on the effectiveness of drug absorption into the inner eye. The majority of ophthalmic drugs are absorbed effectively by a diffusional mechanism over the corneal membrane. The effectiveness of absorption is proportional to the rate and extent of transport activities. The flow of any drug molecule over a biological membrane is determined by the permeating molecule's physicochemical qualities and its interaction with the membrane. The extent to which transport or absorption occurs is also dependent on the physiological mechanism governing precorneal fluid drainage or turnover. [13]

In the event of structurally comparable corneal stroma, the primary mechanism of drug penetration through the sclera is expected to be diffusion through the intercellular aqueous media. As a result, the potential of division cannot be ruled out. While the conjunctiva, like the cornea, is formed of an epithelial layer covering a stroma, the conjunctival epithelium provides significantly less resistance than the corneal epithelium.

2.6 Ocular Drug Delivery

Ophthalmic drug delivery is one of the most fascinating and difficult areas of research for pharmaceutical professionals. The structure, physiology, and biochemistry of the eye render it impenetrable to external chemicals on an exquisite level. [14] The formulation's difficulty is to penetrate the eye's protective barriers without inflicting irreversible tissue damage. The primitive ophthalmic solution, suspension, and ointment dosage formulations are no longer adequate for the treatment of certain modern aggressive illnesses. Despite ongoing research and the regular introduction of novel ophthalmic drugs, ocular drug delivery does not appear to be progressing at the same rate as oral, transdermal, or transmucosal drug delivery.

The overwhelming majority of currently available ocular drug delivery technologies are quite basic and inefficient. Successful drug delivery into the eye is extremely challenging due to the eye's extensive defence mechanisms, which make it impossible to achieve an effective concentration of the drug in the target area of the eye. [15] The low bioavailability of pharmaceuticals administered via ocular dosage forms is mostly attributable to tear formation, non-productive absorption, brief residence period, and the corneal epithelium's impermeability.

When the volume of fluid supplied topically exceeds the volume of lachrymal fluid (7 to 10l), the dose is drained via the nasolachrymal system into the naso pharyngeal and gastrointestinal tract. Thus, the drug's contact time with ocular tissue is brief (1–2 minutes), owing primarily to leakage of the injected eye drops from the pre corneal area. Thus, both transconjunctival and transnasal absorption following nasolachrymal duct drainage are generally undesirable, not only for the loss of active component to the systemic circulation, but also for the possibility of adverse effects. Thus, prolonged contact duration with the corneal surface and increased penetration into the cornea are required to optimise topical ocular drug delivery systems. [15]

3. CONVENTIONAL OPHTHALMIC DOSAGE FORMS

The majority of the ophthalmic drugs are administered topically in the form of conventional formulations. Conventional ophthalmic dosage forms include solutions, suspensions and ointments.

3.1 Solutions

It is the most often used method and makes it simple to deliver drugs that act on the eye's surface or within the eye following passage via the cornea or conjunctiva. Despite their limitations (i.e., rapid removal from the pre ocular area, resulting in low bioavailability), they continue to be accorded top priority by formulators due to their ease of preparation, filtering, and sterilisation, as well as their cost effectiveness. [16]

3.2 Suspensions

Suspension formulations are frequently employed for poorly soluble medicines such as anti-inflammatory medications. However, ocular suspensions have a number of problems. Proper shaking is necessary, which if not done properly, can result in dosage discrepancy. A fine sediment may accumulate and is difficult to dislodge even with mild shaking. The suspended medication undergoes polymorphism, resulting in a less soluble or insoluble form of the drug. [16]

3.3 Ointments

A significant characteristic of the ointment is that it lingers in the conjunctival culde sac, establishing a reservoir for the medication. Furthermore, when compared to the typical lachrymal turnover, the disappearance of a drug supplied in an ointment carrier from the pre-corneal areas is extremely slow (0.5 percent per minute) (about 16 per min). These preparations have a number of disadvantages, including greasiness and blurred vision, and are typically used at night. [17]

3.4 Drawback of traditional ophthalmic formulations [18]

1. They have poor bioavailability because of

a) Rapid precorneal elimination

b) Conjunctival absorption

c) Solution drainage by gravity

d) Induced lacrimation

e) Normal tear turnover

2. Frequent instillation of concentrated medication is required to achieve a therapeutic effect.

3. Systemic absorption of the drug and additives drained through nasolacrimal duct may result in undesirable side effects.

4. The amount of drug delivered during external application may vary. The drop size of ocular medication is not uniform and those delivered is generally not correct.

5. Presence of viscous vehicles can cause blurred vision.

3.5 Novel Ophthalmic Delivery Systems [19]

Ocular drug delivery is one of the most difficult problems that pharmaceutical researchers face. The capacity to maintain a therapeutic level of the drug at the site of action for an extended period of time is a significant hurdle in ocular therapy. Increase the contact time of an eye medication with the corneal surface to increase its therapeutic efficacy. To prolong the length of drug-eye contact, viscosity enhancers are added to preparations or the drug is manufactured in a water-insoluble ointment formulation. Regrettably, these dose forms provide only a significantly longer duration of drug-eye contact than eye drop solutions and do not provide consistent drug bioavailability. Throughout the therapy, repeated drugs are required.

To counter these disadvantages, several formulation strategies have been developed to boost ocular bioavailability. Numerous strategies for increasing the bioavailability and duration of therapeutic activity of ophthalmic drugs fall into two categories. Maximizing drug absorption through the cornea and decreasing pre-corneal drug loss. A regulated and continuous delivery method for ophthalmic drugs to the pre- and intra-ocular tissues. However, initial failures resulted in the development of novel ways in the field of ocular drug delivery. [20]

3.5.1 Mucoadhesives

These systems can be polymeric solutions or suspensions of microparticles. They are kept in the cul-de-sac by adhesive bonds formed with the mucus or epithelium, so extending the time of corneal contact. [20]

3.5.2 Polymeric solutions

Polymers such as methyl cellulose, polyvinyl alcohol, hydroxypropyl cellulose, and poly vinyl pyrrolidone are added to the eye drop solution to improve the drug's corneal penetration. This is apparently owing to an enhanced tear viscosity, which reduces or otherwise accelerates early drainage, prolongs corneal contact duration, and therefore maintains to some extent the drug's initial tear concentration. [21]

3.6 *In situ* activated gel forming system

A more preferable dosage form would be one that can be supplied via drop, has little to no refractive index effect on vision, and is dosed no more than once or twice day. This is accomplished by the use of an in-situ gel-forming ophthalmic medication delivery device. This technology, which is composed of polymers with reversible phase transitions (sol-gel-sol) and pseudoplastic activity, is designed to minimise blinking interference, increase pre-corneal residence duration, and maximise ocular bioavailability. [22]

3.6.1 Nanocarriers

Niosomes are non-ionic surfactant-containing vesicles that can entrap both hydrophilic and lipophilic medicines either in an aqueous layer or in a lipid-based vesicular membrane. It aids in preventing the drug from being metabolised by enzymes found on the tear/corneal surface. Liposomes are small vesicles consisting of lipid layers that resemble membranes and surround aqueous compartments. They are capable of encapsulating hydrophilic compounds in an aqueous compartment and incorporating hydrophobic molecules into lipid bilayers. Nanoparticles are polymeric solid particles ranging in size from 10 to 1000 nm. Due to their small size, these are not easily washed away by tears. Pharmacosomes are amphiphilic pharmaceuticals' vesicles. On dilution with tear, they are transformed to pharmacosomes.

3.6.2 Contact lenses

Contact lenses are a popular alternative to spectacles. It has been suggested that soft contact lenses soaked in medication solution be used for slow but extended drug delivery, particularly to ocular tissue. [22]

3.6.3 Ophthalmic inserts

Inserts are characterised as thin discs or small cylinders composed of a suitable polymeric material and designed to fit into the lower or upper conjunctival sac. Their prolonged retention in the preocular region may result in increased drug availability in comparison to liquid and semisolid formulations. Ocular inserts are a solid dosage form that maintains the effective concentration of the drug in the target tissues while minimising the number of applications required by controlled release systems. The limited popularity of ocular inserts has been ascribed to psychological factors such as patients' reluctance to abandon traditional liquid and semisolid drugs, as well as to rare therapeutic failures (e.g., unrecognised expulsion from the eye, membrane rupture, etc.). [23]

3.7 Microemulsion

Microemulsions are an intriguing alternative to topical ocular drug administration since they may be rapidly generated via emulsification, are easily sterilizable, are stable, and have a high capacity for drug dissolution. In this instance, these systems operate as penetration enhancers, facilitating drug transport to the cornea. Microemulsions are available in a variety of formulations for ocular application.

3.8 *In Situ* Gelling System

Ophthalmic in-situ gelling is composed of environmentally sensitive polymers that will undergo structural changes in response to modest changes in environmental parameters like as pH, temperature, and ionic strength. In-situ forming gels are liquids that are injected into the eye and then rapidly gel in the cul-de-sac of the eye in response to environmental changes (Fig. 3); they then slowly release the drug under physiological conditions [23]. As a result, the residence period of the in-situ gel is prolonged and the drug is administered in a sustained manner, resulting in increased bioavailability, decreased systemic absorption, and a less frequent dosing schedule, all of which result in improved patient compliance. Additionally, in-situ gelling systems have demonstrated several other potential benefits such as a simple manufacturing process, convenience of administration, and exact dose delivery. [22]

4. MECHANISMS OF GELLING SYSTEM

In situ gel formation can be accomplished through a variety of methods, including temperature, pH, and ion-activated systems. Temperature-triggered in-situ gelation technology that utilises temperature-sensitive polymers that reside in liquid form below their low critical solution temperature (LCST) and gel at or above the LCST [33]. The pH-induced in-situ gel is composed of polymers with acidic or alkaline functional groups inside the chain molecule and undergoes a sol-gel phase transition when the pH environment changes from low to high. Ion-activated systems, also known as osmotically induced in-situ gel systems, are those in which the polymer undergoes a sol-gel transition in response to changes in ionic concentration, most often Na^{+}, Mg^{2+}, and Ca^{2+} in tear fluid [24]. Additionally, it has been demonstrated that enzyme cross linking and photon polymerization can trigger the sol-gel phase change. [25] However, the pH, temperature, and ion-induced in-situ gel methods are the most thoroughly explored.

Hydrogels that form in situ in the ocular cul-de-sac are liquid preparations that undergo phase transition in the ocular cul-de-sac to create viscoelastic gel in reaction to environmental changes. Ophthalmic drug delivery systems featuring in situ gel formation made of polymers that display reversible phase transitions (sol-gel-sol) and pseudoplastic behaviour to decrease blinking interference. Such a system can be constructed as a liquid dosage form suited for instillation into the eye that transforms to a gel phase upon exposure to physiological circumstances, therefore increasing the delivery system's pre-corneal residence period. The great majority of described in situ forming drug delivery methods are based on polymeric materials that when administered form gel matrices. Polymers studied include polysaccharides such as alginate, gellan, and xyloglucan, polyesters such as PLA and PLGA, polyethers such as PEG-PPG-PEG (Poloxamers), and mixtures of polyesters and polyethers such as PEG-PLGAPEG. [26]

4.1 Characteristics of ocular drug delivery systems

The following characteristics are required to optimize ocular drug delivery systems.

- A good corneal penetration.
- A prolonged contact time with corneal tissue.
- Simplicity of installation for the patient.
- A non-irritative and comfortable form (the viscous solution should not provoke lachrymation and reflex blinking).
- Appropriate rheological properties and concentration of viscolyzer.

4.2 Advantages of Ocular in situ gel

- Prolonged drug release
- Reduced systemic side effects
- Reduced number of applications
- Better patient compliance.
- Generally more comfortable than insoluble or soluble insertion.
- Less blurred vision as compared to ointment

4.3 Approaches for in situ gel formation

- In situ gel formation due to physiological stimuli:
- In situ gel formation due to ion-activated system
- In situ gel formation due to physical mechanism
- In situ gel formation due to chemical reactions

4.4 *In situ* gel formation due to physiological stimuli [25]

Some polymers undergo dramatic and surprising physical and chemical changes in response to modest changes in their external environment. These polymers are referred to as stimulus-responsive polymers. Additionally, they are referred to as stimuli-sensitive, intelligent, intelligent, smart, or environmentally sensitive polymers. These polymers interpret a stimulus as a signal, determine its magnitude, and then modify their chain confirmation in response.

The most extensively investigated class of environmentally responsive polymer systems in drug administration is temperature sensitive polymers. This is because temperature is a reasonably simple parameter to manage and is also simply applicable in vitro and in vivo. Gelling of the solution is initiated in this system by temperature changes, hence continuing the drug release. These hydrogels are liquid at ambient temperature (20–25°C) and gel when exposed to bodily fluid (35–37°C). The use of biomaterials whose sol-gel transition is induced by an increase in temperature is an appealing method to in situ creation. The optimal critical temperature range for such systems is ambient and physiological temperature; this allows for therapeutic modulation and eliminates the need for external heat sources other than the body to initiate gelation. [26]

Three main strategies are used in engineering the thermo-sensitive sol-gel polymeric system. Hence they are classified into

- Negatively thermosensible, which contract upon heating
- Positively thermosensible, which contractupon cooling
- Thermally reversible gel

Polymers which show temperature induced gelation are poloxamers/pluronics, cellulose derivatives [HPMC, ethyl (hydroxy ethyl) cellulose (EHEC), methyl cellulose], xyloglucan, tetronics, etc.

pH is another physiological trigger that promotes in situ gel formation. This family of polymers contain either an acidic or a basic group that accepts or releases protons in response to changes in the environment's pH. As a result, these are referred to as pH sensitive polymers. This method is mostly used in ophthalmic drug delivery systems. By utilising in situ gelling methods, it is possible to improve the drug's precorneal residence duration and thus its bioavailability. The formulation is a normal solution at pH 4.4, but gels at pH 7.4, the pH of tear fluid. Polyelectrolytes are polymers with a large number of ionisable groups [26].

4.5 *In situ* gel formation due to ion activated system

Gelation of the instilled solution is induced in this case by a change in ionic strength. It is believed that the pace of gelation is determined by the osmotic gradient across the gel's surface. The aqueous polymer solution forms a transparent gel in the presence of mono and divalent cations found in tear fluids. When the solution is administered into the conjunctival cul-de-sac, the electrolyte present in the tear fluid, particularly Na^+, Ca^{2+}, and Mg^{2+} cations, plays a critical role in initiating gelling. Gelrite or gellan gum, hyaluronic acid, and alginates are all examples of polymers that show osmotically induced gelation.

4.6 *In situ* gel formation due to physical mechanism

Gelling occurs in this process as the material collects water from the surrounding environment and then expands to fill the desired space. Myverol 18-99 is an example of such a drug (glycerol mono-oleate). Diffusion is a process that occurs when solvent from a polymer solution diffuses into surrounding tissue, precipitating the polymer matrix. Nmethyl pyrrolidone (NMP) is an excellent solvent for this type of system.

4.7 *In situ* gel formation due to chemical reaction

Certain polysaccharides, such as gellan gum, pectin, and sodium alginate, undergo phase transitions when exposed to certain ions. Gellan gum, an anionic polysaccharide, gels in situ in the presence of monovalent and divalent cations, namely Ca^{2+}, Mg^{2+}, K^{+}, and Na^{+}. Although in situ production catalysed by natural enzymes has received little attention, it does have some advantages over chemical and photochemical methods.

For instance, an enzymatic process functions well under physiological settings without the need of potentially dangerous compounds such as monomers and initiators. By adjusting the amount of enzyme, it is possible to control the rate of gel formation, allowing the combination to be injected prior to gel formation.

Photopolymerisation is frequently used to produce biomaterials in situ. A solution of monomers or reactive macromers and an initiator can be injected into a tissue location and the gel formed with the help of electromagnetic radiation. Acrylate or similar photopolymerisable functional groups are commonly employed as the photopolymerisable groups on individual monomers and macromers because they photopolymerize rapidly in the presence of a sufficient photoinitiator. Typically, ultraviolet and visible light with long wavelengths are employed. Short wavelength ultraviolet is rarely employed since it penetrates tissue poorly and is biologically damaging.

5. EVALUATIONS OF IN-SITU GEL SYSTEM

Clarity, pH measurement, gelling capability, drug content, rheological study, in vitro diffusion study, isotonicity, antibacterial activity, in vivo visual testing in rabbits, and accelerated stability studies are all evaluation factors for in situ gel formulations. The formulation should have an optimal viscosity that enables easy instillation into the eye as a liquid (drops) that rapidly converts to a gel (initiated by pH, temperature, or ion exchange). [24]

5.1 Physical parameters

Clarity, pH, gelling capacity, and drug content estimation are the physical criteria to be investigated for insitu gel solution.

5.2 Capacity

The gelling ability of the prepared formulation is tested visually by dropping a drop of it into a vial containing 2.0 ml freshly manufactured simulated tear fluid.

5.3 Rheological studies

The viscosity can be determined using a Brookfield viscometer, a cone viscometer, or a plate viscometer. The sample tube is filled with the in-situ gel composition. The formulation should have a viscosity of between 5 and 1000 m Pas before gelling and between 50 and 50,000 m Pas after gel formation. [24]

5.4 In vitro drug release studies

The Franz diffusion cell is used to analyse the in vitro release of an in situ gel solution. The best-fit model is determined by examining the diffusion mechanism underlying their kinetics. [25]

5.5 Texture analysis

The consistency, stiffness, and cohesiveness of insitu gel are determined using a texture profile analyzer. The texture profile analyzer primarily indicates the gel's strength and ease of administration in vivo. Gels with a higher adhesiveness are required to maintain an intimate contact with the mucus surface.

5.6 Isotonicity evaluation

Isotonicity is a critical property of ophthalmic preparations. To avoid tissue damage or eye discomfort, isotonicity must be maintained. All ocular preparations undergo isotonicity testing to ensure they have the desired release properties, gelling capacity, and viscosity.

5.7 Drug-polymer interaction study

Fourier Transform Infrared (FTIR) spectroscopy should be used to examine the interaction. The nature of the interacting forces can be determined throughout the gelation process by applying the FTIR and DSC method. [26]

5.8 Ocular irritancy test

The Draize irritancy test is used to determine an ophthalmic product's potential for eye irritation prior to marketing. According to the Draize test, 100l of drug is generally placed into the lower culdesac and various criteria are observed at predetermined time intervals of 1 hour, 24 hours, 48 hours, 72 hours, and 1 week following administration. [25]

6. CONCLUSION

Several infections related to the eye have been quickly rising in recent years, even though they are not life-threatening, action should be taken since eye issues require rapid recovery and relief from symptoms. Thus, several dosage forms are developed to avoid causing irritation to the eye and to facilitate administration, as the eye contains secretions such as lacrimal fluid, which results in increased drug loss, and naso-lacrimal drainage, which results in decreased bioavailability and contact time for the drug. To circumvent these issues, ophthalmic formulations can be made in solution forms containing some polymers. These polymers can aid in the production of gel when the formulation comes into contact with the eye. Numerous medications, such as those used to treat conjunctivitis and cataract, can be manufactured as in-situ gel-forming dosage forms.

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