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Ophthalmic drug delivery system for glaucoma : A Promising system

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Abstract

Poor bioavailability (<1%) of drugs from conventional delivery system to eye is mainly due to the various precorneal loss factors which include rapid tear turnover, systemic drug absorption through naso-lachrymal duct, transient residence time of the drug solution in the cul-de-sac and the relative impermeability of the drugs to corneal epithelial membrane. To provide better Patient compliance by the ease of installation and reduce the frequency of instillation .The eye is a vital organ, faces challenges in drug delivery with traditional ophthalmic formulations due to the rapid loss of medications before reaching the cornea. This review explores novel drug delivery systems for ocular administration, emphasizing innovative dosage forms, i.e., in situ gels and also nanoemulsion incorporated gelling system. This system aims to prolong drug contact time in the eyes, overcoming bioavailability issues associated with conventional delivery methods. The article further delves into in situ gelation approaches, highlighting pH-triggered, temperature-dependent, and ion-activated systems. It explores the use of excipients like polymers and solubilizing agents in the preparation of in-situ gels. The frequently used polymers and their applications in ocular drug delivery are detailed. Studies on the incorporation of nanoparticles in this gelling system for ocular drug delivery. Methodologies for evaluating in situ gels, including pH determination, rheological studies, drug content analysis, in vitro gelation, accelerated stability studies, and FTIR analysis, are presented. The advantages & applications of in situ gels are discussed, along with its limitations. The review concludes by emphasizing the benefits of novel ocular drug delivery systems, particularly in situ ophthalmic systems, which offer controlled and sustained drug release, and the future perspective of in situ gel. These advancements hold promise for more effective therapeutic outcomes in the field of ocular drug delivery.

Keywords: In situ gel, Nanoparticles, drug penetration, Ocular drug delivery, pharmacokinetics, Polymer,

A) Introduction

Glaucoma is a progressive optic neuropathy and medical therapy is the initial option for the treatment of this potentially blinding condition. Topical instillation of eye drops from the bottle is the common ophthalmic drug delivery form. Eye drops usually penetrate via corneal or scleral route, although some

conjunctival contribution is noted . The administration of pharmacological compounds from drip bottles sometimes can be problematic for a variety of reasons. First, the anterior ocular surface has limited permeability and is continuously washed by tears. The lacrimal apparatus and nasolacrimal duct drains tears and other substances from the eye to the nasal cavity. Due to limited permeability of anterior ocular surface, natural clearance and drainage, eye drops contain large amounts of inactive ingredients. Effective penetration enhancers are known as irritants causing ocular discomfort . Other disadvantages of topically used eye drops include problematic treatment schedules and difficulty in application of eye drops. Various adverse effects associated with topical medication may have a negative effect on patient adherence to medical treatment, doctor-patient relationship and patient quality of life . However, topical drugs have clear topical administration advantages and constitute a more convenient way of administration as well as avoiding hepatic first-pass metabolism . Current implantable drug delivery devices addressing patient non-compliance and fluctuations of intraocular pressure (IOP) issues, however, also have a clear limitation—it is not possible to change, increase or decrease, or stop drug delivery once it is introduced into the eye. For chronic conditions such as glaucoma, it would be optimal to regulate drug delivery depending on the therapeutic response and progression of the disease. Another difficulty with the implantable drug delivery system is that the surgical procedure for implanting is invasive and requires skillful vitreoretinal surgeon. Clinical testing is provided for drug-eluting punctal plugs investigated as sustained-release drug delivery systems for some glaucoma medication. The studies have not yet been published, but initial data from one of the trials indicates that the device did not significantly lower IOP.[1]

i) Physiological Aspects of ocular drug delivery system

The drug concentration at the receptor site is a critical determinant of rate of onset, intensity and duration of a pharmacological effect. The drug effect depends on its activity, affinity for a receptor or enzyme and ability to reach the site of action in sufficient concentration. Drug pharmacokinetics investigates drug absorption, distribution and elimination within the body . Topically administered drugs on the delivery to the site of action face medias with different vascularization (from highly vascularized inner retina to avascular lens or cornea), as well as multiform consistency tissues, from liquid aqueous humor to solid lens, thus determining different drug diffusion . After topical administration through absorption process, a drug enters the aqueous humor. Absorption is influenced by drug solubility in tears and ocular surface permeability. Conjunctival and scleral tissues have similar permeability to hydrophilic drugs, while cornea is 15–25 times less permeable. Bioavailability in ophthalmology refers to the amount of drug entering the aqueous humor. The drug is further transferred and distributed within intraocular tissues—

conjunctiva, cornea, lens, iris, ciliary body, choroid, vitreous body, retina and optic nerve. Several factors might influence availability of topical ophthalmic medication: flush by tear film, limited capacity of conjunctival cul-de-sac, dilution by tears and aqueous humor, drainage into the nasolacrimal duct, binding to melatonin or proteins, metabolism within ocular tissues. All ocular tissues are able to accumulate drugs. Large conjunctival surface and nasal mucosa allows a portion of topical drug that is not absorbed into the eye to enter the systemic circulation. Elimination from the eye occurs usually during aqueous humor turnover or passage across blood-ocular barrier.[2]

Various approaches are used to increase bioavailability of eye drops by increasing corneal penetration or drops viscosity. Ocular absorption is increased by adding cyclodextrins, solid inserts and colloidal systems to ophthalmic drugs. Higher viscosity drops are constituted of high molecular weight molecules hardly crossing biological membranes. Having a longer wash-out from the tear film viscous drops stay longer on periocular surface and increase drug delivery to the deeper ocular structures . On the other hand, high viscosity interferes with eyelid movements, vision and patient comfort. Economic situation obligates seeking for cheaper and generally conventional treatment options. Still some doubts exist if generics are exactly as effective and tolerable as branded drugs. Even having the same active ingredient, bioequivalence, however, can not be guarantied. Different size of drug particulates and pH can change its pharmacokinetics and distribution in tissues. Moreover different inactive ingredients and preservatives can determine different penetration, absorption and availability of the active agent at the site of action. Ocular surface sensitivity to inactive ingredients and preservatives in ophthalmic preparations, which are known to vary between generics and branded agents, may considerably alter distribution of drug within tissues and tolerability. Slight alteration in the IOP-lowering efficacy of anti-glaucoma drugs can have a deleterious effect on the eyes in the long-term, as it is well-known that even slight increase in IOP can aggravate progression of glaucomatous visual field loss.[3]

ii) Importance of Tear Film

The tear film is essential for maintaining the health of the cornea and conjunctiva. Since the tear film is the first and most powerful refracting surface of the eye, irregularities in the tear film thickness can cause optical aberrations in the eye. To maintain a healthy ocular surface the quantity of tears is important, but also proper chemical composition in order to nourish and protect ocular surface cells. The tear film consists of: lipid component containing wax esters, sterol esters, fatty acids and fatty alcohols; mucous component comprised of mucins that are constituted largely of sugars; aqueous component, which constitutes the bulk of the tear film, composed of 98% water but also salts, mucins, and proteins including

hyaluronan, lysozyme, lactoferrin, lipocalin, and secretory immunoglobulins. Disruption of the homeostasis of the tear film results in ocular surface inflammation, which may lead to cell damage. Abnormalities of any tear component can result in tear film instability and hyperosmolarity.[4]

The pH of healthy tears is reported to range from 7.3 to 7.7, it is influenced by dissolved substances, especially by the bicarbonate–carbon dioxide buffer system. Tear pH is lowest upon wakening due to acid byproducts associated with prolonged eyelid closure. When the eyelids are open, pH increases rapidly due to carbon dioxide loss . It is known that eye drops within pH 6–9 range do not cause discomfort, while drops with pH outside these levels increase production of tear fluid due to irritation and decrease its bioavailability by overflowing drug .[5]

Osmolarity is the measure of solute concentration, defined as the number of osmoles (Osm) of solute per liter (L) of solution (osmol/L or Osm/L) . As a measure of tear film chemistry, osmolarity can be useful for evaluating the quality of patients' tears. In general terms, osmolarity describes the quantity of solutes in a solution; in tears, it specifically refers to the concentration of small proteins and electrolytes, including sodium, potassium, and chloride. Although measuring osmolarity does not reveal the exact chemical composition of tears, it quantifies how concentrated they are, and research has shown that knowledge of tear film osmolarity can be clinically valuable for assessing dry eye disease. Tear film osmolarity could be either too low or too high. According to the generally accepted concept, the tears are isosmotic with a 1.4 per cent sodium chloride solution, and the recommendation for adjusting the osmotic concentration of collyriums to this presumed tonicity has found worldwide acceptance. Human tear film—305–310 mOsm/L. Hyperosmolarity causes ocular surface cell damage, which can be visualized by ocular surface staining. This damage occurs because ocular surface cell membranes are permeable; when they are exposed to hyperosmotic tears, water flows out of the cells in an attempt to balance the osmolarity of the intracellular fluid with the osmolarity of the surrounding tears. When this happens, ocular surface cells can become dehydrated, which damages cell membranes and changes the way proteins protect the ocular surface. A hypoosmolarity of 150 mOsm/L is subjectively well accepted by patients, but 75 mOsm/L produces irritation of the eye. The absolute hypoosmolarity (0 mOsm/L) is distillated water, which causes itching and swelling of the epithelium.[6]

iii) Innervation of the Ocular Surface

The exposed surface of the eye is richly innervated by sensory nerve fibers originated at trigeminal ganglion neurons. They reach the cornea and bulbar conjunctiva as thin myelinated or unmyelinated nerve fibers lacking of morphological terminal specialization. However, electrophysiological studies have

shown that sensory neurons innervating the eye are functionally heterogeneous. Based upon their response to specific stimuli, different functional types of sensory nerve fibers have been identified in the cornea and bulbar conjunctiva. Mechanonociceptor fibers (~20% of the total) react only to mechanical forces; polymodal nociceptor fibers (~70%) respond to mechanical forces but also to heat, exogenous chemical irritants and endogenous inflammatory mediators; cold-sensitive fibers (~10–15%) display an ongoing impulse activity at basal corneal temperatures and increase markedly their firing frequency with moderate cooling. During inflammation, surgical injury, dryness of the ocular surface activity of ocular sensory nerve fibers changes markedly as the result of short-term changes in ion channel expression secondary to local release of inflammatory agents and growth factors, and of long-lasting modifications in gene expression. This leads to the development of spontaneous activity and of abnormal responsiveness to natural stimuli. In addition to their role in the production of conscious innocuous and noxious sensations referred to the eye surface, sensory fibers appear to play a role in the maintenance of the ocular surface homeostasis, including basal and reflex modulation of tearing and trophic maintenance of corneal and conjunctival tissues .[7]

iv) Effect of Topical Medication on Ocular Surface

Topical glaucoma medications have been associated with ocular surface disease as after instillation drops interact with ocular surface tissues. This interaction can involve the active agents themselves or the preservatives used to keep the bottles sterile and/or to stabilize the active agents in solution. Most preservatives act like detergents and might also influence corneal permeability of topical drugs by causing epithelial separation . The most popular preservatives are the cationic surfactants including the widely used benzalkonium chloride . As a surfactant, benzalkonium chloride can increase solubility of drugs that are hydrophilic and exert their bactericidal effect by emulsification of bacterial cell walls. Ocular damage from these agents is most likely due to emulsification of the cell membrane lipids . BAK has been shown to be toxic to conjuctival and corneal endothelial cells . It has also been shown to cause opacification increased hydration and corneal thickness and also cause irritation and redness of the eye. BAK being cationic detergent causes epithelial toxicity and is also responsible for a shortening of the tear film break-up time, disruption of surface cell layer and slowing down of the epithelial healing process. Studies have shown that other preservatives had similar effects on ocular surface . Overall, it seems that preservatives damage corneal epithelium but they enhance the permeability of the cornea at the same time. Higher drug penetration is usually associated with a better pharmacological effect. However, the systemic absorption of the drug via the conjunctiva or the nasal mucous layers also enhances . This effect is often problematic for drugs with potent systemic activity, like timolol. It could be argued for the cautious use of these

compounds. Nowadays single dose containers are available that do not contain preservatives. It could increase patient's compliance for those who have sensitive or dry eye but should be considered for older or patients with movement restriction in arms, hands or fingers. One of the ways to increase corneal penetrations is by increasing the lipophilicity of the drug. Latanoprost (Xalatan), travoprost (Travatan) are examples of prodrugs developed for this purpose. The ester group in these compounds increases their lipophilicity and enhances corneal permeability. These prodrugs are then converted into the active drugs, the acidic forms, by the esterase enzymes in the cornea. Prodrugs allow increase penetration into the anterior chamber and may reduce local and systemic side effects by decreasing the concentration of drug required .[8]

Ocular surface disease becomes increasingly more common with age and glaucoma is also more common in older age. Elderly patients on long-term glaucoma treatment with multiple topical medications ultimately have an increased risk ocular surface disease that might contribute to poor patient compliance and disease progression . It is also important to note that with age there is an activation of glia within the optic nerve head, an increase in extracellular matrix a decrease in retinal ganglion cells, leading to accelerated progression of the glaucomatous process and more aggressive treatment is required.[9]

v) Mechanism of Action of Topical Hypotensive Medications

For the treatment of glaucoma IOP can be lowered by three basic mechanisms: suppression of aqueous humor formation, increase of trabecular outflow and increase of uveal outflow. To influence the conventional outflow pathway, drugs must be delivered to the trabecular meshwork and the longitudinal portion of the ciliary muscle and possibly to the episcleral vessels and myofibroblast of the scleral spur. To influence uveoscleral outflow drugs must be get to the interstitial tissue of the ciliary muscle. To affect aqueous secretion drugs must be targeted to the ciliary processes, which is the chief target of the beta-blockers. Beta-adrenergic receptors (β1 and β2) are widely distributed in the eye. They are found at the ocular surface, in the ocular vessels, trabecular meshwork, lens epithelium, ciliary body and retina. B2-receptors predominate in the ocular tissues, including the ciliary processes, where they represent 75–90% or more of the β receptors . Beta blockers are competitive antagonist of the β-adrenergic receptors. They inhibit the activation of these receptors in the ciliary processes by blocking the binding of endogenous adrenergic neurotransmitters. By this blockade cyclic AMP level is decreased and consequently aqueous humor production is suppressed . Carbon anhydrase in the eye is most abundant in the ciliary body, mainly type II and IV, but can be found in other ocular tissues as well. Carbonic anhydrase inhibitors (CAI) inhibit the carbonic anhydrase in the ciliary epithelium and reduce the production of bicarbonate

ion, which is critical component for active ion transport in aqueous formation. A reduction in bicarbonate limits sodium and fluid transport across the ciliary epithelium and decreases aqueous humor production The primary mechanism by which most prostaglandins (PGs) reduce IOP is by increasing outflow, especially through the uveoscleral outflow pathway, possibly by relaxation of the ciliary muscle and lysis of the extracellular connective tissue matrix rather than by reducing aqueous humor production . PGs specifically bind to PG receptors present in almost all ocular tissues.[10]

B) Nanotechnology for ocular delivery

The eyes are the most important part of the body . The ocular system is particularly intriguing due to its unique drug disposition characteristics. In the treatment of eye ailments, topical delivery is favoured over systemic delivery. Any medicine taken through the ocular route must first pass through the precorneal barriers . When a drug, in an appropriate dosage form, is instilled, it causes tear production, which lowers drug availability . These limitations impose restrictions on controlled drug delivery to the eye. The creation of viscous gels can also extend precorneal drug retention. Microparticle/Nanoparticle suspensions or polymeric solutions may serve as bioadhesive systems .Furthermore, these systems offer better sustained release properties compared to drops. They are currently used in various eye diseases such as glaucoma, dry eye syndrome, and eye infections . The bioavailability problem with conventional ocular eye drops can be addressed by employing a gel system. These systems, when administered as eye drops, covert into the gel and provide high bioavailability of the drug. Upon phase transition, the resulting gel should exhibit sufficient strength, ensuring prolonged residence times in the eye. Its capability to provide prolonged drug release is decreasing the necessity for frequent administration. Depending on the approach used to induce the transition from a solution to a gel state on the eye surface.[11]

i) Materials used for preparing in situ gel

A particular ingredient must be used in the creation of in situ gels to obtain the appropriate gelation characteristics.[12]

a) Polymers

In the context of medication delivery, a polymer is a big molecule made up of structural units that repeat and are usually joined by covalent connections. Because polymers can regulate drug release, increase bioavailability, and boost therapeutic efficacy, they are essential components of drug delivery systems .Polymers are frequently utilised to create sustained-release systems for in situ ocular drug administration, which allow medications to be administered to the eye over an extended period of time. This system can

reduce side effects, increase patient compliance, and extend the duration that medications remain on the surface of the eyes .[13]

Carbopol 934P:

Carbopol is a cross-linked polyacrylic acid derivative with a high molecular weight and high mucoadhesive properties, also known as acrylic acid polymer or carbomer. This polymer,is sensitive to pH. When the pH is increased above its pKa value of around 5.5, it exhibits the sol to gel transition in an aqueous solution. The acidic nature of Carbopol may irritate the eyes as its concentration rises. Cellulose addition will lower the concentration of polymers and enhance the gelling property.[14]

Cellulose Acetate Phthalate:

Cellulose Acetate Phthalate shows a buffer capacity enough to gel successfully in the eye's cul-de-sac with cellulose acetate phthalate & derivatives. The very fluid latex transforms into viscous gel nearly instantly upon the formulation's instillation into the eyes, resulting in a pH shift of around 2.8 units. Because latex is a free-running solution at pH 4.4, it becomes gel when the pH is elevated to pH 7.3 by tear fluid. Cellulose acetate phthalate latex is a polymer with potentially beneficial features for prolonged medication administration to the eye .[15]

Chitosan:

Chitosan is an amino polysaccharide .It is a cationic, pH-dependent, biodegradable, biocompatible, and temperature-sensitive polymer. Because of its electrostatic interaction with charged mucosal surfaces, it possesses exceptional mucoadhesive characteristics and antibacterial properties .Chitosans can interact with ions of opposite charges in a typical pH range of 4–6, leading to gelation .[16]

Poloxamers:

Pluronics, a commercial name for poloxamers , is used in thermosensitive in situ gels that are known for their exceptional thermal setting properties, which extend the duration that medications remain effective. The two segments of these water-soluble tri-block copolymers are polyethylene oxide (PEO) and polypropylene oxide (PPO). The most widely used poloxamer in the pharmaceutical industry, Pluronic F127, is chosen because it can create clear, colorless gels. Pluronic F127, which is composed of 70% PEO and 30% PPO, functions as a useful polymer in in situ gel compositions. Pluronic F127-g-poly (acrylic acid), a copolymer, has been used as an in situ gelling agent to increase bioavailability and lengthen the duration of drug residence in ocular applications .[17]

Gellan gum:

Gellan gum is a polysaccharide obtained by the fermentation of Pseudomonas elodea .It is commercially known as GelriteTM. It is a water-soluble, hetero-anionic polysaccharide that exhibits temperature-dependent characteristics. It is thermally stable. Like alginate, gellan gum can gel when it comes into contact with divalent or monovalent metal cations or monovalent cations . Double-helical junction zones are formed during the gelation process, and these segments then aggregate to form three-dimensional networks by complexing with cations and forming hydrogen bonds with water. It is noteworthy as one of the polymers that is used most frequently in the manufacture of in situ gels .The gellan gum in situ gel exhibited significantly better stability compared to commercially available brinzolamide eye drops .[18]

b) Solubilizing agent

A solubilizing agent is a material that improves a drug's solubility in a certain formulation. Solubilizing compounds are essential for increasing the solubility and bioavailability of pharmaceuticals in the setting of in situ ocular drug administration .This helps to ensure that the drugs can be transported to the targeted ocular tissues efficiently. These substances can be especially helpful when handling medications that are hydrophobic or have low water solubility. One popular class of solubilizing chemicals utilised in ocular formulations is surfactants. They can interact with lipids and water because they have both hydrophilic and hydrophobic areas. This helps solubilize medications that are hydrophobic. Surfactants have the ability to encapsulate drugs in micelles or other structures, thereby increasing their solubility. For instance, a hydrophobic medication is used to treat a particular eye ailment. The drug's solubility in the eye drops can be improved by incorporating a surfactant, like cremophor or polysorbate 80, into the formulation .This guarantees that the medication is evenly distributed within the tear film at the time of instillation, resulting in enhanced absorption and therapeutic effectiveness.[19]

ii) Various approaches for making in situ gelation

pH-Triggered Systems:

Using pH-sensitive polymers with basic or acidic groups, the in-situ gelling technique forms gels at a pH of 7.4. Polyelectrolytes, or polymers that react to pH variations, are used in ocular formulations. Depending on changes in the pH of the surrounding medium, namely between the pH during production and the pH of lacrimal fluid, these polymers go through a sol-gel transition. Alterations in the ionisation state of weakly basic (ammonium) or weakly acidic (carboxylic or phosphoric) groups within the polyelectrolyte affect this transition. These groups' pKa values, which range from 3 to 10, and the

molecular weights of the polymers dictate the pH at which they ionize. A change in ionisation causes modifications to the system's swelling, solubility, and conformation. Certain pH-responsive polymers' gelling methods and properties are influenced by temperature, ionic strength, and salt content, among other things .[20]

Temperature-Dependent Systems:

One popular kind of stimuli-responsive gel that may be easily inserted into the eye without causing discomfort or blurriness is temperature-sensitive in-situ gel. At 35 °C, the precorneal temperature, it turns into gel.At temperatures below the lower critical solution temperature (LCST), thermo-responsive systems that experience a phase shift begin as transparent, homogeneous, and freely flowing polymeric solutions. The solution becomes hazy as the temperature approaches the LCST because of the polymeric chains breaking, aggregating, and increasing light scattering. Phase separation takes place beyond the LCST, separating the solution into a gel phase and a solvent phase—typically water. The primary force behind this separation is the entropy effect, which favours phase separation as temperature rises.[21]

Ion-Activated Systems:

Ion-activated systems undergo conversion due to changes in ionic concentration. They crosslink with the cation present in the tear film and form gel.A sol-gel transition and an increase in polymer viscosity can be caused by crosslinking anionic polysaccharides with cations available in lacrimal fluid. There is a clear correlation between the concentration of cations and the increase in polymer viscosity . As a result, increasing tear production in an effort to dilute the viscous solutions would raise the concentration of cations. Consequently, this would lead to an increase in polymer viscosity, which would prolong the duration of drug retention in eyes, decrease nasolacrimal drainage, and improve drug bioavailability.[22]

iii) Method of Preparation of in situ gel

The required quantity of polymers and co-polymers is dispersed in water to generate the polymeric solution. The final solution contained preservatives like benzalkonium chloride, buffering agents such as NaOH and citric acid to adjust the solution to the required PH, and osmolality agents such as NaCl to maintain the osmotic pressure according to the eye. The final volume of the resultant in situ gel eye drop is maintained using the distilled water .These formulations with stimuli-responsive polymers are sensitive to pH, temperature, and ion concentration form gel instantaneously upon ocular instillation. Combining multiple stimuli-responsive polymers in one formulation may improve gelation results.[23]

iv) Evaluation of in situ gel

Visual Appearance and Clarity: To detect the presence of any particle matter, visual appearance and clarity were assessed using fluorescent light against a white and black background. In order to assess clarity, the formulation must be visually assessed against a backdrop of black and white in appropriate lighting. Generally applied to liquid forms (suspensions excepted), it is thoroughly documented in Pharmacopoeia.[24]

Rheological Studies: Determining the length of time a drug remains in the eye is crucial taking into account the injected formulation's viscosity .The ready-made mixtures were left to gel at physiological PH, and a Brookfield viscometer was used to determine the viscosity after that. The flow pattern examined by plotting the shear rate vs. shear stress graph. A drug's bioavailability and comfort level following injection can both be impacted by the rheological parameter. Tears quickly lose their fluids or solutes, resulting in a brief period of contact with the eye, high drainage rates, and improved drug bioavailability. Increases in viscosity are possible, but they may be uncomfortable because vision problems, a feeling of a foreign body, and harm to the ocular epithelia as a result of an increase in reflex tears and blinks caused by shear stress during blinking lead to quicker elimination .[25]

Drug Content Analysis: A spectrophotometric approach used to analyse the drug content of manufactured in-situ gelling solutions. Pipetting 0.1 ml of each optimised formulation and diluting it with up to 100 ml of Simulated Tear Fluid (pH 7.4). The absorption was measured with a UV-Visible spectrophotometer .[26]

In vitro gelation: The formulations combining sodium alginate and HPMC had a gelling capability of Assessed. To execute the procedure, a drop of polymeric solution was added to vials holding one millilitre of Simulated Tear Fluid to equilibrate at 340 degrees Celsius. The gel formation then visually evaluated .[27]

Studies on Accelerated Stability: The stability testing done on the optimised sterile formulation. Glass vials containing sterile, optimized ocular formulations were filled, sealed, and fastened with grey butyl rubber closures. An aluminium bottle. A few sterile formulations were kept at room temperature, 4±1 °C. 27.11 °C, drug content evaluated at periodic intervals, clarity, PH, rheology, in vitro drug release, and sterility.[28]

Sterility Testing: This procedure carried out to identify the existence of living microorganisms in the sample. The samples underwent sterilisation using UV radiation. A Soyabean Casein Digest Medium sterilised through autoclaving at 121 °C for 15 minutes under 15 lbs of pressure. Subsequently, the

sterilised preparations were introduced into bottles containing the nutrient medium and allowed to incubate for 7 days to monitor microbial growth .[29]

C. Nanoparticles incorporated in situ gels

Nanoparticles have been incorporated into in situ gel systems to enhance drug permeation and drug bioavailability at the ocular surface while using the benefits of in situ gelling systems to improve precorneal retention . A heterogeneous system of liquid-in-liquid dispersions composed of oil and water stabilized by surfactant and co-surfactant molecules, with a drop of the sub-micron size range of 5-200 nm, is known as a nanoemulsion. It is also referred to as a miniemulsion, ultrafine emulsion, and a submicron emulsion. It is kinetically and thermodynamically stable, optically clear and transparent . According to the definition, there are three different forms of nanoemulsions. Water in oil (W/O) is a dynamical framework in which an O/W or W/O emulsion is allocated in oil or water separately when oil is dispersed in continual fluid phases in an oil-in-water (O/W) system. Other conceivable emulsions include those that are either O/W/O or W/O/W . The charge on the surface of a nanodrop determines whether an emulsion is neutral, anionic, or cationic. Nanoemulsions have higher solubilization volume contrasted with basic micellar fluids and are helpful over different scatterings like emulsions and suspensions because of their thermodynamic solidness prompting expanded timeframe of realistic usability. Because of their little size, nanoemulsions have more noteworthy surface region per unit volume, optical straightforwardness, tunable rheology, uniform size circulation and more prominent soundness with practically no shallow flocculation or mixture during long haul stockpiling. Their drawn-out security, simplicity of definition and high solubilization of medication particles make them a competent medication conveyance implies .[30]

i) Preparation Techniques

Blending oil and watery stages shapes a coarse emulsion in the presence of emulsifier that might change into nanoemulsion immediately or by spreading high shear generally used to decrease the bead size to the nanoscale. Nanoemulsion requires the inclusion of an enormous amount of either surfactants or energy and at times blend of both.[32]

High energy techniques

High-pressure homogenization, ultrasonication, and micro fluidization are examples of high-energy procedures that use mechanical devices to produce highly disruptive forces that can break down oil and water phases into nanoscale droplets. While ultrasonication is primarily used at the laboratory size,

nanoemulsion synthesis by high-pressure homogenization and micro fluidization can be done on an industrial scale as well.High- pressure homogenization (HPH) . Delivering nanoemulsions with tiny beads as small as 1 nm and predicted polydispersity records employing a few powers like water-driven, main areas of strength for shear, and cavitation is known as high-pressure homogenization. In this strategy, two fluids, watery stage and oil stage alongside surfactant/cosurfactants are gone through a little hole at high tension (500-5000 psi) Most importantly, the emulsion is outlined in a gigantic piece of the dissipated stage and maybe debilitated consequently. During emulsification by using the high stage volume extents, the issue of mix could arise, in any case, this can be lessened by adding an additional proportion of surfactant. You can utilize surfactant mixtures that exhibit a greater decrease in surface tension over the main components . The surfactant is likely added in the dispersion stage, followed by an addition in the persistent stage, which typically results in smaller drops. Expanding the force in advances is likewise valuable, especially with nanoemulsions having an exceptionally thick scatter stage. The significant drawback of this procedure is the age of bountiful intensity that might prompt debasement of emulsion parts exactly those are thermolabile and can create just oil-in-water type fluid nanoemulsion having under 20% of oil part while nanoemulsions of high thickness with a mean drop breadth under 200nm can't be formed .[33]

Phase inversion composition (PIC)

In this method, water is combined with an oil-surfactant mixture to form an emulsion. The higher propensity of surfactant for water aids in emulsification with handling, where a compound energy is set by the change from positive to negative (getting water- in-oil nanoemulsions) or from negative to positive (getting oil-in- water nanoemulsions) because of bend changes in surfactant particles and is responsible for the development of nano beads .[34]

Phase inversion temperature (PIT)

This technique is dependent on the non-ionic surfactants' temperature-dependent dissolvability. In this procedure, the components of the emulsion, such as the oil, surfactants, and water, are mixed at room temperature. The development of oil-in- water nanoemulsions is enabled by the highly hydrated (hydrophilic) headgroups of non-ionic surfactants at low temperatures, and the surfactant monolayer exhibits a positive turn. At higher temperatures, the bottom o/w emulsion undergoes phase inversion, pushing toward the configuration of water-in-oil nanoemulsions, and the surfactant fully dissolves in the sleek stage. As temperature increases gradually, the surfactant headgroups become bit by bit dried out (lipophilic). Subsequently, the surfactant monolayer shows negative curve. As this method includes

warming techniques, it conceivably will stay hard to consolidate thermolabile medications. In any case, the utilization of a mix of surfactants with suitable designs can have the option to decrease the PIT of scattering, reducing the corruption of emulsion parts .[35]

Spontaneous emulsification

This process produced nanoemulsions at ambient temperature without the need of any natural solvent or heat, which attracted the attention of inventors in a variety of sectors, including the medicinal sciences .Dynamically steady nanoemulsions with minor drop size really low created by blending the scattered stage in with a surfactant which is taking a high partiality to the ceaseless stage and afterward adding this homogeneous combination to the consistent stage with slight mixing at a constant temperature. The stage changes during the emulsification interaction are responsible for the unconstrained nano emulsification and incorporate lamellar fluid translucent stages. The unconstrained nano emulsification process produces nanoemulsions, however despite their potential for high dynamic energy and long-term colloidal strength, they are not thermodynamically stable .[36]

ii) Applications of nanoemulsions

Nanoemulsions as reasonable vehicles are finding applications in different regions like food, beauty care products, drugs, and material combination and quality treatment. Coming to the medication conveyance perspectives, nanoemulsions have proactively demonstrated as ideal medication conveyance frameworks at the examination level likewise couple of items accessible on the lookout. Nanoemulsions gained rising interest as good vehicles for cosmetics mostly used as moisturizers and creams due to its lipophilic interior with small-sized droplets that transports the lipophilic active in a controlled and effective manner supporting the skin diffusion and up rolling their concentration in the skin. Nanoemulsion is gainful as its parts hold their bioactive properties like reinforcing the skin boundary capability by diminishing the trans-epidermal water misfortune and creating a smooth skin feel. Moreover, its ability to overcome the stability difficulties associated with microemulsions like creaming, sedimentation, flocculation or coalescence ended up nanoemulsion appropriate for the cosmetic world . The fundamental detriment connected with the foundational organization of visual medications is that, without a doubt, very little part of the regulated medication compasses to the objective. Visual medication conveyance can be changed into nano- sized definitions that can conquer downsides of regular eye drops .Because of their many advantages, such as supported drug delivery and high capacity to expand the medication pervasion through the visual blockades prompting enhanced remedial degrees of medication into the deeper layers of the visual design and the fluid humour, stable nanoemulsions that are stable upon weakening continue

to be effective medication conveyance frameworks for ophthalmic use. The targeting of visual or medicine to particular cell foci in the organs has not yet yielded any investigation outcomes. Nonetheless, it is plausible to foster nanocarriers for focusing on medication to suitable cells in the visual fields with the proof of the pathophysiological as well as latent focusing on approaches utilized in malignant growth chemotherapy .[37]

D) Future perspectives for in situ gel

In-situ gel technology is an innovative drug delivery system that employs sol to gel transitions upon administration, enabling controlled and sustained drug release .These gels are made from crosslinked polymer networks and have numerous applications in drug delivery and disease treatment. However, further research is needed to address issues such as drug degradation. The technology can be customised to meet individual patient needs, enhancing patient compliance. Additionally, it can carry multiple drugs simultaneously, potentially transforming the treatment of complex diseases. Future uses of in situ gels include the delivery of proteins, peptides, and drug molecules, protecting them from degradation by providing targeted and localised release .The in situ gelling system for ocular drug delivery is a well-studied strategy that can prolong precorneal residence time and provide sustained drug release, improving ocular bioavailability and therapeutic efficacy while reducing systemic absorption and toxicity. Exploring the integration of different drug delivery approaches, such as nanoparticles loaded into in situ gels, is an attractive strategy for enhancing ocular drug delivery. Given the eye's sensitivity, safety is a crucial parameter for ocular formulations. Most studies reviewed indicate that in situ gels do not cause significant cytotoxicity or irritation. However, further research is needed to assess the potential toxicity of repeated and long-term use, as well as the materials used in nanoparticle-based systems. Increased viscosity in in-situ gels can cause issues like blurred vision and discomfort, leading to faster elimination due to reflex tears and blinking. Therefore, careful control of viscosity is essential during formulation design and optimisation to mitigate these limitations .

Future strategies should focus on developing formulas with multiple ingredients, such as traditional Chinese medicine, which uses a multi-target approach. Additionally, there is an expectation for new and more reliable in-situ forming polymers responsive to biochemical markers associated with eye diseases. Improved ocular permeation over longer durations would provide sufficient contact time for managing ocular diseases. The simple and economical preparation methods will facilitate industrial scale-up. These formulations can be further processed for large-scale batches and pharmacological evaluation through in-vivo studies.

The future of in situ gels is promising, with potential for innovative drug delivery solutions and applications across various industries, including cancer and ulcer treatment. In situ gels can also be utilised as templates for tissue engineering and cell transplantation by releasing growth factors and other bioactive molecules in a controlled manner to promote tissue regeneration. Combining in situ gels with 3D printing technology could lead to patient-specific drug delivery systems . Different types of stimuli-responsive gels, such as temperature, pH, and ionic, can be developed for remote drug release control. Incorporating in-situ gels into implantable devices like wound dressings can provide sustained drug release at target sites. The in-situ gel system is a dynamic field with ongoing research, and further technological advancements may lead to new applications beyond those currently envisioned.

Conclusion

Novel drug delivery has the benefit of enhancing drug bioavailability and surrounding ocular barriers to ensure more effective therapeutic outcomes. The controlled and sustained release offered by these systems stands out, allowing for prolonged therapeutic effects and minimising the need for frequent administrations. Improved patient compliance is another noteworthy advantage, as the convenience of less frequent dosing and reduced side effects contribute to better treatment adherence. The present review article discusses in situ gel formulations that hold significant promise for ocular drug delivery due to their ability to overcome various challenges associated with conventional eye drops. The materials used specially the polymers used for making in situ gel were discussed. The method of preparation outlined in this article provides a systematic approach to developing in situ gels, ensuring uniformity and reproducibility in formulations. Evaluation of various parameters such as visual appearance, pH, rheology, drug content, gelation, stability, FTIR analysis, and sterility testing confirms the quality and reliability of the formulations. Further research and development in this area is warranted to explore new formulations and optimise existing ones for enhanced therapeutic outcomes in ocular treatments. Within the realm of novel ocular drug delivery systems, in situ ocular systems present unique advantages. Their transformation capabilities enable the transformation of solutions into gels upon exposure to physiological conditions, ensuring prolonged drug retention. The ease of administration, coupled with the ability to form a gel in situ, makes these systems user-friendly and convenient for patients.

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