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"Developments In In Situ Gelling Drug Delivery Systems For Non-Parenteral Administration Routes: Recent Progress"

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Abstract

The creation of an efficient delivery method for ophthalmic medications is hampered by the physiology, living structure, and natural chemistry of the eye. Conventional formulations lead to low bioavailability and insufficient pre-corneal residence time. Sustained-release in-situ gels are one novel drug delivery technique that addresses these problems. They prolong the time that the drug remains in the mucosa, decrease ocular haze, and delay the release of the drug. Furthermore, in-situ gels reduce the frequency and quantity of pharmaceutical delivery, prevent drug accumulation and side effects, and give precise and repeatable dosages. It also provides in situ gelling nano emulsions, liposomes, nanospheres, and microspheres. This review focused on definitions, types, advantages, disadvantages, polymers used and suitable characteristics of polymers, preparation of in situ gels and approaches of in situ gels.

Keywords: In-situ gel, sustained release, bioavailability, polymer, approaches of in situ gel

Introduction

Many challenges stand in the way of developing an efficient method for delivering ophthalmic medications due to the distinct physiology, living structure, and natural chemistry of the eye. Moreover, the traditional ophthalmic formulations quick and thorough removal of the medicines from the pre-corneal lachrymal fluid by solution drainage, lachrymation, and ineffective absorption by the conjunctiva result in a brief pre-corneal residence time and low bioavailability.[1] Sustained release in-situ gels are one of the novel drug delivery techniques that have been studied in an attempt to mitigate the shortcomings of traditional ophthalmic formulations.[2] A sol-gel transition occurs when in situ gel-forming solutions are instilled as drops into the eye. Prior to being delivered, they exist in a sol-state and can gel in response to a range of endogenous stimuli, including changes in pH, temperature, and the presence of ions. [3,4]

Polymer chains can be crosslinked chemically (covalent crosslinking) or physically (non-covalent crosslinking), and this is what causes gelation. Next, an in-situ-produced gel releases a medicine in a controlled and sustained manner. Biodegradable polymers that are both synthetic and organic are used to create in-situ gels. Examples of these polymers include xyloglucan, gellan gum, pectin, and alginic acid. [5,6]

Anatomy of the Ocular System

Among the five senses, vision is used the most and is the main way we take in information from our environment. Visual information makes up about 75% of the information we are given about the world we live in. The sclera on the outside, the choroid layer in the middle, the ciliary body and iris, and the retina (which is made of nerve tissue) on the inside make up the three layers that make up an eye's wall. The eye is a sphere-shaped organ thick fibrous covering known as the sclera shields the cornea, a transparent area at the front of the eye that allows light into the lens, from the white interior tissues of the eye. [7] The choroid layer, situated in the sclera, contains many blood vessels that have transformed into the pigmented iris, or colored area of the eye (blue, green, brown, hazel, or grey). the clear, translucent cornea that swells in front of the eye and transfers images to the brain's core. The developed cornea has a radius of roughly 7-8 mm and is made of vascular tissue. Oxygen and nutrients are supplied to the cornea by blood vessels at the junction of the sclera, lachrymal fluid, and aqueous humor. The five layers that make up the cornea—the epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium are the main entry points for medications into the eye.[8]

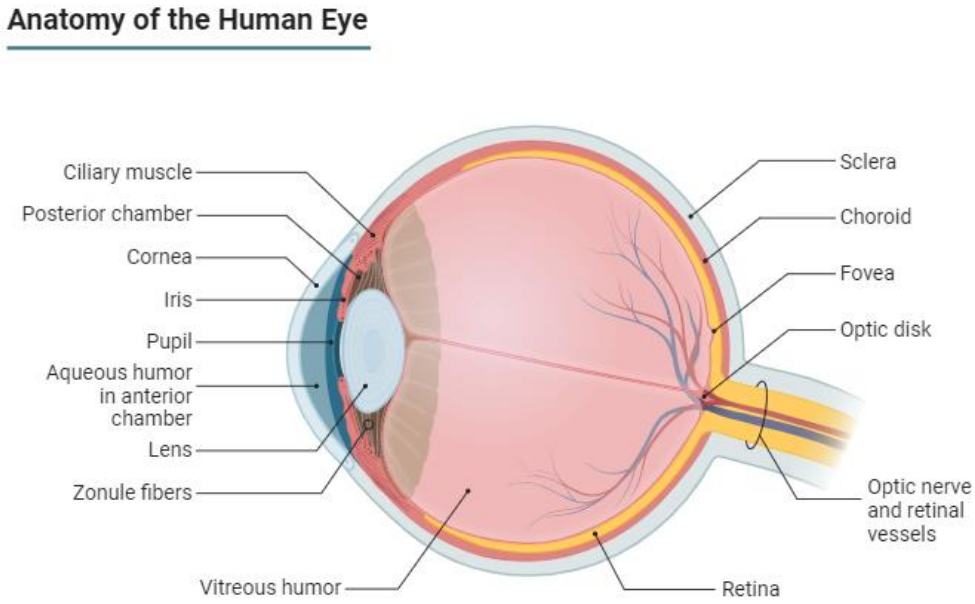

Fig.- Anatomy of eye

Ocular Barriers

The term ocular barriers typically refer to protective mechanism or structures associated with the eyes that prevent or limit the entry of foreign substances or pathogens. These barriers are essential for maintaining the health and proper functioning of eyes. Here are some key ocular barriers:

Corneal barriers

The cornea serves the crucial functions of guiding and safeguarding light on its path to the retina. The presence of endocrine cells acts as a barrier against large molecules and hydrophilic therapeutic substances. Meanwhile, the hydrophilic thick stroma prevents lipophilic medicines from passing through (Varela-Fernández). Maintaining corneal transparency is not the sole purpose of the endothelium; it also selectively permits the entry of hydrophilic medications and macromolecules into the aqueous humor. Several factors influence corneal penetration, including drug ionization, molecular mass, charge, and hydrophobicity. The transcorneal penetration mechanism restricts the movement of drugs from tears to the aqueous humor.[7]

Blood-ocular obstructions

Exogenous chemicals encounter obstacles in reaching the circulatory system due to the presence of two protective barriers in the eye: the blood-retinal barrier (BRB) and the blood-aqueous barrier (BAB). The BAB, situated in the anterior part of the eye, acts as a filter, hindering the passage of numerous intraocular drugs but allowing the entry of hydrophobic and smaller treatments, In comparison to larger and hydrophilic pharmaceuticals, these medications are excreted from the body more quickly in the frontal area. For example, inulin clears more slowly than pilocarpine.

These cells, known as retinal pigment epithelium and endothelium, are found in BRB, the back of the eye. It prevents water, plasma, and poisons from damaging the retina. [9]

Drug loss by lacrimal fluid

Tear film, the precorneal barrier, lowers the effective concentration of medications administered because of drug molecule binding to tear proteins, faster clearance, and dilution by tear turnover (1µl/min). While the size of a cul-de-sac is just 7–10 µl, the dosage amount of an instillation is typically 20–50 µl. The extra volume may escape through the nasolacrimal duct or overflow onto the cheek.[8][10]

Conjunctiva

The conjunctiva is a thin, transparent membrane that covers the front surface of the eye (except the cornea) and lines the inside of the eyelids. It helps protect the eye from pathogens and foreign objects and produces tears to keep the eye moist.[9]

In situ gel

A sol-gel transition occurs when in situ gel-forming solutions are instilled as drops into the eye. Prior to being delivered, they exist in a "sol-state" and can gel in response to changes in endogenous stimuli, including changes in pH, temperature, and the presence of ions. Gelation is the result of either covalent or non-covalent crosslinking in polymer chains, which can occur chemically. After that, a medication is released gradually and under controlled using an in-situ-produced gel. In-situ gels are made from both synthetic and organic, biodegradable polymers. Alginic acid, xyloglucan, gellan gum, and pectin are a few examples of these polymers.[11]

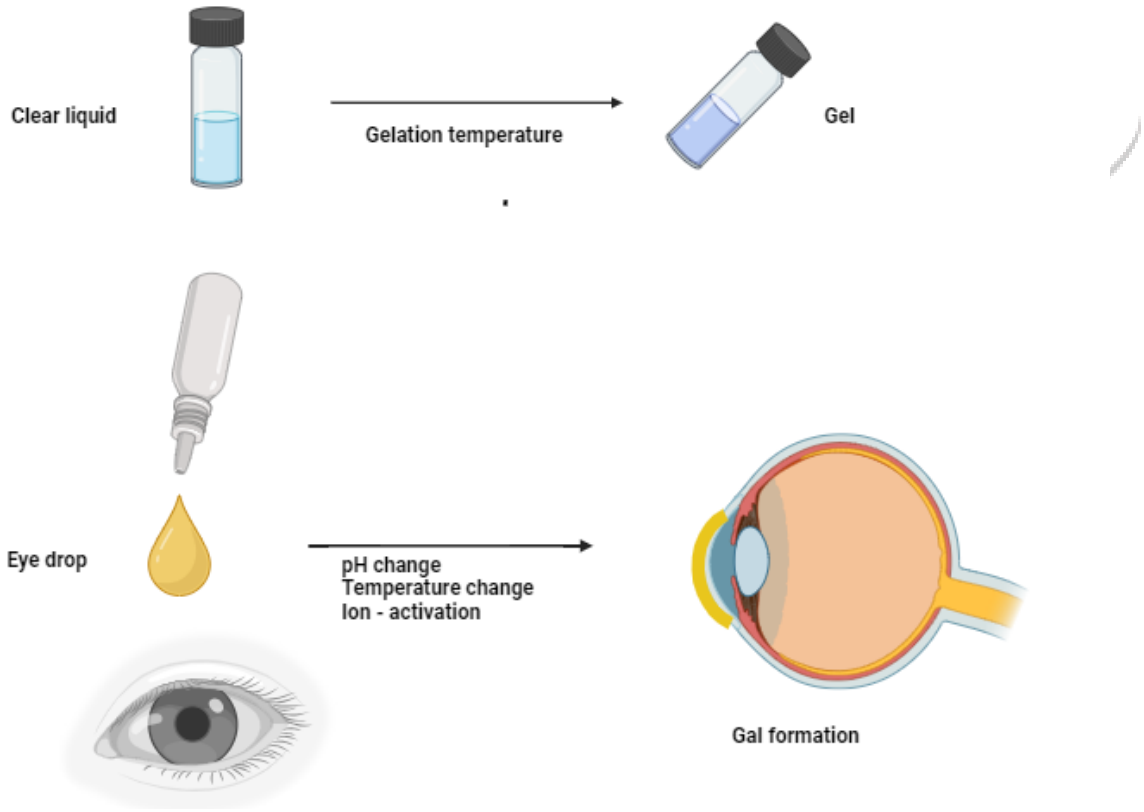

Fig. – In-situ forming gels process. The formulation is liquid when instilled into the eye which undergoes gel formation rapidly in the cul-de-sac of the eye in response to environmental changes such as pH, temperature and ion; finally release the drug slowly under physiological conditions.

Ideal requirements of ophthalmic in situ gels

- It should undergo sol-gel transition immediately after the ocular administration.[12]
- Provide sustained drug release for prolonged periods.[13]
- It should have good contact time with corneal tissue to improve corneal drug residence. [11,13]
- Should have appropriate rheological and bioadhesive properties. [6,14]
- It should be sterile and isotonic with eye secretions. [14]
- It should to non-irritant and non-toxic to ocular tissues. [14]

Advantages of in situ gel

- It offers more bioavailability. [15]
- Reduced dosing frequency. [16]
- The low dose will prevent drug accumulation and reduce drug toxicity. [16]
- To deliver controlled and sustained medication delivery. [17]
- To extend the corneal contact time in order to boost the drug's ocular absorption. Effective adhesion to the corneal surface can accomplish this.[15,17]
- To get across barriers such as conjunctival absorption, lacrimation, and drainage.[18]
- To provide the patient more comfortable, increase their compliance, and enhance the medication's therapeutic effect.[18]
- To give the delivery system superior housing.[18]

Disadvantages

- High levels of fluids are necessary. [19]
- The drug's solution form is more prone to degradation [20].
- Stability issues could arise as a result of chemical degradation [21].
- After taking the medication, there should be a few hours of limited eating and drinking [22].
- Merely modest dosages were given [23].
- It may dissolve too soon because of its limited mechanical strength [24].
- The quantity and uniformity of drug loading into hydrogels may be restricted, especially for hydrophobic medicines. [25]

Suitable characteristic of polymers

A polymer is a necessary component in the production of preformed and in situ gel. The following list of appropriate polymer properties for in situ gels: [25-28]

- It ought to be harmonious.
- It shouldn't have any harmful effects.
- It ought to possess strong optical clarity and tolerance.
- It should exhibit pseudo-plastic behavior.
- It should be able to stick to mucous membranes.
- It should be capable to reduce viscosity when shear rate increases.

Classification of in situ gelling polymer

Polymers can be categorized according to the method of gelation or their place of origin. A source in situ claims that there are two categories for gelling systems.

i. Natural polymers, such as xanthan gum, xyloglucan, alginic acid, carrageenan, chitosan, guar gum, gellan gum, pectin, and sodium hyaluronate.

ii. Polymers that are synthetic or semi-synthetic (such as poloxamers, CAP, HPMC, MC, PAA, and PLGA).[28]

Preparation of in situ gel

The polymer might differ based on the advancement of in situ gelling technologies.

A

Specified amount of drug

+

Selected buffer solution

↓

B

polymer + distilled water

↓

covered and left for at least 24 hrs

↓

After that using magnetic stirrer until the polymers completely dissolving

↓

After aqueous drug solution, transferred to a primarily prepared polymeric solution with continuous stirring until to get a homogeneous solution

↓

add excipients based on the delivery system

↓

Finally, make up the volume with distilled water

Approaches of in situ gel drug delivery

- Physiological stimuli
- Physical mechanism
- Chemical reaction

IN SITU FORMATION BASED ON PHYSIOLOGICAL STIMULI

1 Thermally Triggered Systems

The most often studied category of temperature-sensitive polymer systems is used in medication delivery research. Polymers that are in liquid form below their low critical solution temperature (LCST) and turn into gels when the ambient temperature reaches or exceeds the LCST are the basis of the in situ activated temperature gelling system. When designing a thermos responsive sol-gel polymeric system, there are three primary approaches available. [12,29] Temperature-sensitive hydrogels are divided into three categories for ease of use: negatively thermosensitive, positively thermosensitive, and thermally reversible gels. The critical solution temperature (LCST) of negative temperature-sensitive hydrogels is lower, and they contract when heated above the LCST. This is accomplished by using polymers with low critical temperature (LCST) transitions between ambient and physiological temperatures. Temperature sensitive polymer like poloxamers, hydroxylpropylmethylcellulose, Xyloglucan. [25,28,29]

Polymers used in temperature triggered in-situ gel systems

Xyloglucan

The Xyloglucan Made from tamarind seeds, xyloglucan is a polysaccharide with a (1-4)-D-glucan backbone chain and (1-6)-D xylose branches that are mostly replaced by (1-2)-D-galactoxylose. By lateral stacking of the rod-like chains, the product of partial xyloglucan breakdown by galactosidase exhibits thermally reversible gelation. The sol-gel transition temperature depends on the extent of galactose elimination. Thermally reversible gels are formed when it warms up to body temperature. [29]

Chitosan

Chitosan is a thermosensitive, pH dependent biodegradable polycationic polymer that occurs naturally. It comes from chitin, which is present in crab and shrimp shells and is alkaline deacetylated. Chitosan is a biocompatible pH-dependent cationic polymer that dissolves in aqueous solutions up to a pH of 6.2. A hydrated gel-like precipitate forms when a chitosan-aqueous solution is neutralized to a pH greater than 6.2. Without undergoing any chemical alteration or cross-linking, the pH-gelling cationic polysaccharide solution transforms into thermally sensitive pH-dependent gel-forming aqueous solutions upon the addition of polyol salts with a single anionic head, such as glycerol, sorbitol, fructose, or glucose phosphate salts, to the chitosan aqueous solution. [28,30]

Poloxamers (Pluronic)

Poly (ethylene oxide)-b-poly (propylene oxide)-b-poly (ethylene oxide) triblock copolymers, or PEO-PPO-PEO, are amphiphilic due to their hydrophilic ethylene oxide domains and hydrophobic propylene oxide domains. At body temperature, concentrations greater than 15% (w/w) of the triple block of copolymers PEO-PPO-PEO (also known as pluronics or poloxamers) gel.[30] Three main theories have been put out to explain the sol-gel phase shift at higher temperatures: increasing micellar aggregation, progressive polymer desolvation, and increased polymeric network entanglement. There are several grades, molecular weights, and physical forms of pluronic triblock copolymers available on the market. The grades are assigned as L for liquid, P for paste, and F for flakes based on the physical description. The poloxamers that are most frequently utilized are 407 (F-127), 188 (F-68), 237 (F-87), and 338 (F-108). Ethylene oxide (70%) makes up Pluronic F-127 (F-127) or Poloxamer 407 (P407) (copolymer PEO106-PPO70-PEO106), which helps explain its hydrophilic quality. F-127 is a copolymer that has a molecular weight of 12,000 da, a PEO/PPO ratio of 2:1, is nontoxic, and at room temperature forms a semisolid gel due to its low viscosity below 4 °C. Furthermore, because of the hydrogen bonds formed at low temperatures, F-127 is more soluble in cold water than in hot. [14,31]

Hydroxy propyl methyl cellulose (HPMC)

This polymer is sensitive to temperature. Other names for it include Methocel and Hypromellose. It is cellulose ether soluble in water. It is made up of glucan chains containing β-(1,4)-D-glucopyranose units that repeat. As the temperature rises, its viscosity increases. Aqueous solutions of HPMC at low concentrations (1–10 wt%) are liquid at low temperatures but gel when heated. Phase transition between 75ºC and 90ºC is visible. Chemical or physical changes can lower these phase transition temperatures. Lowering HPMC's hydroxyl propyl molar substitution will result in a transition temperature of 40°C. [31,32]

Gellan gum

Known by its trade names Gelrite TM or Kelcogel TM, gellan gum is an anionic polysaccharide that is deacetylated and secreted by Pseudomonas elodea. It consists of two β-D-glucuronic acid residues, one β-D-glucuronic acid, and one α-L-rhamnose. There is a temperature-dependent or cation-induced tendency for it to gel. The double helical segments aggregate to create a three-dimensional network through complexation with cations and hydrogen bonding with water in this gelation process, which begins with the production of double helical junction zones. Calcium chloride and sodium citrate complex were combined to create the gellan solution. [31,33]

pH triggered systems

pH variations can also cause gel to develop in situ and are another physiologic stimulus that can do so. Acidic pendants are present in all pH-sensitive polymers. or fundamental groups that take up or release protons in reaction to pH alterations in the environment. The Changes in pH can cause gel to develop in situ in addition to other physiological stressors. In reaction to changes in the pH of the surrounding environment, all pH-sensitive polymers include pendant acidic or basic groups that either receive or release protons. Polyelectrolytes are polymers that contain a lot of ionizable groups. When weakly acidic (anionic) groups are present, hydrogel swelling increases as the external pH rises, but it decreases when weakly basic (cationic) groups are present. The majority of anionic pH-sensitive polymers (Carbopol, carbomer) are based on PAA or its derivatives. [13,34]

Polymers used in pH triggered in-situ gel systems

Carbopol

The well-known pH-dependent polymer carbopol forms a low-viscosity gel at alkaline pH levels but remains in solution at acidic pH levels. Utilizing HPMC together with carbopol gives the solution more viscosity while lowering its acidity. pH-induced in-situ precipitating polymeric systems include a variety of water-soluble polymers, including the carbopol system, the hydroxypropylmethylcellulose system, and the poly (methacrylic acid)-poly (ethylene

glycol) system. This idea served as the foundation for the development and assessment of an indomethacin ophthalmic delivery system used to treat uveitis. Indomethacin was found to release continuously for eight hours in vitro, making this method a strong contender for ocular administration. [11,35]

Alginic acid or sodium alginate

The linear block copolymer polysaccharide, which is hydrophilic, non-toxic, and biodegradable, is composed of β-D-mannuronic acid and α-L-glucuronic acid residues connected by 1,4-glycosidic connections. It serves as a carrier for compositions intended for eye usage. When alginate is exposed to divalent cations (Ca+2, Mg+2), the carboxylate groups are cross-linked, causing the alginate to become a stable gel that is resistant to erosion by tear fluid. [36,37]

In situ formation based on physical mechanism

Swelling

The substance used in this process of in situ gel production collects water from its surroundings and expands to fill the appropriate region. For instance, the polar lipid glycerol mono-oleate expands in water to generate lyotropic liquid crystalline phase structures. It has some bioadhesive qualities and is susceptible to enzymatic degradation in vivo. [36]

Diffusion: In this technique, the solvent from the polymer solution diffuses into the tissue around it, causing the matrix to precipitate or solidify. It has been demonstrated that a good solvent for such systems is N-methyl pyrrolidone (NMP). [38]

Chemical processes

Precipitation of inorganic solids can result from chemical reactions that lead to in-situ gelations by using the following procedures. [39,40]

Ionic cross-linking chemical polymerization

Different ions can cause phase transitions in polymers. A subset of polysaccharides belongs to the ion-sensitive polymer class. carrageenan primarily produces elastic gels in the presence of Ca2+, whereas k-carrageenan creates stiff, brittle gels in response to tiny amounts of K+. Commercially accessible under the brand name Gelrite®, gellan gum is an anionic polysaccharide that goes through in situ gelling when mono- and divalent cations such as Ca2+, Mg2+, K+, and Na+ are present. Divalent cations, particularly Ca2+, can induce the low-methoxy pectin to gel. The interaction of alginic acid with the glucuronic acid block in alginate chains causes it to gel in the presence of divalent or polyvalent cations, such as Ca2+. [31,40]

Polymers used in ion triggered in-situ gel system

Sodium Alginate

This polymer reacts with ions. It is also known by the name's sodium polymannuronate, kelcosol, E401, sodium salt, algin, and alginic acid. Sodium alginate is a gum that can be extracted from brown algae. It's a salt of alginic acid. Made comprised of β-D-mannuronic acid and α-L-glucouronic acid residues joined by 1,4-glycosidic linkages, this polysaccharide is a linear block. The carboxylic group gives it strong mucoadhesive qualities. It is biodegradable and non-toxic. The range of its molecular weight is 20–600 k Da. [37,41]

Gellangum

One way to create ion-sensitive hydrogels is by using gellan gum, a polysaccharide. Glucuronic acid, glucose, and rhamnose repeat in a tetrasaccharide unit, making it a linear anionic heteropolysaccharide with a 2:1:1:1 ratio. Using hydrogen bonds and/or electrostatic attractions, gellan's carboxylic and hydroxyl functional groups can interact with other polymers. Gelrite®, a low-acetyl gellan gum those gels when exposed to mono- or divalent cations, is a commercially marketed product. Once the liquid solution is injected into the cul-de-sac, the electrolytes of the tear fluid—particularly the Na+, Mg2+, and Ca2+ cations—are specifically known to cause the polymer to gel. [31,42]

Enzymatic cross-linking or polymerization

As the gel was created by cross-linking with the bodily fluid enzymes, this method offers certain advantages over chemical and photochemical methods. For example, an enzymatic process works well in physiological conditions without requiring potentially dangerous chemicals like initiators and monomers. Insulin-releasing hydrogels have been employed in stimuli-responsive intelligent delivery systems that have been researched. Catalytic pH-sensitive polymers with glucose oxidase and immobilized insulin can swell in response to blood glucose levels, pulsatily

releasing the trapped insulin. By modifying the amount of enzyme, it is also feasible to conveniently control the rate of gel formation, enabling combinations to be injected before gel formation. [2,11,43]

Polymerization triggered by light

It is the most practical and widely utilized method for creating in situ gels. Injecting monomers or reactive micromere solutions, initiators, and electromagnetic radiation into a tissue site are utilized to create a gel. Short-wavelength polymers are not employed because they are biologically hazardous; instead, long-wavelength UV (such as ketones) and visible (such as camphor-quinone and ethyl eosin) wavelength polymers are typically used. [43,44,45]

New methods for in situ gels

To increase the drug delivery using in situ gelling systems, a wide range of distinctive techniques are used. These technologies enhanced drug molecule corneal penetration and postponed the clearance of active components from the eye. [46]

Nanoparticle incorporated in situ gel

The idea of nanoparticles has become more and more popular in the last few decades. Medication is delivered to its target areas at different rates using polymeric nanoparticles. dosage schedules and rates that are suitable for therapy. The size of a nanoparticle might vary from ten to a few nanometers. There are four different types of nanoparticles: protein, lipid, polymeric, and metallic. From 1 to 100 nanometers is the range of their sizes. Benefits: Controlled release, better cellular absorption, and increased medication stability. [47] Nanoparticle-loaded in situ gel is an advanced drug delivery system that combines the benefits of in situ gel with the properties of nanoparticles. In addition to the polymers that facilitate the sol-gel transition, nanoparticle-loaded in situ gels contain nanoparticles. Obstacles Creating Complexity: Exact compatibility and stability calculations may be necessary to formulate stable in situ gels loaded with nanoparticles. Nanoparticles can be incorporated into the in-situ gel during its formulation. Techniques include physical mixing, sonication, or in situ synthesis of nanoparticles within the gel. The incorporation of nanoparticles enhances the drug delivery system's capabilities by providing a carrier for the therapeutic agent. Nanoparticles can encapsulate drugs, protect them from degradation, and control their release kinetics. [48,49,50]

Liposome incorporated in situ gel

Liposomes are typically composed of phospholipids that form a lipid bilayer. This structure allows them to encapsulate both hydrophobic and hydrophilic substances. Several studies have demonstrated the several advantages of liposomes as ocular medication carriers, such as their easy corneal penetration, high histocompatibility, lack of toxicity, and lack of immunogenicity. Nevertheless, the technique needs to be improved because the low viscosity of liposomes prevents the medication from having enough time to come into contact with the eye. One method for reducing the liposomes' precorneal drainage rate is to distribute them into an ion-sensitive gel. Liposome-loaded in situ gel combines liposomes with the polymer-based gel matrix of in situ gels. Liposomes can be loaded into the gel using various techniques, such as physical mixing, sonication, or extrusion. The liposomes are typically dispersed or incorporated within the gel structure. Functionality: The liposomes in the gel system act as drug carriers, offering protection to the encapsulated drug and controlling its release. The in-situ gel matrix enhances the residence time and provides a sustained release platform. [51,52]

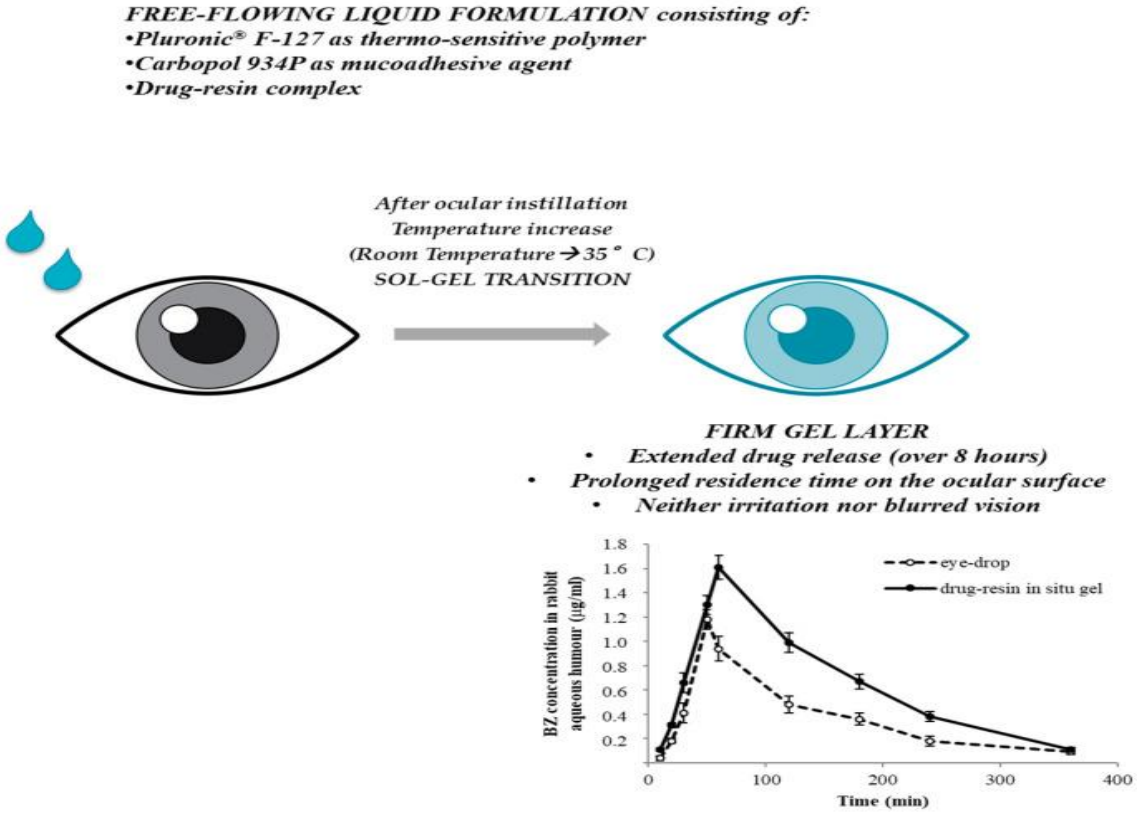

Figure: 1 Drug–resin thermo-sensitive in situ gelling system for ophthalmic use: After instillation, an increase in temperature is responsible for the transition of the polymeric liquid formulation loaded with brinzolamide (BZ) into a mucoadhesive gel layer on the ocular surface. The graph represents the concentration–time profiles of BZ in the rabbit aqueous humour: BZ amount in the aqueous humour is significantly higher when BZ is instilled as drug–resin in situ gel than as eye drops. Such results demonstrate that the drug–resin in situ gel is responsible for a higher BZ absorption into the eye: the formation of a gel in the conjunctival cul-de-sac guarantees a prolonged residence time in the pre-corneal area and provides sustained BZ release

In situ gelling ocular films/inserts

Ocular inserts and films typically consist of a polymeric vehicle that contains the medicine and is sized and shaped specifically for ophthalmic delivery. They can be semisolid or solid in consistency. Ocular inserts containing ketorolac tromethamine bioadhesive in-situ gelling were made by solvent casting process with sodium alginate, chitosan, and glycerin as a plasticizer. Functionality: The in-situ gel formation enhances the residence time of the dosage form on the ocular surface, while the film or insert structure ensures sustained drug release and improved drug delivery efficiency (Prolonged Contact, prolonged contact with the ocular surface, enhancing the absorption of the drug, Improved Patient Compliance, Enhanced Bioavailability). [53,54]

Nanoemulsified in situ gel

Nanoemulsions are colloidal dispersions of nanoscale droplets of one immiscible liquid (usually oil) within another immiscible liquid (usually water). In situ gels, as mentioned earlier, undergo a phase transition in response to specific physiological conditions. These systems usually consist of nano emulsions incorporated into a gel matrix made of polymers. The droplets of the nanoemulsion are distributed throughout the gel. Because of its many intrinsic advantages, such as extended drug release into the cornea, enhanced penetration into deeper layers, and enhanced solubility, stability, and bioavailability of poorly water-soluble medicines, nanoemulsions are frequently utilized. [55,6,57]

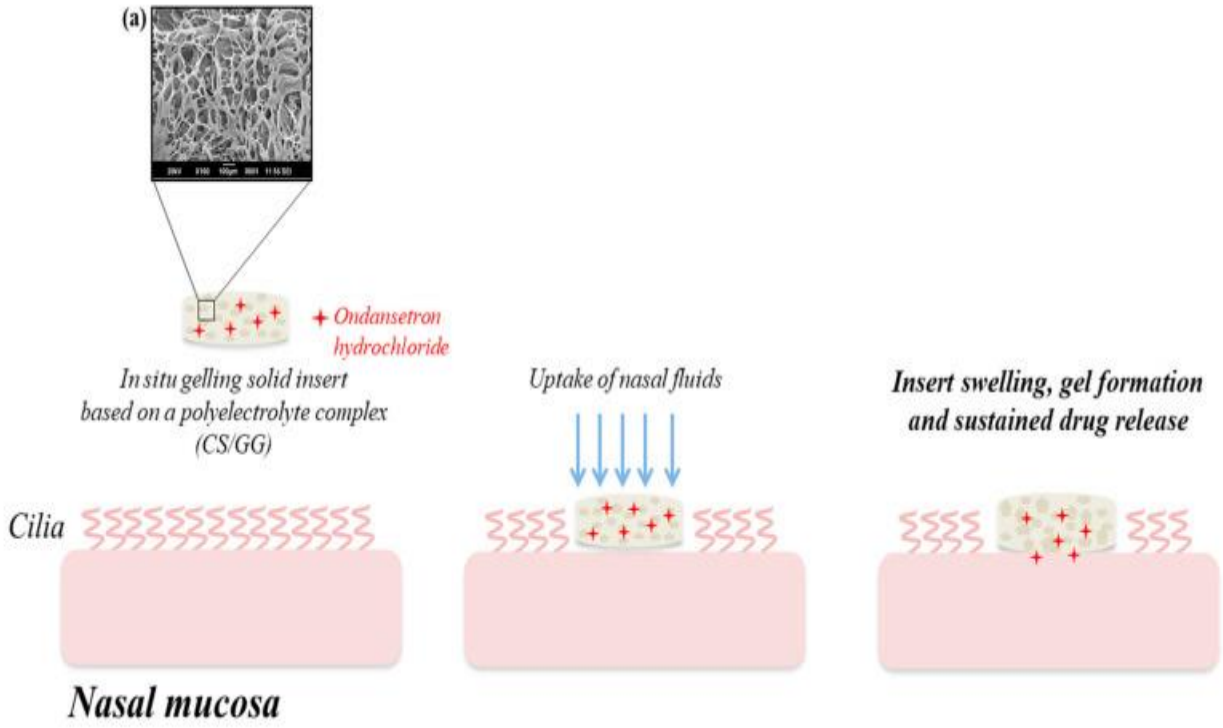

Figure 2: In situ gelation of a solid nasal insert loaded with ondansetron hydrochloride, prepared by freeze-drying of an aqueous polymeric solution consisting of chitosan (CS) and gellan gum (GG); (a) scanning electron micrograph of the freeze-dried insert (Adapted from [58], ELSEVIER, 2016). Upon contact with the nasal mucosa, the porous structure of the insert allows rapid hydration of the cross-linked polymeric matrix and the consequent formation of a gel that guarantees a controlled drug release

Conclusion

In conclusion, improving patient compliance is the main need for a controlled-release product, and in situ gels meet this need. The utilization of polymeric in-situ gels for the controlled release of diverse pharmaceuticals offers several benefits in comparison to conventional dosage forms. The in-situ gel dosage forms have good stability, a prolonged and sustained release of the medication, and biocompatibility properties. In situ gel formulations can be improved as effective drug delivery methods by using water-soluble and biodegradable polymers.

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