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Review on in situ gel formulation

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ABSTRACT
Environmental variables such as changes in pH, ionic concentration, temperature, osmolarity, radiation, etc. can cause a formulation's physical state to change from free to immobile. A fluid solution that becomes a thick gel. In situ gelling is the term used to describe this type of phase change from "sol to gel" caused by the causes outlined above. For formulations that are easily washed away from their site of administration, such as eye drops (in solution form) or nasal drops, in situ gel is a highly helpful approach. When compared to other drug delivery methods including parenteral, nasal, rectal, vaginal, etc., in-situ gel is widely used in ophthalmic medication delivery. The goal of this new research is to highlight all potential applications for in-situ gel technology to increase bioavailability. As a result, we have covered the uses of the in-situ gel approach in the delivery of drugs via the nasal, oral, rectal, and vaginal routes. In-situ gel's primary need is the availability of appropriate and Biodegradable polymer that is compatible. Therefore, we have included a list of polymers, both biodegradable and not, that may be useful for researchers.

I. INTRODUCTION:

One of the greatest innovative drug delivery methods is the "in situ gel" system, which, thanks to its unique feature, promotes increased patient comfort and compliance as well as prolonged and regulated drug release.'Sol to Gel' transition feature. An in situ gelling system is a formulation that, before entering the body, is in solution form but transforms into a gel under different physiological circumstances. Temperature, pH change, solvent exchange, UV light, and the presence of certain molecules or ions are only a few of the variables that affect the sol to gel transition. The medication delivery methods with the aforementioned characteristics For the creation of sustained delivery vehicles, the term "sol to gel transition" can be used widely [2]. The "In situ gelling system" has a number of benefits, including simplified dosage administration, a reduction in the frequency of administration, and even protection of the drug against changes in the environment. It Is possible to use a variety of natural and synthetic polymers [2] for oral, ophthalmic, transdermal, buccal, intraperitonial, parenteral, injectable, rectal, and vaginal routes by allowing them to form gels in situ. Recent developments in in situ gels have made it possible to take advantage of the physiological variations [3,4] in various GI tract regions for better drug absorption as well as patient convenience and compliance. Some of the natural polymers utilised for in situ gelling systems include pectin, gellan gum, chitosan, alginic acid, guar gum, carbopol, xyloglucan, xanthan gum, HPMC, poloxamer, etc.Some of the natural polymers utilised for in situ gelling systems include pectin, gellan gum, chitosan, alginic acid, guar gum, carbopol, xyloglucan, xanthan gum, HPMC, poloxamer, etc. Several uses exist, and the benefits of in situ gelling in modern life. It has taken a lot of study to develop polymeric drug delivery systems. Over the past few years, in situ gel system development has drawn a lot of interest. The benefits of in situ forming polymeric delivery systems, including as simplicity of administration, decreased frequency of administration, greater patient compliance, and comfort, have inspired this interest. Smart polymeric systems offer a potentially effective way to distribute medications; after administration, these polymers go through a sol-gel transition. One or more combinations of several stimuli, such as pH change, temperature modulation, and solvent exchange, lead to in-situ gel formation. In the early 1970s, research into natural and manmade polymers for Compounds with controlled release. For the formulation development of in situ forming the drug delivery systems, many natural and synthetic polymers are utilised. The precorneal loss factors, which include rapid tear turnover, nonproductive absorption, temporary residence time in the cul-de-sac, and the relative

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impermeability of the drugs to corneal epithelial membrane, are the main causes of the poor ocular bioavailability of drugs from conventional eye drops. [51,52] another negative aspect of The nasal cavity, with its larger surface area and higher permeability of the nasal mucosal membrane than that of the cornea, is responsible for removing topically applied medicines from the precorneal area. [53-55]

IN SITUGELLING SYSTEM IMPORTANCE

- Its unique "Sol Gel transition" contributes to the drug's controlled and sustained release.
- It aids in lowering the frequency of drug administration to the body.
- There won't be any drug accumulation and no adverse effects because only a small amount of the medication is needed.
- The medicine will have a higher bioavailability.
- Due to gel formation, the drug's residence period will be prolonged.
- The in situ gel method reduces drug wastage.
- The best dosage form for drugs is a liquid that can maintain drug release and stay in touch with the cornea of the eye for a long time.
- The medicine drained through the nasolacrimal duct may have less systemic absorption, which could have certain unwanted side effects.

ADVANTAGES

- Controlled medication release that lasts for a long time.
- Medication administration is simple.
- Patients who are unconscious can receive it.
- Increased patient comfort and compliance.
- Higher uses systemic and local toxicity.
- It was given to elderly and unconscious patients.
- It aids in the prolonged or extended release of medications.
- It prevents the buildup of drugs.[27,28]
- Bioavailability [25,26]
- It makes administration simple.
- More bioavailability is provided.
- It cuts down on drug waste.
- The frequency of administration is decreased.
- It enables patient comfort and compliance.

DISADVANTAGES

- It calls for a lot of fluids.
- The medication is more prone to deterioration in its sol form.
- It need a lot more fluids.
- It is only possible to provide very modest dosages.
- There is a potential for instability because of chemical deterioration.
- Following medicine administration, restrict your intake for a few hours.
- Due to its weak mechanical strength, it could dissolve too quickly.
- Toxic effects from the use of organic solvent.
- Only applies to strong medications.
- Potential for negative effects.
- The implanting process is challenging when the implant is larger.
- The gel can be changed, leading to unreliable findings.

MECANISMS OF IN SITU GELLING SYSTEM

Two different mechanisms, such as a physical mechanism and a chemical mechanism, are used to create the in situ gel system.

Physical Process:

According to physical mechanism, in situ formation includes the following:

Diffusion

A type of physical method employed in the formulation of in-situ gels is diffusion. This approach calls for the solvent from the polymer solution to diffuse into the tissue around it, causing the matrix to precipitate or solidify. In-situ gelling systems frequently use the polymer N-methyl pyrrolidone (NMP).

Swelling

Swelling is a form of physical strategy utilised to enclose the fluids present in the outer environment and swell from the outside to the interior of polymer imbibes. Drugs release gradually. A polar lipid known as myverol (glycerol mono-oleate) expands in water to generate lyotropic liquid crystalline phase structures. This material can degrade in vivo by enzymatic action and exhibits certain bioadhesive characteristics.

Chemical Mechanism:

Based on chemical reactions, in situ gelling formation.

The following steps may be involved in chemical reactions that lead to in situ gelation:

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Cross-linking by enzymes

The most effective technique employed in the development of in situ gelling systems is enzymatic cross linking. In this technique, gel is created by cross-linking using the available enzymes. Bodily fluids. Although little research has been done on in situ production caused by natural enzymes, it does seem to have certain advantages over chemical and photochemical approaches. An enzymatic method, for instance, can manage efficacy in physiological conditions without the requirement for potentially harmful chemicals like monomers and initiators. Researchers have looked into the usage of hydrogels in intelligent, stimuli-responsive delivery devices that can release insulin.

Cross-linking of ions

The ion sensitive polymer is utilised in this process. When various ions including Na+, K+, Ca+, and Mg+ are present, ion sensitive polymers may go through a phase transition. Some Ion-sensitive molecules include polysaccharides in their class. While i-carrageenan produces elastic gels primarily in the presence of Ca2+, k-carrageenan creates hard, brittle gels in response to tiny amounts of K+. Gelrite is the most common brand of gellan gum. It is an anionic polysaccharide that experiences in situ gelling in the presence of monovalent and divalent cations.

Photo-polymerization

Electromagnetic radiations are used in the photo-polymerization method19 to create an in-situ gelling system. A tissue location may be injected with a reactive macromere or monomer solution, and the injection of electromagnetic radiation.

ARRANGEMENTS OF IN SITU GELS

The in situ gel formation of biomaterial is initiated by well-defined mechanisms.

1. Physical triggers (e. g., temperature and pH).
2. Physical influences (e. g., solvent exchange or diffusion and swelling).
3.Chemical stimulation. (e. g., enzymatic, chemical and photo-initiated polymerization).

Physiological stimuli-induced in situ gel formation:

A small number of polymers experience significant and abrupt physical and chemical changes as a result of external environmental changes. Stimuli-responsive polymers are those that respond to stimuli. They are also referred to as intelligent, smart, and stimuli-responsive polymers. These polymers interpret an improvement as a sign, evaluate the strength of the signal, and then adjust their chain confirmation in accordance.

In situ gel system with temperature trigger:

The most popular class of naturally responsive polymer frameworks for drug delivery is thermosensitive polymers. This is because temperature is relatively easy to control and additionally Successfully applicable to in vivo and in vitro research. In this technology, a change in temperature triggers the gelling of the solution, which sustains the release of the drug. These hydrogels are fluid at room temperature (20–25 °C), but when they interact with bodily fluids (35–37 °C), they become gel. An intriguing way to approach in situ formulations is to use biomaterials that change from sol-gel when the temperature rises. The ideal baseline temperature range for such a system is ambient and physiological temperature, with the ultimate goal of promoting clinical control and preventing any external heating source. The thermosensitive sol-gel polymeric framework is designed using three main methods. They are consequently placed in:

- A negative thermosensitive substance that contracts when heated B a positive thermosensitive substance that contracts when chilled
- Thermally reversible gel
- Polymers such as poloxamers, polyethylene glycol (PEG), pseudo latexes, and others exhibit temperature-induced gelation.

Ion-activated system-induced in situ gel formation:

The change in ionic strength in this case causes the imparted solution to gel. It is widely acknowledged that the osmotic gradient across the gel's surface determines the rate of gelation. When mono- and divalent cations, which are frequently found in tear liquids, are present, the watery polymer solutions form a decent gel. The electrolyte in the tear liquid, especially the cations Na+, Ca2+, and Mg2+, play a crucial role in the development of when the design is imprinted in the conjunctival cul-de-sac, it gels. Gel rite or gellan gum, hyaluronic acid, alginates, and other substances are all found in polymers that exhibit osmotically induced gelation.

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POLYMERS USED IN IN – SITU GEL:

Sodium alginate is a polymer that comes from nature. Chemically speaking, sodium alginate is an alginic acid salt that has 1,4-alginates-glycocidic linkages connecting residues of -D-mannuronic acid and glucuronic acid. A gel-based solution is frequently prepared using sodium alginate, Drug, peptide, and protein delivery. When preparing oral administration fluids continuously, sodium alginate, a water-soluble polymer used in pharmacies, is highly helpful since it acts as a stabilising and viscosity-increasing agent. [27]

Pectine

These polysaccharides, which include – (1-4) -D-galacturonic acid residues, have anionic characteristics of plant origin and can be split into two groups according to their polysaccharide structure. In the presence of a moderate amount of gel, pectin prevents the creation of a strong gel. A complex polymer called pectin mostly binds to D-galacturonic acid residues.

Pectine

These polysaccharides, which include – (1-4) -D-galacturonic acid residues, have anionic characteristics of plant origin and can be split into two groups according to their polysaccharide structure. Pectin Strong gel is created; inhibits gel formation in the presence of moderate. A complex polymer called pectin attaches to D-galacturonic acid residues primarily in the series (1-4).

Agar agar

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. Derivatives of guar gum are used.

Carbopol

A polymer made of polyacrylic acid (PAA), carbopol transformed into a gel when the pH was increased from 4.0 to 7.4. When the pH is acidic, carbopol remains in solution form but changes into a low at an alkaline pH, viscosity gels. In order to increase the viscosity of the carbopol solution and lessen its acidity, HPMC is employed in conjunction with carbopol. [29]

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. Poloxamer, for example, gels at elevated refrigerator temperatures.

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. Gellan gum is treated to produce gelrite, which is deacetylated gellan gum. To remove the acetyl group from the molecule using alkali. Gel Rite gels as a result of instillation due to the presence of calcium ions. Gellan gum is a stabilising and suspending agent in the food business.

Alcoholic acid

It is a linear block copolymer polysaccharide made up of 1,4-glycosidic links connecting residues of -D-mannuronic acid and -L-glucuronic acid. Depending on the algae source, there are differences in each block and the way the blocks are arranged along the molecule. On the addition of divalent and trivalent metal, diluted aqueous solutions of alginates form solid gels.

Gum Xanthum

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's principal structure is composed of a cellulosic backbone (D-glucose residues) and a trisaccharide side chain comprising D-mannose, D-glucuronic acid, and D-mannose connected to alternating glucose residues of the main chain.

Chatoyant

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, chatoyant is a biodegradable, thermosensitive, polycationic polymer made from chitin that has been subjected

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to alkaline deacetylation. Chatoyant is a cationic polymer that is pH dependant and biocompatible. It may dissolve in aqueous solutions up to a pH of 6.2. Precipitation by the formation of crystals results from neutralising chitosan aqueous solution to a pH higher than 6.2. of a moistened gel.

HPMC

The glucan chain that makes up cellulose has repeated –(1, 4)-D-glucopyranose units.

Some naturally occurring polymers, including HPMC, MC, and EC, have temperature-sensitive sol-gel phase transitions. When temperatures drop, cellulose material will become more viscous, and its derivatives, such as HPMC and MC, will do the same. The temperature rises. An alternative methyl substitution group has been added to the chain of native cellulose to create the natural polymer known as MC. The solution is liquid at low temperatures (under 300C), but when the temperature rises (between 40 and 500C), gelation takes place.

Poloxamer

Tri-block copolymers called poloxamer are soluble in water. It is made up of two polyethylene glycol and polypropylene glycol.

PERFECT POLYMER CHARACTERISTICS FOR MAKING IN SITU GEL

- The polymer need to have mucous membrane adhesion properties.
- It should be completely compatible and have no adverse consequences.
- It ought to behave in a pseudo-plastic manner.
- When the shear rate is increased, the polymer should be able to reduce the viscosity.
- Polymer's preferred pseudoplastic tendency.
- Better optical clarity and good tolerance are preferred.
- It ought to affect how tears behave.

APPLICATIONS OF IN SITU GEL FORMULATION

1. Oral drug delivery system

pH-sensitive hydro gels may be used to deliver medications to particular sites. Certain GI tract areas. 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 as amid added pectin's, insulin and guar gum were examined in order to develop a prospective colon-specific drug delivery system, whereas cross-linked dextran hydro gels with a quicker swelling under high pH circumstances. Both sodium alginate and gellan formulations include a complexed calcium ion that travels through a gelation process.

2. **Ocular medication delivery system**

Natural polymers including alginic acid, insulin, and xyloglucan are frequently employed in ocular delivery systems. Various chemicals for local ophthalmic delivery systems to relieve intra ocular tension in glaucoma, medications such autonomic medicines, anti-inflammatory agents, and antibiotics are employed. Because of the quick elimination of drugs from the eye caused by high tear fluid turnover and dynamics and conventional administration systems, ocular in-situ gel was created to address the bioavailability issue. Carboxyl Methyl Cellulose, Hydroxyl Propel Methyl Cellulose, Carbomers, and Poly Vinyl Alcohol are examples of viscosity enhancers that are used to raise formulation viscosity in order to maximise formulation bioavailability and lengthen precorneal residence time. Carboxyl Methyl Cellulose, Hydroxyl Propyl Methyl Cellulose, Carbomers, and Poly Vinyl Alcohol are examples of viscosity enhancers that are used to increase the viscosity of formulations in order to extend the Precorneal residence duration, which enhances bioavailability and is simple to produce. To develop corneal medication penetration, penetration enhancers such preservatives, chelating agents, and surfactants are employed. [37,38]

3.Drug delivery system for the nose

Momethasone furoate is tested for its effectiveness in the treatment of nasal in-situ gel system using xanthan gum and gallan gum as in-situ gel producing polymers. Nasal allergies 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. When compared to the commercially available product noisome (Momethasone furoat suspension 0.05%), in-situ gel was demonstrated to reduce the occurrence of nasal symptoms.

4. Drug delivery systems for the vagina and rectus [31]

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,

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is made into a liquid suppository known as a rectal in situ gel by employing the synthetic polymers creating in situ gelling agents polycarbophil, poloxamer F188, and poloxamer 407.One efficient approach, in situ gelling liquid suppositories, showed improved bioavailability.

5. Drug distribution via skin and transdermal means

The evaluation of Plutonic F127 in thermally reversible gel as a carrier for indomethacin percutaneous delivery. 20% w/w aqueous gel may be employed as a suitable foundation for topical medication administration, according to in-vivo investigations. Ion tophoresis and chemical enhancers worked together to increase insulin penetration in a synergistic way.

6. Vaginal medication

administration methods Other than tourism, it is a rather unexploited place.It is a potential delivery method for a range of medical treatments, such as chemotherapy and the delivery of vaccines. Smooth systemic drug distribution may be possible due to the vaginal epithelium's blood supply and huge surface area. Thermo reversible mucoadhesive gels and pessaries have been investigated as formulation platforms for the delivery of antibiotic and antiviral drugs, labor-inducing hormones, and even intra-vaginal vaccines.

II. CONCLUSION

The in situ gel system has emerged as one of the best innovative drug delivery technologies, the in situ gelling system aids in the sustained and effective drug delivery. Regulated medication release, enhanced patient comfort and compliance, It is possible to administer medications by oral, ophthalmic, transdermal, buccal, intraperotonial, parenteral, injectable, rectal, or vaginal routes using a variety of natural and synthetic polymers that go through in situ gel formation. In situ gel system research has a lot of potential for developing cutting-edge medication delivery methods.