EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 10
Issue: 9
155-159
Year: 2023

A REVIEW ON IN-SITU GELLING IN OCULAR DRUG DELIVERY SYSTEM

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Article Received on 11/06/2023 **Article Revised on 01/08/2023** **Article Accepted on 21/08/2023**

ABSTRACT
Polymeric formulations known as "in situ gelling systems" transition from their sol state before entering the body to their gel state once inside it. The pH shift, temperature modulation, solvent exchange, UV radiation, and the presence of certain ions or molecules are only a few of the stimuli that can cause the sol-gel transition. Such characteristics make drug delivery systems well suited for preparing bioactive compounds for sustained distribution. The eye is the body's most sensitive organ. There are significant efforts being made to develop innovative drug delivery systems for ophthalmic administration in order to increase the bioavailability of ophthalmic medications. The efficiency of drug administration is increased by altering the release profile, and these innovative drug delivery methods also lessen drug toxicity, giving them a number of advantages over conventional systems. There is a lot of research being done in this field that supports the idea that in situ gelling systems can be useful for the administration of ocular medications. This study will provide a brief overview of in situ gels, distinct in situ gelling system techniques, the many types of polymers utilised in in situ gels, their gel formation mechanisms, and evaluation of polymeric in situ gels.

KEYWORDS: In situ gels, ophthalmic administration, Polymers, pH shift.

INTRODUCTION
One of the most vital and intricate organs in the human body is the eye. It is a sensory organ with distinct physiological and anatomical functions. Due to the eye's robust mechanism and barrier protection, drugs for the eyes are administered using a variety of preparations. Medication is absorbed and penetrated through the posterior portion of the eye. At the cornea sclerotic junction, conjunctiva is placed on top of the epithelial layer that makes up the cornea of the eye.[1,2]

Endothelium covers the posterior surface of the body. There are plenty of nerve endings in the cornea. The opaque white sclera, a stiff fibrous tissue, is present to the posterior region of the cornea. The stroma of the cornea has 200–250 lamellae as well. The lamellae that make up the stroma have lagged down collagen. Epithelial, endothelial, and stromal cells act as the primary obstacles to the absorption of ocular medicines. Drugs that are hydrophilic can pass through the outer epithelial membrane, but those that are hydrophobic must pass through the stroma, which serves as a barrier. Human lacrimal glands are fully filled with fluid. This fluid's presence hinders the elimination of foreign particles and eye dryness. When a small amount of medication is administered to the eye, the majority will be the last to enter the fluid in the anterior chamber. The most popular methods for making eye medications are solutions and suspensions, although these types of formulations have a low or poor bioavailability. In-situ hydrogel preparations are being created as part of more recent research in ocular medication delivery systems to increase ocular bioavailability.[3,4]

Natural or synthetic polymer has led to the development of numerous in-situ gel delivery techniques. Gels are typically semi-solid by nature, heavier than liquids despite being greater in size. The primary advantage of the in-sites polymer delivery technology is increased patient convenience. Sol-to-gel transitions in polymers occur as a result of the alteration in their physiochemical characteristics. The three types of systems - PH triggered system, temperature dependent system, and ion-activated system are recognised based on the technique utilised to induce sol-to-gel transition. For the treatment of various disorders, the topical application of in-sites gels to the eyes is a well-established route of administration. The duration of the drug's action is prolonged by this method of delivery. Due to the inclusion of both natural and synthetic polymers, they are taken via a variety of routes, including intraperitoneal, rectal, vaginal, oral, and ocular.[5,6]

Advantages of In-Situ gel formulation[7]

1. Ease to administer.
2. Very simple to manufacture.
3. Low dose requires.
4. Economic.
5. Local or system's site specific and prolonged release drug delivery.
6. Enhanced patient compliance by reducing the frequency of application.
7. Good stability and biocompatibility characteristics.
8. Less invasive

Disadvantages of In-Situ gel formulation

1. Initially rapid drug will release prior to solidification of the polymer.
2. Toxicity may increase because of organic solvents used.
3. High viscosity of the polymer solution, may leads to problems during administration

Polymers Used

2.1 Carpool

It is a pH sensitive polymer. It is also called as carbomer, acrylic acid polymer Carpool is a high molecular weight, cross linked polyacrylic acid derivative and has strongest mucoadhesive property. It is a water soluble vinyl polymer. It shows sol to gel transition, in aqueous solution, when the pH is raised above its pKa value of about 5.5. As the concentration of carpool increases, its acidic nature may cause irritation to eye. Addition of cellulose will reduce polymer concentration and will also improve gelling property.[8]

2.2 Poloxamer

It is a temperature sensitive polymer. It is commercially called as Pluronic. It is a water soluble tri-block copolymer consisting of two polyethylene oxide (PEO) and polypropylene oxide (PPO) core in an ABA configuration. Polypropylene oxide is the hydrophobic central part which is surrounded on both sides by hydrophilic Polyethylene oxide. It has good thermal setting property and increased drug residence time. It gives colourless, transparent gel. Concentrated aqueous solutions of Poloxamer form thermoreversible gels.[9]

2.3 Gellan gum

It is an ion-sensitive polymer. It is also known as Gel rite® (trade name). Gellan gum is a linear, anionic heteropolysaccharide secreted by the microbe Sphingomonaselodea.[8,9] The backbone of the polymer consists of glucose, glucoronic acid and rhamnose in the molar ratio 2:1:1. These are linked together to give a tetrasaccharide repeat unit. Gelrite is deacetylated gellan gum, obtained by treating gellan gum with alkali to remove the acetyl group in the moleculeUpon instillation, gelrite forms gel due to the presence of calcium ions. The gelation involves the formation of double helical junction zones followed by aggregation of double helical segment to form three dimensional networks by complexation with cations and hydrogen bonding with water. It is widely used in ophthalmology because of its thixotropy, thermo plasticity and pseudo plasticity.

2.4 Sodium alginate

It is an ion-sensitive polymer. It is also known as algin, alginic acid, sodium salt, E401, Kelcosol, Keltone, Protanal, sodiumpolymannuronate Sodium alginate is a gum extracted from brown algae. It is a salt of alginic acid. It is a linear block polysaccharide consisting of two types of monomers-β-D-Mannuronic acid and α-L-glucouronic acid residues joined by 1,4-glycosidic linkages. It exhibits good mucoadhesive property due to presence of carboxylic group. It is biodegradable and non-toxic. It has high molecular weight of 20 to 600 kDa.[8]

2.5 Chitosan

Chitosan is a cationic polysaccharide which consists of copolymers of glucosamine and N-acetyl glucosamine, these are natural polymer obtained by deacetylation of chitin. Chitosan has mucoadhesive property due to electrostatic interactions between positively charged amino group and negatively charged mucin.[8] It is a polycationic polymer and also called as ophthalmic vehicle It is biodegradable, biocompatible and non-toxic polymer It exhibits pseudo plastic and viscoelastic behaviour It has good antibacterial and bio adhesive property It has ability to convert into hydrogel at ocular pH.[10]

2.6 HPMC

It is a temperature sensitive polymer. It is also known as Hypromellose, Methocel

It is water soluble cellulose ether. Widespread acceptance of HPMC due to [11]

a) Solubility characteristics of the polymer in organic and aqueous solvent system.
b) Non-interference with drug availability.
c) Flexibility and absence of taste and odour.
d) Stability in the presence of heat, light, air or reasonable levels of moisture.

It is composed of glucan chain with repeating β-(1,4)-Dglucopyranose. It increases its viscosity when temperature increases. [8] At low concentrations (1-10 wt.%) aqueous solutions of HPMC are liquid at low temperature but gel upon heating. It shows phase transition between 75ºC and 90ºC.These phase transition temperatures can be lowered by chemical or physical modifications. By reducing the hydroxyl propyl molar substitution of HPMC, its transition temperature can be lowered to 40^0C.

In-Situ Formation Based On Following Chemical Reactions Cause Gelation

3.1 Ion cross linking

A polymer may go through a phase transition when there are different ions present, and some polysaccharides are ion-sensitive. While k-carrageenan responds to tiny

amounts of K+ by forming hard, brittle gels, i-carrageenan responds to Ca+2 by primarily forming elastic gels. Gellan gum, also known as gelrite in the marketplace, is an anionic polysaccharide that gels in-site when exposed to mono- and divalent cations like Ca+2, Mg2+, K+, and Na+. Divalent cations, in particular Ca+2, have the potential to gel the low-methoxy pectins. Similar to how alginate chains interact with gleve guluronic acid, alginic acid gels when divalent or polyvalent cations, such as Ca2+, are present.[12]

3.2 Enzymatic crosslinking

Although it hasn't received much attention, in-situ gel creation mediated by neutral enzymes appears to offer certain advantages over chemical and photochemical methods. For instance, an enzyme-based method can function effectively in physiologic circumstances without the use of potentially hazardous chemicals like initiators and monomers. Hydrogels that can release insulin are used in intelligent stimuli-responsive delivery systems. When blood glucose levels rise, a cationic PH-sensitive polymer with immobilised insulin and glucose oxidase can expand, releasing the insulin that has been trapped in a pulsatile manner. The ability to control the rate of gel formation by varying the amount of enzyme also makes it possible to inject the mixes prior to gel formation.[13]

3.3 Photo polymerisation

In-situ gel production of biomaterials frequently uses photo-polymerization. The formation of gel can be accomplished by injecting a solution of monomers or reactive macromere and initiator into a tissue location. Because they photo-polymerize quickly in the presence of a suitable photo initiator, acrylates or other polymerizable functional groups are often utilised as the polymerizable groups on the individual monomers and macromeres. Long wavelength ultraviolet and visible wavelengths are frequently employed. Because it has a limited ability to penetrate tissue and is biologically hazardous, short wavelength UV is rarely used. When injected into the target place, photo polymerizable systems become photo-cured there with the aid of fibre optic cables, allowing the release of the medicine over an extended period of time. At physiological temperatures, the photo-reaction offers quick polymerization rates. Additionally, the systems are simple to install in volumes with complex shapes that result in the production of implants.[14]

3.4 pH triggered in situ gelation

As the pH fluctuates in this system, gel is created. This technique makes use of pH responsive or pH sensitive polymers. In pH-sensitive polymers, there are hanging acidic or basic groups that could release or receive protons in opposition to variations in the pH of the surrounding environment. Polyelectrolytes are the numerous polymers with ionisable groups. The presence of poly electrolytes in the formulation causes an increase in the external pH, which causes the hydrogel to swell and form an in situ gel. The polymers with anionic groups that are particularly useful for this method include cellulose acetate phthalate (CAP), carbomer and its derivatives, polyethylene glycol (PEG), pseudo latexes, and poly meth acrylic acid (PMC), among others.

3.5 Temperature triggered insitu gelation

In the formulation of in-situ gelling polymer systems that are environmentally responsive, temperature is a stimulus that is frequently exploited. The employed temperature change is simple to manage and is ideal for both in vitro and in vivo experiments. In this mechanism, gelation takes place as a result of body warmth and does not require additional heat. These hydrogels are liquid at room temperature (20–25 °C), but due to the temperature rise when they come into contact with bodily fluids (35–37 °C), they begin to gel. Thermostatically induced systems come in three different flavours. They are thermally reversible type (e.g., poloxamer, pluronics, Tetronics), negatively thermosensitive type (e.g., poly (N-isopropyl acrylamide), positively thermosensitive type (e.g., polyacrylic acid).[16]

3.6 Ion activated in situ gelation

In this approach, a change in the ionic strength causes the solution to gel. It is presumable that the osmotic gradient across the gel's surface will affect the pace of gelation. Gellan gum, hyaluronic acid, alginates, and other polymers exhibit osmotically induced gelation.[15]

Evaluation Tests

4.1 Clarity

A clarity test for the presence of any particle matter is run in an in-situ gel formulation. In the presence of fluorescent light and against a dark background.[17]

4.2 pH measurement

The ocular In-situ Gel preparation's typical pH falls between 7.3 and 7.4.A ph metre can be used to measure it. Ph will have an impact on the drug's stability and solubility, so that the formulation must be stable and shouldn't irritate the patient when used.[18]

4.3 Gelling capacity

A drop of the formulation can be used to test its ability to gel by adding it to a vial containing 2ml of prepared tear fluid.by visually measuring how long it takes for gel to form and how long it takes for gel to disappear. The time needed to transform the gel into tear fluid determines how the gelling capability is classified. When gelation lasts a longer duration, the formulation has a good gelling capacity.

4.4 Drug polymer interaction study and thermal analysis

Fourier Transform Infrared (FTIR) Spectroscopy should be used to conduct the compatibility investigation. The KBr pellet approach can be used throughout the gelation process to estimate the type of interacting forces. To

determine how much water is present in the hydrogel, thermogravimetric analysis (TGA) can be performed on an in-situ forming polymeric system. To determine whether thermograms have changed as compared to materials used for gelation, differential scanning calorimetry is performed.[19]

4.5 Drug Content

The test for drug content will be conducted by taking 1ml of gel formulation in a 10ml volumetric flask. The above created solution will be diluted with 10ml of distilled water, and then the volume will be made up to 10ml from this solution. A U.V. visible spectrophotometer is then used to test the prepared solution's absorbance at a specific drug wavelength.[20]

4.6 Viscosity measurement

Viscosity measurement can be analysed by Brookfield viscometer and Ostwald viscometer. The prepared in situ gel preparation is kept in a test tube. The viscosity of the formulation should be between 5-1000 mPas before gelation and between 50-50,000 mPas after gelation. The preparation should not cause difficulties when administered to the patient, especially parenterally and ocular administration.

4.7 *Invitro* drug release

The in vitro drug release from the in situ gel formulation is performed using a Franz diffusion cell. Recently prepared tear fluid is stored in the receiver chamber. A dialysis membrane is placed between the receiver and donor chambers. The entire set is kept under thermostatically controlled magnetic stirring for in vivo stimulation and the temperature must be maintained at 37 °C/–0.5 °C with substrate agitation at 20 rpm. 1 ml of the prepared preparation is placed in the donor chambers. The samples are examined using a UV spectrometer (or HPLC).[21,22]

4.8 Ex-vivo drug release

Ex vivo drug release studies are also performed using a Franz diffusion cell. Goat cornea can be used to study corneal penetration. The cornea is removed with 5-6 mm of surrounding scleral tissue and cleaned with cold saline. Washed corneas are placed in cold, freshlyprepared tear buffer solution with a pH of 7.4. In this method, half of the cornea remains in contact with the preparation in the donor chamber. The receptor consists of (STF) thickening fluid pH 7.4 at 34 °C+/-0.5 °C. This medium is moved by magnetic stirring. Samples are taken and the drug content analysed.[23]

4.9 Antimicrobial efficacy testing

To demonstrate antimicrobial resistance to microbes, a test is performed with antibacterial preparations. This test is studied using the agar diffusion method. the nutrient medium is pre-inoculated with test organisms, i.e., Pseudomonas aeruginosa and Staphylococcus aureus, stored in petri-wells and 0.5 ml standard solution, and the prepared preparation is kept in soil culture cups. Plates are incubated at 37°C for 24 hours. The incubation zone is measured and analysed with a control drug.[24]

4.10 Ocular Irritation Test

Three rabbits weighing 1.5-2 kg are used in the study. The sterile preparation is instilled twice a day for 7 days and crossover is done. Rabbits are periodically monitored for redness, swelling and eye discharge. The Draize irritation test must be designed based on the eye irritation potential of the eye product before marketing. According to Draize's test, the amount of substance applied to the eye is usually placed in a 100 l lower cooling tank, following various criteria at a planned necessary interval pf 1h, 24h, 48h, 72h, 1 week after administration.[25]

CONCLUSION

The review concludes that development of ophthalmic drug delivery system has advantageous results as compared to the conventional system. The in-situ gel system has developed as one of the greatest novel drug delivery system. Sustained and controlled release of drug, patient compliance, stability and biocompatibility are the major characteristics that make the dosage forms more reliable. The in-situ methods are also helpful in paediatric and geriatric patients. The usage of water-soluble polymers in in-situ gel formulations can make them more excellent drug delivery systems. They also provide better sustained release abilities than other drugs. These type of in-situ dosage forms are used in the treatment of glaucoma, dry eye syndrome, trachoma, ARMD. The various natural and synthetic water soluble polymers undergo in-situ gelling and are used for several routes such as ocular, oral, buccal, transdermal, rectal, vaginal. The present article provides various valuable information and high scope for researchers who are involved in in-situ gelling system in order to provide better drug delivery system.

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