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In-Situ Gel-New Formulation Trend

Azad Nabilal Dhage[1], Zinat Isak Mulla[2], Abhijeet Shashikant Kulkarni[1], Aniket Ramesh Borge[1], Mayur Krishnat Ghosalkar[1]

[*1]Department of Pharmaceutics, Dr. Babasaheb Ambedkar Technological University, Lonere, Ashokrao Mane Institute of Pharmaceutical Sciences and Research, Save, Kolhapur, Maharashtra, India.

[2]Department of Chemistry, Shivaji University, Kolhapur, Government College of Pharmacy, Vidyanagar, Karad, Satara, Maharashtra, India

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ABSTRACT

This review on in situ gel was written to fill in any gaps in the current body of knowledge, with a special emphasis on in-situ gelling systems that prolong the residence time of drugs at their targets. Drugs with very short half-lives and high solubility are especially interested in in-situ gels. The use of in-situ gelling systems as drug delivery systems for both local and systemic effects has recently been developed. The advantages of in-situ polymeric delivery systems, such as ease of administration, decreased frequency of administration, enhanced patient compliance, and comfort, have drawn the most attention in current in-situ gelling system development. The studies that evaluated the use and performance of these systems are summarized in this review. This review paper is prepared to highlight formulation considerations employed during the development of an in-vivo drug delivery system, pertinent biodegradable polymers for the sol-gel transition, characterization, assessment criteria, and commercial formulations of the in-vivo polymeric system.

Keywords : Residence time; Systemic effects; Patient compliance.

I. INTRODUCTION

Over the past 30 years, the creation of a regulated and sustained medication delivery system has received more attention. A significant amount of research has gone into developing polymeric drug delivery systems. Over the past few years, in situ gel system development has drawn a lot of interest. A growing variety of in situ gel forming systems have been studied in recent years, and there have been numerous patents recorded for their usage in diverse biochemical applications, including drug delivery. The benefits of in situ forming polymeric delivery systems, including ease of administration, decreased frequency of administration, greater patient compliance, and comfort, have prompted interest in the field.[1]

In situ gel formulations present an intriguing alternative to parental routes, which may be cumbersome or oral routes, which may result in

unacceptable low bioavailability and pass the hepatic first-pass metabolism, particularly of proteins and peptides, in order to achieve systemic drug impact.[2] This innovative drug delivery technology supports the crucial ease and convenience of administration, the delivery of an appropriate dose, as well as the extension of the drug's residence time in contact with mucosa, issues that are typically present in semi-solid dosage forms. pH change, temperature variation, and solvent exchange are just a few of the different stimuli that can lead to in situ gel formation.[3]

This innovative drug delivery system supports the crucial ease and convenience of administration, delivery of an exact dose, and prolongation of the residence period of the drug in contact with mucosa, which are issues often present in semi-solid dosage forms. One or more combinations of several stimuli, such as pH change, temperature modulation, and solvent exchange, result in in situ gel formation.[4]

A) Various Approaches of In-situ Gelation:

A.1) pH Triggered In-situ gelation:

pH sensitive polymers are those that contain functional groups with acidic or alkaline properties that react to changes in pH. Materials that are pH responsive can be used to address the pH, which is a significant signal. When the pH reaches 7.4, the fluid begins to gel. After the formulation is infused into the tear film, the pH changes by around 2, 8 units, which causes the very fluid latex to virtually instantly turn into a thick gel. The polymers having a lot of ionizable groups are called polyelectrolytes. In the case of weakly acidic groups, hydrogel swelling increases when the external pH rises, but decreases in the case of weakly basic groups.[5]

A.1) Temperature Triggered in situ gelation:

The most frequently employed stimulus in environmentally sensitive polymer systems is temperature. In addition to being reasonably simple to control, the temperature change is also conveniently applicable both in vitro and in vivo. In this method, a change in temperature causes the fluid to gel, continuing the drug release. These hydrogels are liquid at normal temperature (20–25°C), but they begin to gel at 35–37°C when they come into touch with bodily fluids. An appealing method to approach in situ formation is to use biomaterials whose transition from sol-gel is triggered by an increase in temperature. Examples of polymers that exhibit temperature-induced gelation include poloxamer or pluronics, cellulose derivatives like methyl cellulose, HPMC, ethyl (hydroxyl ethyl) cellulose (EHEC), and xyloglucan.[6]

A.2) Ion activated in situ gelation:

In this approach, a change in the ionic strength causes the solution that has been injected to gel. It is presumable that the osmotic gradient across the gel's surface determines the pace of gelation. In the presence of the mono- or divalent cations commonly present in the tear fluids, the aqueous polymer solution crystallises into a transparent gel. When injected as a liquid solution in the conjunctional cul-de-sac, the electrolyte of the tear fluid, and specifically Na+, Ca2+, and Mg2+ cations, are particularly well-suited to induce gelation of the polymer. The polymer that exhibits osmotically induced gelation includes alginates, hyaluronic acid, and gelrite or gellan gum. [6]

B).Polymers used as in situ gelling agents:

B.1) Pectin:

Pectin is a member of the polysaccharide family, and its primary component is (1-4)-D galacturonic acid residues. Low methoxy pectin rapidly forms gels in aqueous solution when free calcium ions are present, and these gels crosslink the chains of galacturonic acid in a way that is consistent with the egg-box hypothesis. Pectin will gel when H+ ions are present, hence a supply of divalent ions—typically calcium ions—is needed to create the gels that are appropriate for use as drug delivery vehicles. When pectin is consumed orally, divalent cations in the stomach cause the transformation from a liquid to a gel. [7]

B.2) Guar gum:

Guar gum, which is a naturally occurring gum made from the endosperm of the seed, is also known as guaran. Guar gum is soluble in water but insoluble in hydrocarbons, lipids, esters, alcohols, and ketones. These demonstrate its ability to dissolve in both hot and cold water and create a colloidal solution at low concentrations. Guar gum derivatives are utilised to create coated matrix systems, nano-microparticles, and hydrogels, which are all forms of targeted delivery systems. Guar gum also has derivatives that are good at targeting the colon, such as graft polymers like polyacrylamide grafted guar gums. Additionally, it can be utilised as a polymer in matrix tablets that demonstrate controlled release.[8]

B.3) Carbopol:

A polymer made of polyacrylic acid (PAA), carbopol transformed into a gel when the pH was increased from 4.0 to 7.4. Carbopol does not change from its solution state in an alkaline pH environment to a low viscosity gel. In order to increase the viscosity of the carbopol solution and lessen its acidity, HPMC is employed in conjunction with carbopol. Comparing various forms of poly (acrylic acid) (Carbopol 940, 934, 941 and 9010), researchers found that Carbopol 940 had the best clarity and look.[9]

B.4) Xyloglucan:

The polysaccharide xyloglucan, often known as tamarind gum, is extracted from the seed's endosperm. The three distinct oligomers that make up xylogulcan—heptasaccharide, octasaccharide, and nonsaccharide—differ in the number of galactose side chains. Due to its non-toxic, biodegradable, and biocompatible qualities, it is mostly employed in oral, rectal, and ocular medication delivery. Similar to poloxamer, when heated to refrigerator temperature or cooled from a higher temperature, it shows signs of gelation.[10]

B.5) Gellan gum:

An anionic hetero polymer called gellan gum is secreted by the bacterium Sphingomonas elodea. It is made up of glucuronic acid, rhamnose, and glucose that have been joined to form a tetrasaccharide molecule. By processing gellan gum with alkali to dissolve the acetyl group out of the molecule, gel rite, also known as deacetylated gellan gum, is produced.[11] Gel Rite gels as a result of instillation due to the presence of calcium ions. During the gelation process, double helical junction zones are formed, then double helical segments are aggregated to create three-dimensional networks through interactions with cations and hydrogen bonds with water. Gellan gum is a stabilising and suspending agent in the food business.[12]

B.6) Alginic acid:

It is a linear block copolymer polysaccharide made up of 1,4-glycosidic links connecting the residues of D-mannuronic and L-glucuronic acids. Depending on the algae source, there are differences in each block and the way the blocks are arranged along the molecule. Alginic acid is employed in ophthalmic formulations because it has beneficial biological characteristics such being biodegradable and non-toxic.[13]

B.7) Xanthan gum:

The fermentation of the gram-negative bacterium Xanthomonas campestris yields high molecular weight extracellular polysaccharide, which is what gives xanthan gum its distinctive flavour. This naturally occurring cellulose derivative has a cellulosic backbone (β - d residues) and a trisaccharide side chain of -D-mannose—D-glucuronic acid—D-mannose coupled with alternate glucose residues of the main chain as its basic structural components. In both cold and hot water, as well as in both alkaline and acidic environments, xanthan gum is soluble. At alkaline conditions, it has good stability. [14]

B.8) Chitosan:

Chitosan gels as a result of two changes, including temperature change and pH responsive change. A naturally occurring substance found in shrimp and crab shells, chitosan is a biodegradable, thermosensitive, polycationic polymer made from chitin that has undergone alkaline deacetylation. Chitosan is a cationic polymer that is pH dependant and biocompatible. It may dissolve in aqueous solutions up to a pH of 6.2. Chitosan precipitates by forming a hydrated gel when its aqueous solution is neutralised to a pH greater than 6.2. [15]

B.9) Poloxamer:

Tri-block copolymers called poloxamer are soluble in water. It is made up of two ABA-configured polyethylene oxide (PEO) and polypropylene oxide (PPO) cores.[16] Commercially available as Pluronic, poloxamer offers an extended drug residence time and good thermal setting properties. It is mostly utilised as a gelling, emulsifying, and solubilizing agent. Poloxamer produces a clear, colourless gel. A variety of molecular weights with varying gelling properties are available, and their ratio and distribution of hydrophilic and hydrophobic chains will determine how they gel. [17][18]

C) In-situ Drug Delivery System:

C.1) Oral drug delivery system:

The pH-sensitive hydro gels may be used for site-specific medication administration to particular parts of the GI tract. Preparing silicone microspheres that create prednisolone in the gastric media or exhibit gastro protecting properties was made possible by hydrogels made of various ratios of cross-linked PEG and PAA derivatives. Other polysaccharides such amidaded pectin's, inulin, and guar gum were studied in order to improve a prospective colon-specific drug delivery method. Cross-linked dextran hydro gels had a faster swelling under high pH circumstances. Both sodium alginate and gellan formulations comprise a complexed calcium ion that goes through a process of gelation by releasing these ions in the stomach's acidic environment.

C.2) Ocular drug delivery system:

Natural polymers including alginic acid, insulin, and xyloglucan are frequently employed in ocular delivery systems. Different substances,

including autonomic medicines, anti-inflammatory agents, and antibacterial agents, are employed for local ophthalmic delivery system to relieve intra ocular tension in glaucoma. Due to tear fluid turnover and dynamics, which frequently result in poor availability and therapeutic response with conventional administration systems, ocular in-situ gel was created to address the bioavailability issue. Carboxy Methyl Cellulose, Hydroxy Propyl Methyl Cellulose, Carbomers, and Poly Vinyl Alcohol are examples of viscosity enhancers that are used to raise formulation viscosity in order to boost formulation bioavailability and lengthen precorneal residence time. To develop corneal medication penetration, penetration enhancers such preservatives, chelating agents, and surfactants are employed.

C.3) Nasal drug delivery system:

Momethasone furoate is used to test the effectiveness of the nasal in-situ gel system in the treatment of allergic rhinitis. Xanthan gum and gallan gum are employed as in-situ gel producing polymers. An animal model of allergic rhinitis was used in the investigation, and the effect of in-situ gel on antigen-induced nasal symptoms in sensitised rats was noted. Comparing the in-situ gel to the commercial product nosonex (Momethasone furoate suspension 0.05%), it was discovered that the in-situ gel inhibited the progression of nasal symptoms.

C.4) Rectal and vaginal drug delivery system:

Many different types of medications that are manufactured as liquid, semisolid (ointments, creams, and foams), and solid dose forms may be administered via the rectal route (suppositories). Acetaminophen, an anti-inflammatory medication, was created as a rectal in situ gel by utilising polycarbophil, poloxamer F188, and poloxamer 407 as synthetic polymers to create an in situ gelling liquid suppository. This method is thought to be beneficial since it increases bioavailability.

C.5) Injectable drug delivery system:

Since no surgical procedure is necessary and patient compliance is also improved, in situ gels have been developed for use in this medication delivery system over the past ten years. Injectable In situ gel is made primarily of synthetic polymers and block copolymers. Bupivacaine is one example of an anti-inflammatory medicine. It is made as an injectable in situ gel utilising poly (D, L-lactide), poly (D, L-lactide coglycolide), and PLGA as a polymer..

C.6) Dermal and transedermal drug delivery:

The effectiveness of Pluronic F127 in thermally reversible gel as a delivery system for indomethacin was examined. 20% w/w aqueous gel may be employed as a suitable foundation for topical medication administration, according to in-vivo investigations. Iontophoresis and chemical enhancers worked together to increase insulin penetration in a synergistic way.[19, 20]

D) In-situ Ophthalmic Drug Delivery System:

Due to its properties for drug disposition, the eye is the most fascinating organ. Due to its ease and safety for ocular chemotherapy, topical administration of medications is typically the method of choice. It is a huge difficulty for the formulator to get around (bypass) the eye's defences without enduring long-term tissue

damage. Traditional ophthalmic formulations, such as solution, suspension, and ointment, have a number of drawbacks that contribute to the drug's poor ocular cavity bioavailability.[21] The primary drawback of using ocular formulation is the quick loss of suspended solids and solutions. Ophthalmic ointments cause impaired vision, which makes patients less accepting of them. [22] Utilizing an in situ gel-forming ocular drug delivery system made of polymer that exhibits sol-to-gel phase transition due to a change in a certain physico-chemical parameter can solve these issues (pH, temperature, ion-sensitive).[23] The pH, temperature, or ion activated systems can all change, causing the sol-gel transition. This kind of gel combines the benefits of gels and solutions to increase ocular bioavailability.[24]

E).Advantages of in situ Ocular Drug Delivery systems:[25-27]

- To offer a controlled and sustained drug delivery system.
- To prolong corneal contact duration in order to maximise drug absorption in the eye.
- Since the effects of the medicine last for a long time, regular injections are not necessary.
- To increase drug therapeutic performance and patient compliance.
- More pleasant than insoluble or soluble insertion, on average
- The system makes administration simple.

F). Mechanism of Ocular Drug Absorption:

While some medications and peptides are difficult to permeate the mucosal membrane, small drug molecules can do so with ease. When a medicine is injected into the eye, it initially penetrates through the cornea before moving on to non-corneal pathways, giving simple solutions a very low bioavailability. Drugs that do not absorb well through the cornea are dispersed across the cornea and sclera.

G) Ideal requirements for in situ gelling systems for ophthalmic applications:

An ideal in situ gelling drug delivery formulation should comply following requirements: [29-31]

H.1) Gelation (sol-gel phase transition):

Under physiological circumstances or in the presence of a trigger for gelation, the system should be delivered as a solution that solidifies into a gel. To avoid precorneal drainage, the formulation should begin to gel immediately after administration.

H.2) Sustained drug release:

To generate the best bioavailability with the fewest side effects, the system should maintain medication release over extended periods of time.

H.3) Optimal pH:

The pH of the system shouldn't be excessively acidic or alkaline as this could irritate or harm tissues.

H.4) Clarity:

For in situ gels that are applied to the eye, the formulation must be transparent, clear, and colourless. Normal vision shouldn't be hampered by it. There shouldn't be any impurities or particles because they could irritate the ocular tissues.

H.5) Sterility:

It should be sterile to avoid any potential microbial harm to tissues at the application site.

H.6) Stability:

The formulation must be stable and shouldn't break down or lose its potency while being stored during its shelf-life.

H.7) Drug content:

The system must have the necessary number of active substances without any chemical degradation or unwanted interactions with the polymers or other excipients.

H.8) Ocular tolerance:

The ocular tissues should tolerate and be biocompatible with the polymers. It shouldn't cause any tissue damage in the form of inflammation, redness, edoema, or any other unfavourable side effects.

H.9) Reproducibility:

On repeated preparation and mass production, the system ought to exhibit the same characteristics. To enable repeatable administration, an ideal in situ gelling method should be a free-flowing liquid.

H. 10) Isotonicity:

In order to prevent tissue damage or eye discomfort, the formulation must be isotonic.

H.11) Adhesiveness:

The polymer need to be able to cling to the eye's precorneal surface.

I) Floating Oral Drug Delivery System:

One of the unique medicine delivery systems is the floating drug delivery system. Numerous dosage forms, including microspheres, microbeads, pills, capsules, films, etc., are created in the form of gastro retentive floating systems. A recent development in floating DDS is the in-situ gelling mechanism. The in-situ gelling technique is used in parenteral as well as oral, nasal, ocular, rectal, vaginal, and genital delivery. There are various benefits to in situ forming polymeric drug delivery systems, including simplicity of administration, higher local bioavailability, decreased dose frequency, and enhanced patient compliance. It also offers a less complex production procedure, which makes it more affordable. Gastro retentive FDDS float in the stomach for a long time without slowing the gastric emptying rate because their bulk density is lower than that of gastric fluid. The medicine is released slowly and at the desired rate from the produced gel when it floats on gastric fluid. The remainder of the medicine is expelled from the stomach after it has been liberated from the floating system. This could improve GRT and stabilise plasma medication concentration swings (PCD). The hydrodynamically balanced system (HBS), also known as the floating system, is a controlled or sustained release dosage form that has characteristics akin to hydrophilic matrices and is characterised by the formation of a low density polymeric gel barrier at the outer surface. Like with traditional hydrophilic matrices, the drug is released from the matrices gradually. This version may float on stomach contents for 8 to 10 hours without slowing down the rate of gastric emptying. Floating medication delivery dosage forms use a variety of polymer systems. [32-33]

I.1). Factors affecting the floating drug delivery system[34-40]

a. Density:

As a function of dosage form buoyancy, which is reliant on density, gastric retention time (GRT) is calculated.

b. Size and Shape:

According to reports, dosage form units with a diameter of more than 7.5 mm had a higher GRT compared to those with a diameter of 9.9 mm. Tetrahedron- and ring-shaped dose forms are said to have improved GIT for 90 to 100% retention at 24 hours compared to other shapes. These forms have flexural moduli of 48 and 22.5 kilo pounds per square inch (KSI).

c. Fed or Unfed State:

The gastrointestinal motility during a fast is characterised by bursts of vigorous motor activity, or migrating myoelectric complexes (MMC), which happen every 1.5 to 2 hours. The MMC removes undigested matter from the stomach, therefore if the formulation is administered at the same time as the MMC, the unit's GRT should be very brief. However, MMC is sluggish and GRT takes a lot longer in the fed condition.

d. Nature of the meal:

Feeding indigestible polymers of fatty acid salts can cause the stomach's motility pattern to transition to a fed state, slowing down gastric emptying and extending the time that the medicine remains in the body.

e. Caloric Content:

With a meal that is rich in proteins and lipids, GRT can be extended by 4 to 10 hours.

f. Frequency of feed:

Due to the low frequency of MMC, the GRT can increase by more than 400 minutes when multiple meals are given instead of only one.

g. Gender:

Regardless of weight, height, or body surface, the mean ambulatory GRT during meals is shorter than that of their age- and race-matched female counterparts.

h. Age:

Over 70-year-olds in particular have a much longer GRT than younger persons.

i. Posture:

Between the patients' supine and upright ambulatory phases, GRT can change.

j. Concomitant drug administration:

Codeine, atropine, and propentheline opiates are anticholinergic medications. Prokinetic medications include metoclopramide and cisapride.

II. Conclusion

The in situ gels provide the increased patient compliance that is a key component of a successful controlled release solution. There are several benefits of using polymeric in- situ gels for controlled medication release as opposed to traditional dosage forms. The in situ gel dosage forms are particularly dependable since they provide a longer and sustained release of the medication together with good stability and biocompatibility features. In situ gel formulations can become more palatable and effective drug delivery methods by using biodegradable and water soluble polymers. The development of liquid orals for their continuous

medication release has a lot of potential thanks to in-situ drug delivery. This floating in-situ gel method is appropriate for medications with a limited window of stomach absorption or medications with local effects. These medications, which are presently accessible on the market in the form of pills or capsules, will also be offered as floating in-situ gels. We might anticipate improving stomach retention and, consequently, the bioavailability of medicinal drugs by fully understanding the floating behaviour of biodegradable polymer. The advantages of in situ gel over conventional ones include improved drug release, superior stability, and biocompatibility qualities.

III. Expected Outcomes

According to the study, there is an increasing need for in-situ gelling drug delivery systems in order to create viable controlled-release products that can improve patient compliance.

This project will assist in learning about the advancements made in the creation of in situ gelling.

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