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IN-SITU GELLING SYSTEM: AN ALTERNATIVE CONTENDER FOR CONVENTIONAL DRUG DELIVERY

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ABSTRACT

The oral route is among the most often utilized methods for drug delivery however it usually presents the disadvantage of reduced bioavailability due to the first-pass metabolism. Many approaches have been developed to deal with it in which the most popular one is the in-situ gelling system. Formulation based upon in-situ gelling systems has shown numerous advantages like better tolerability, better bioavailability as well as better patient compliance. In-situ gelling systems usually undergo sol-state transition into gel state depending upon the temperature, ion as well as pH condition. The mechanism of the in-situ gel is of three types which are swelling, diffusion and chemical reaction. In the first one, there is the absorption of water due to which there is swelling of the formulation, in the other one there is a precipitation of the polymer in the tissues whereas in the last one there is a formation of the in-situ gel due to the various chemical reactions. Gelling systems are usually classified divided into three groups: systems that are pH, ion, and temperature sensitive. In-situ gelling systems are usually formulated with the help of cross-linking

of the co-polymers by numerous approaches. Formulation based upon in-situ gelling system is the best candidate for medication administration owing to its lower dose requirement along with fewer side effects.

Keywords: Gels, In-situ gelling system, ion, pH, Cross-linking, Sol-state, Transition

1. INTRODUCTION

Gels are semi-solid preparations, in which solid objects compact with liquid phases that are large but heavier than liquid. Because hydrogels are classified as aqueous gels. The means of hydro, substance are already mixed with water. The cross-linked network of hydrophilic polymers is hydrogels. Hydrogel can maintain its 3D shape although it possesses a large capacity for water absorption and swelling. Hydrogels exist into two forms hydrogels that are pre-formed and in situ. The basic viscous liquid gels that do not change after administration are known as preformed hydrogels while the gels that change nature after approaching the particular site are known as in-situ gels.(1)

The systems for in situ gel formations have been highly researched for the continued distribution of drugs. The importance of an in situ polymer delivery system are easy for the administration of drugs and decreases administrative rate, better tolerance by patient and convenience. This gel formulation is the result of one or more combinations of factors, like pH dependent and change in temperature and solvent exchange. In situ gelling methods can be formulated via various routes, including nasal, oral, ophthalmic and so on. In the synthesis of in situ gels both Polymers, natural and artificial, are employed. such as gums which include gellan gum, sodium alginate and caprolactone etc.(2)

For the most part, these systems manifest as gelling into the body and in a sol-state prior to injection. Their simplicity of use, lengthy residence period, administration location, and sustained drug release, together with lower administration frequency and better patient compliance, define them. This formulation's significant success can be attributed to its versatility in terms of delivery methods, which allow for either a systemic or localized pharmacological action. They are effective as vehicles for delivering both nano- and microdrugs (3). The presence of ions, temperature increases, and pH changes are some of the variables that might bring about the sol-gel transition. The temperature-sensitive in situ gelling systems undergo a temperature-dependent sol-gel transition that approaches physiological values, typically between 32 and 37 ^{0}C, depending on the administration site. At ambient temperature, they are in a sol-state (4).

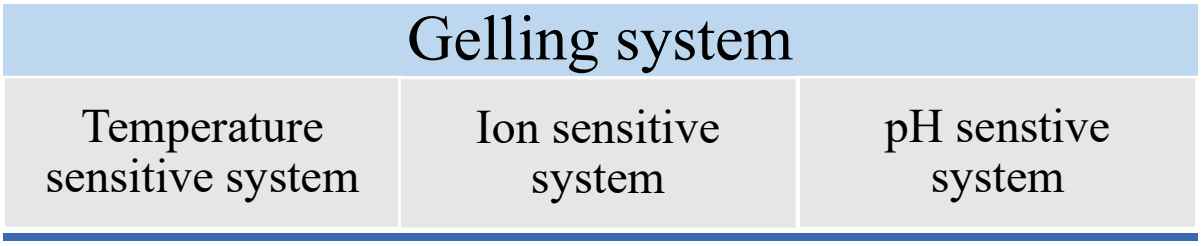
The existence between hydrophilic and hydrophobic groups in the structure of polymers causes them to alter significantly in terms of how soluble they are in water, which serves as the basis for the phase transition process. A change in the interactions between a polymer and water caused by a rise in temperature leads to rapid polymer precipitation and solvated polymer chain dehydration. Amphiphilic polymers that self-assemble into micelles at certain concentrations in water above the crucial concentration of micellar substances begin to gel as the temperature rises. Temperatures

above the micelle ordering is induced by a crucial micellar temperature, and this ordering results in gelation (5).

Poly (N-isopropylacrylamide), poloxamers and derivatives of cellulose constitute among the most commonly used thermosensitive polymers used in medication delivery. Alginate and gellan gum are examples of ion-sensitive polymers cross-linked by sodium, magnesium and calcium cations which are present in physiological fluid. This phenomenon converts solution into gel forms and thus there is gel formation after the sol-gel phase transition. The rate of sol-gel transition depends upon the type and concentration of cation in physiological fluid(6).

2. TYPES OF GELLING SYSTEM

In situ gelling formulation is generally of three types based upon temperature, ionic concentration and pH level based stimuli. Although they are included in this analysis, other stimuli like as light and redox potential are not as beneficial for medicinal applications. By combining When covalent gel formation reagents are applied, in situ gel formation can be achieved primarily(7).



2.1 **Temperature sensitive system**

The entropy of mixing increases as Higher than the lower critical solution temperature (LCST), which can cause the sol-gel transition. It also accelerates the dehydration of the chains of solvated polymers and increases hydrophobic contacts. Usually sol-like, one-phase systems in an aqueous media, thermosensitive in situ gelling systems Because they may transform into a solid or liquid, these systems also exhibit thermoreversible behavior(1). Systems using in situ hydrogel that are thermosensitive or thermoreversible are present in the form of sols below the body temperature but when it administered to the body it attain body temperature then it convert into in situ gelling system. The principal polymer used to make thermoreversible in situ gel poloxamer 407 (pluronic F127) and poloxamer 188 (pluronic F68) are examples of poloxamers or pluronics(8).

The polymer that is used in the thermosenstive in situ gel should have specific properties such as triblock copolymers that are biocompatible, nonionic, and composed of intricate hydrophilic and lipophilic elements. Thermoreversible gels are produced by dehydrating polymer blocks at high temperatures, resulting in concentrated aqueous solutions of these poloxamers that kind of nonchemical crosslinking results in the formation of a hard, very viscous hydrogel.

Thermoreversible hydrogels based on poloxamer possess the physicochemical characteristics required to effectively deliver medication for joint conditions. Poloxamers have the added benefits of being non-toxic and biodegradable and can help make drugs that aren't very soluble in water more soluble. Because the solutions are low viscosity, injection is made simple(9).

It is difficult to evaluate thermoreversible gels rheologically. The rheological terms A material's storage modulus (G′) and loss modulus (G″) provide information about viscous and elastic properties, respectively. Flexible Materials undergoing applied deformation regain their structural integrity while Materials that are viscous obstruct the flow without recovering. The temperature, the time sweep test and ramp test are used, respectively, to assess the temperature and duration of the in-situ gelling compositions during gelation. Well, it is anticipated that samples would maintain their low viscosity condition at < 25 ◦C. before administration and while being stored to enable its capacity to syringe. After thereafter, the medication composition ensures that it is kept on sites for extended periods of time by gradually changing to its gel form in situ at the location's temperature; encouraging cellular(10)

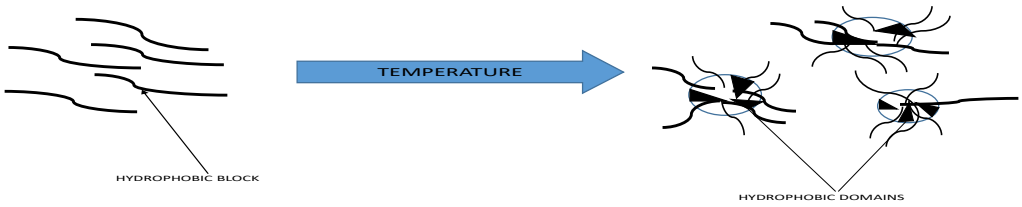


Fig .1 Temperature sensitive system as in situ gelling system

2.2 Ion sensitive system

The ionic strength shift in this case causes the implanted fluid to gel. The osmotic gradient that takes place throughout the gel's surface controls how quickly gelation happens. When mono- and divalent cations are present as normal. The aqueous polymer found in the tear fluids results in a transparent gel. The ionic solvent in the tear fluid, particularly Na+ the Ca2+ additionally and essential part of initiation is played by Mg2+ cationsof gelling once the mixture is injected into the conjunctival cul-de-sac. Materials that show Gelrite or other osmotically generated gelations Alginates, hyaluronic acid, gellan gum, etc(11).

Following an electrostatic contact between the biological fluid and the drug-carrying organisms that have opposing charges, they exhibit a sol–gel transition. How viscous the cross-linked polymer is, and how pace at which the polymeric system transitions from a sol-gel state depend on the kind as well as cation concentration used to the ion-sensitive polymers should be cross-linked. Furthermore, pathological situations that alter the target locations' ionic composition and potency may make it easier to transition ion-sensitive dosage forms from sol-gel form(12).

Adding resemblance through the combination of in-situ gelling samples with biological fluid (such as tear, nasal, or vaginal fluid), the ion-sensitive delivery system's gelation capability may be examined. Changes in the rheological profiles of these samples can then be examined utilizing turbidimetric or viscometric analysis (13).

Methacrylated gellan gum, gellan gum, sodium alginate, and pectin are examples of ion-sensitive drug delivery techniques. The polysaccharide gellan gum is used in an anionic compound. It contains 1,3-(d-glucose), 1,4-(lucoronic acid), 1,4-δ--glucose, and 1,δ-Δ-Δ-R rhamnose repeating units(14). Gellan gum experiences pH-responsive, ion-dependent, and temperature-dependent gelation. It becomes a gel via hydrogen bonding with water and complexing with cations. Its formation yields a three-dimensional gel network and a double helical junction zone. Ion sensitivity is demonstrated by clay gels during the gelation process(15).

2.3 pH sensitive systems

The polymer's pKa influences the gelation behavior of a formulation that is sensitive to pH. A pH-sensitive polymer solution that is slightly acidic or basic usually gels at pH values that are either higher or lower than its pKa. Furthermore, the ionization state (pKa), conformation, or solubility of the polymer to gelate may all be affected by changes in pH in the physiological environment. the drug carrier. Usually, a pH sensitive polymer has ionizable weak base or weak acid moieties on its backbone. For instance, a polymer with weak acid groups (such as methacrylic acid that contains carboxylic acid) deprotonates at an alkaline pH level (beyond its pKa value) and gains a negative charge, hence enhancing the electrostatic repulsivity among polymer molecules and potentially causing physical transitions(16).

In order to achieve gel conformation, pH values below the pKa can thereby increase polymer-polymer relations, which are comparable to the H-relating between COOH dyads. When the pH rises A polyelectrolyte will form from the polymer above the pKa, which will usually provide thick results and cause polymer aversion. Other elements that may influence this transition include the polymer's molecular weight and ionic strength. Similar to amines, weakly introducing polymers are protonated at acidic pH values below the conjugate acid's pKa (pKaH). Above this point, they are often uncharged and exhibit weakly acidic systems (17). By taking usage of chemical reactions that lead to covalent trade between chains and are either favored or disfavored depending on pH, pH-responsive devices may also be constructed in an alternative manner. Phrasings that are sensitive to changes in pH include xanthan-grounded systems that release The bovine serum albumin is regulated at physiological pH, and the in situ gelling packets (Carbopol 934), which parade at nasal pH ≈8.3 in rhinitis instances, are grounded in polyacrylic acid(18).

3. Importance of In situ gelling system(19)

Comparing the in situ gel to a previously made gel, the primary benefit is the capacity to portion exact and repeatable doses of medication. Among the other benefits of in situ forming gel are

• Treatment requires a low dosage with the fewest possible local and systemic negative effects

• simplicity of use;

• decreased frequency of medication administration;

• enhanced patient comfort and compliance;

• longer duration of stay;

• enhanced bioavailability.

4. Advantage of In situ gel(20)

• Reduced systemic unfavorable effects due to decreased nasolacrimal outflow of the medication, which might result in unintended side effects because of systemic absorption.

• Less clouded vision as compared to ointment. Unlike formulations that have already gelled, the potential is to provide precise and repeatable dosages while also encouraging precorneal retention.

• Extended and sustained drug release with a mostly stable plasma profile.

• Less frequent applications, which leads to increased patient comfort and compliance.

• Usually more pleasant than insertion that is soluble or insoluble.

• Greater absorption and residence duration of precorneal compounds, leading to improved local bioavailability.

• Because of its simpler manufacture, there is less of an investment and manufacturing expense.

5. Mechanism of In-situ gel

The mechanism of In-situ gel for the drug release follows three pathways which are as follows:

1. **Swelling:**
   The substance employed in the in-situ gel formation process has the natural ability to absorb water from its surroundings and expand to the desired region. As an illustration, polar lipid glycerol mono-oleate swells in water to create lyotropic liquid crystalline phase formations. It has some bioadhesive properties and is enzymatically degradable in vivo(21).
2. **Diffusion:**
   This process precipitates or solidifies of polymer matrix by allowing solvent from the polymer solution to diffuse into the surrounding tissue. The useful solvent of this system is N-methyl(22).
3. **Based on chemical reaction mechanism:**
   Enzymatic, photo-initiated, and precipitation of inorganic particles from supersaturated ionic solutions are examples of chemical reactions that lead to in situ gelation(11).

6. ROUTE OF IN SITU GELLING DELIVERY

The in situ gelling formulation is administered intraperitoneally, intravesically, ocularly, vaginally, and nasally to different body locations. Table 1 provides a summary of the clinical and rheological features of in situ gelling systems studied over the past ten years; more details will be provided in the manuscript's next section.

6.1 Buccal formulation

Therapeutic agents have been delivered the mouth cavity's buccal mucosa by use mucoadhesive in situ gelling delivery systems relieve the discomfort caused by oral mucositis and esophagitis, which are common in those having treatment for head and neck cancer. K-carrageenan is a copolymer that responds to ions and temperature comprising 3,6-anhydrogalactose, sulphated ester, and galactose, with one negative charge per disaccharide residue, and it is used to manufacture buccal dosage forms. It has anti-inflammatory and antioxidant characteristics. When exposed to high temperatures and ions like K+, Na+, Mg2+, and Ca2+, it transitions from a coil to a helix conformation, and then helix aggregation occurs which turns it into gel(23).

Using a rheometer, Vigani and colleagues produced bioactive Hibiscus sabdariffa extract (HSE; 0.2%)-based in situ gelling systems that contained calcium chloride (0.04%), k-carrageenan (0.4% or 0.6%), and hydroxypropyl cellulose (HPC; 1%). Saliva ions and calcium chloride caused the formulation to turn into a gel, however K-carrageenan showed wound-healing properties and enhanced the formulations' mucoadhesive properties(23).

The formulations containing 0.4% and 0.6% HSE showed normalized rheological synergism values of The results indicate that there was a comparable level of interaction between the two formulations and saliva ions, with 1.44 ± 0.9 and 1.19 ± 0.06, respectively. The formulations containing 0.4% and 0.6% HSE showed normalized rheological synergism values of 1.44 ± 0.9 and 1.19 ± 0.06, respectively. This indicates that the two formulations demonstrated a commensurate level of interaction with saliva ions. Furthermore, adding a higher concentration of the bioactive extract improved the formulation's gelling capacity by reducing its decrease tangent values relative to the empty formulations. The formulation's capacity to encourage cell proliferation and better bind to human dermal fibroblasts was enhanced by the use of hibiscus extract. After being exposed to cells, HSE and formulations containing HSE showed similar inflammatory characteristics in terms of the release of interleukin-8(24). Gellan gum, xyloglucan, and pectin are the polymers employed in oral in situ gel delivery methods. There have been reports on the possibility of using an oral in situ gelling pectin formulation to distribute paracetamol over time. There have been reports of using Oral theophyllin delivery using in situ gelling gellan formulation.The creation of silicone microspheres, which in the stomach media released prednisolone and shown protective properties, was aided by hydrogels composed of different ratios of PAA derivatives and cross-linked PEG(22).

6.2 Ocular delivery

Organic polymer including xyloglucan, gellan gum, and most often, alginic acid is employed in ocular delivery systems. Several substances, including antimicrobials, anti-inflammatory pharmaceuticals, as well as autonomic agents meant to lower intraocular tension in glaucoma, have been administered locally via the eye. Poor bioavailability and limited therapeutic response resulting from fast the dynamics of tear fluid turnover that lead to the medication to be rapidly eliminated from the eye are issues when using conventional drug delivery systems. Therefore, in situ gels were designed to solve this issue. Viscosity enhancers, such as HPMC, CMC, Carbomers, and PVA, are used to raise the bioavailability even more by extending the precorneal residence period. Producing them is simple. To improve the penetration of drugs into the cornea, penetration enhancers such surfactants, chelating agents, and preservatives are also utilized. A large portion of gellan gum's medicinal relevance has been focused on its use in the transport of medications to the eyes. The medication Indomethacin is utilized in ocular in-situ gelling devices(22).

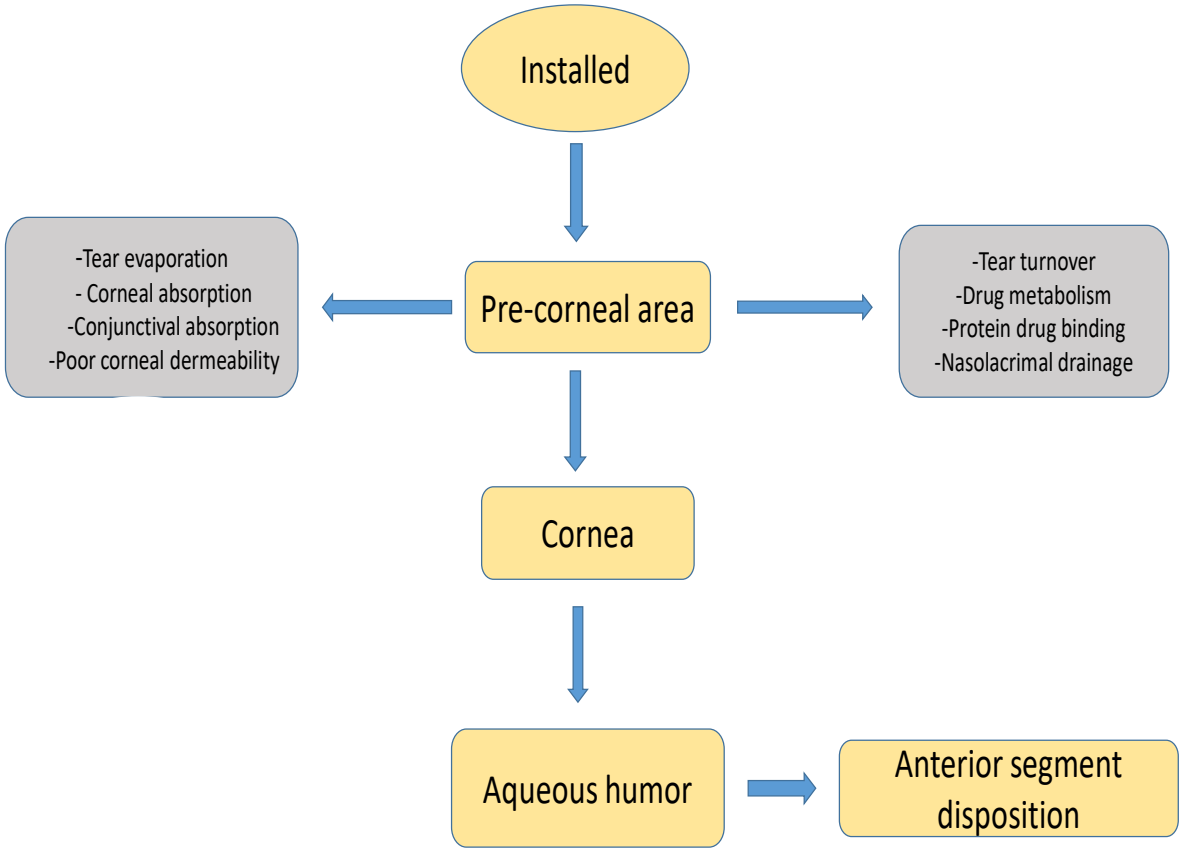


Figure 2. Working of In-Situ gelling system

6.3 Nasal drug delivery

For the nose, in situ gel systems frequently use polymers such as gellan gum and xanthan gum. Methasone furoate was developed for use in nasal in situ gel delivery devices, and its efficacy in treating allergic rhinitis was evaluated. When compared to the commercially available product Nosonex (methasone furoate solution 0.05%), nasal in situ gel administration is more efficient and appropriate for the delivery of drugs and proteins (23).

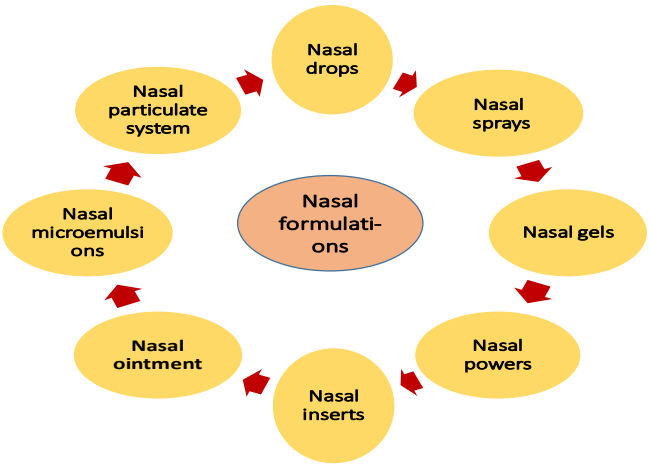


Figure 3 Type of Nasal formulation

6.4 Rectal drug delivery system

Numerous medication kinds that are manufactured as liquid, semisolid, or solid dose forms can be administered via the rectal route. Certain conventional suppositories frequently cause irritation when inserted. Furthermore, because suppositories are unable to properly remain at a fixed spot in the rectum, they may occasionally go upward into the colon, potentially experiencing the first-pass effect of the medication. The gelation temperature of the temperature range for the new in-situ gelling liquid preparation is 30 to 36 degrees Celsius. To impart the temperature-sensitive gelation characteristic, poloxamer 407 or poloxamer 188 were utilized. One example is a thermoreversible gel based on xyloglucon that is used to administer Indomethacin via the rectal canal (24).

6.5 Vaginal drug delivery system

An essential reproductive organ that may be used as a delivery system for drugs is the vagina. This thermosensitive, mucoadhesive, extended-release vaginal gel containing clotrimoxazole-β-cyclodextrin complex is designed to treat vaginal infections and improve patient adherence while increasing therapeutic effectiveness.

6.6 Injectable drug delivery system

Much research has been conducted in the past ten years on injectable in situ medication delivery devices. A new in situ gelling formulation for tumour treatment was developed. The hydrogel was composed of drug-loaded Chitosan, neutralized by a neutralizing agent, and contained the drug Paclitaxel. The injection of paclitaxel locally using this formulation intratumorically was studied in albino mice with EMT-6 tumors implanted subcutaneously. Poloxamer gels have been tested in i.m. & s.c. growth hormone administration or for the formulation of a long acting single-dose Lidocaine injection.

7. Classification of in-situ gelling formulation

In situ gelling system is classified on the basis of the route if administration.

Table 1: Medication following different routes with observations.

ROUTE	MEDICATION	OBSERVATION	REFERENCE
ORAL	Mucoadhesive formulation containing sodium Chondroitin sulphate, xyloglucan and glycerol	Formulation shown more mucoadhesive property than marketed one.	(25)
OCULAR	Ocular inserts potentially formulated with controlled release gelatin hydrogel and lyophilisation.	Carbodimide-crosslinked gelatin is a potential candidate for ocular drug delivery as an ocular insert.	(26)
NASAL	Formulation of nasal in situ gel with Chitosan microparticle is the factor that Influence particle size during ionic gelation.	To determine the effect of selects factor on the size of chitosan microparticle prepared by means of ionic gelation.	(27)

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8. Methods of preparation

Many techniques have been documented for the production of the in situ gel. Some of the aforementioned techniques connect co-monomers via polymerization or the use of chemical cross-linking agents, while other techniques included polymer irradiation or chemical cross-linking.

a) Solution polymerization or cross linking

This process involves combining multipurpose cross-linking substances that neutral or ionic monomers. Devices that employ heat, UV light, or redox initiators are helpful in starting the polymerization process. As a heat sink, the solvent reduces the temperature problem. Distilled water washing is required to remove any remaining particles from the finished hydrogel. Hydrogels made of poly(2-hydroxyethyl methacrylate) consist of hydroxyethyl methacrylate and ethylene glycol dimethacrylate, which acts as a cross-linking agent comprise the greatest examples of this approach(28).

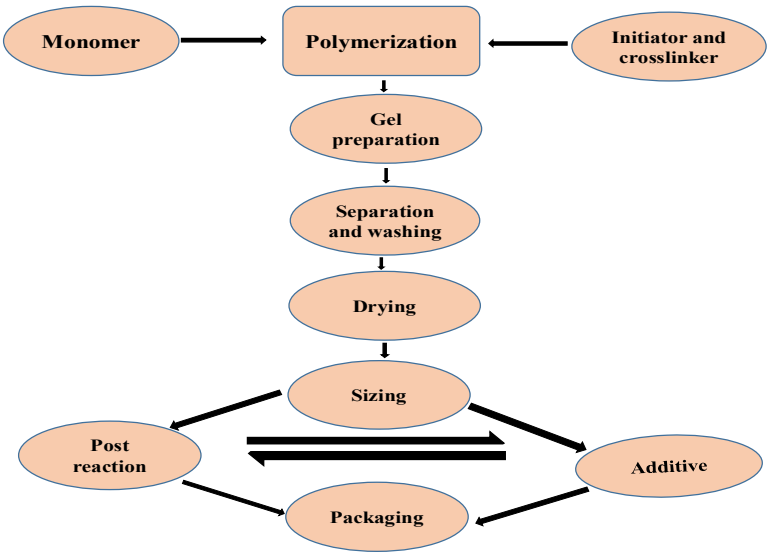

Figure 4- Representation of Cross-linking mechanism

b) Suspension polymerization

The spherical microparticles produced by this process have from 1µm to 1mm in size. Fine droplets are formed when the monomer solution disperses within the solvent less state. Adding stabilizer to create microparticles as small as micrometers is a popular application of this technique (29).The breakdown of free radicals by heat initiates the polymerization process.The generated microparticles must be rinsed in order to get rid of the monomer, cross-linking agent, and initiator that have not yet reacted Suction polymerization was used to create hydrogel microparticles of Poly(Vinyl Alcohol) and Hydroxyl Ethyl Methacrylate process(13)(11).

c) Polymerization by irradiation

Hydrogels made belonging to unsaturated substances are produced with the use of high-energy radiations such as gamma and electrons. Applying radiation to an aqueous polymer solution causes radicals to form on the chains of polymers, leading to the generation of micro-radicals (19). After the micro-radicals recombine on different chains to generate covalent bonds, a cross-linked structure is finally produced. a second polymerization With nitrogen or argon gas (30), an inert atmosphere is used since radiation may interact with oxygen. Three polymers—vinyl alcohol, ethylene glycol, and acrylic acid—are examples of this approach (31).

d) Chemically crossed linked hydrogels

Functional groups such as -OH, -COOH, or -NH2 are dissolved by water in polymers. It is possible to employ the polymer chain because of these functional groups in Schiff's base formation, acidic amine, isocyanate -OH or -NH2, or via covalent bonding between Chains of polymers and complimentary reactivity to generate hydrogels. As a cross-linking agent, glutaraldehyde can be used to hydrogelize amine-containing polymers, such as polysaccharides, albumin, and gelatin or -OH groups (vinyl alcohol) (1). Through an addition reaction, this cross-linking agent interacts with the polymer's functional groups. Unreacted substances are especially hazardous because cross-linking agents must be eliminated. Furthermore, the cross-linking agent and water may react, therefore the reaction needs should be done using organic solvents. Typically, first-order release occurs because the medicines are added after the hydrogel forms (13).

e) Physically cross linked hydrogel

Practically Each and every covalent cross-linking substance is recognized to be hazardous, even at extremely low doses. To circumvent this problem and avoid the requirement for a purification stage, hydrogels are therefore created via ionic cross-linking that is reversible. The cationic polymer of polymers chitosan forms a system of ionic bridges connecting its polymeric chains positively charged materials, such ions or molecules, contact with it. Numerous studies have been conducted on ionic molecules that include groups of phosphate, particularly sodium triphosphate. It is easy to understand how ionic cross linking works. While covalent cross bonding requires auxiliary molecules, catalysts are not required in this case. A polyelectrolyte complex can also be produced using chitosan and poly (acrylic acid) (32).

9. Evaluation and characterization

9.1 Clarity:

A visual assessment is conducted on a monochromatic background to evaluate the sharpness of the generated solution (33).

9.2 Texture analysis:

In order to make the formulation easy to inject in vivo, the texture analyzer is used to evaluate the hydrogels' cohesiveness, hardness, and consistency. This tool also significantly indicates the syringe ability of the solution. Gels having greater adhesiveness values are required to maintain a tight contact with the surface (34, 35).

9.3 pH of gel:

The mixture is placed in a beaker, and 1 milliliter of NaOH is added dropwise while stirring constantly. The pH is measured using a pH meter(35).

9.4 Sol-Gel transition temperature and gelling time:

This is how the temperature at which sol-gel transitions may be explained: the phase transition of the meniscus at various temperatures is first observed when a sol meniscus is Temperature-controlled and heated within a sample tube. When the tube tilts, there is no meniscus movement, which indicates that gel has not formed (36).

9.5 Gel strength:

The gel's strength is determined by using a thermometer. How well the gelling ingredient works determines how strong the gel . A certain volume of gel is produced in the sol form in a beaker. Gently insert a probe into the gel after it has reached a certain elevation in the beaker gel. The variation in strain on the gel surface is determined by the depth to which the probe is submerged below it(37).

9.6 Rheological studies:

For in situ gel evaluations, this variable is among the most crucial ones. Ostwald's viscometer, the Brookfield rheometer, and other viscometers are used to measure the vessel viscosity and rheological characteristics of in situ gelling drug delivery systems. Specifically for parenteral and ocular administration, in situ gelling solutions should have a viscosity that makes it easy for the patient to deliver. The range of viscosity profiles for the formulation should be 5 to 1000 MPS (38).

9.7 High performance liquid chromatography:

A packed column of 150 mm in length and 3.9 mm in diameter is analyzed using a Nova pack C18 when using HPLC in reversed mode(39).

9.8 Drug-polymer interaction study and thermal analysis:

Research on interactions makes use of Fourier Transform Infrared (FTIR) spectroscopy. This technique may be used to evaluate the type of interacting forces that occur throughout the gelation

process by employing the KBr pellet approach. In the insitu gelling device, thermogravimetric analysis is used to determine the hydrogel's water content. Differential scanning calorimetry (DSC) is used to compare thermograms to pure active ingredients used in gelation in order to detect any alterations (40).

9.9 In vitro drug release studies:

Plastic dialysis cells are used in the drug release experiments for in situ gel formulations administered orally, ocularly, or rectally. Cell membranes aid in order to distinguish between the donor and receptor compartments, which comprise the two half cells that comprise the cell(21). Within the donor compartment lies the formulation's sol form. An incubator is then used to shake the formed cell horizontally. Analytical techniques are used to assess the drug release from the receptor solution in its whole (41). In order to create Receptor media are placed into vials containing the formulation for injectable in situ gels adjusted to the proper temperature and oscillation rate in a shaker water bath. Samples are taken out and examined on a regular basis(42).

9.10 Antimicrobial activity:

To find out how biologically active the sol-gel system is against microbes, antimicrobial investigations are conducted. Here, "Cup Plate Techniques" are utilized with an agar diffusion media. The technique known as serial dilution is used in microbiological assays to quantify the microbiological growth of bacteria by contrasting their concentration with those obtained from typical antibiotic medicines at recognized doses(11).

9.11 Sterility Testing:

According to IP 1996, sterility testing is done.At least 14 days (30–35°C) in the fluid thiencolate medium and 20–25°C in soybean casein digest are required for the formulation to be incubated in order to identify the growth of bacteria. Medium; 20–25°C To identify fungal growth in the formulation, use soybean casein digestion media(43).

9.12 Accelerated stability studies:

As per the guidelines of the International Conference on Harmonization (ICH), the formulation is refilled into vials with an amber color and sealed with aluminum foil for a short-term accelerated research at 40 ± 2°C and 75 ± 5% RH. The sample is reanalyzed every month to evaluate its rheological analysis, in vitro dissolution, solvent content, pH, gelling ability, and clarity(44).

CONCLUSION:

Drug delivery systems include those that use in situ gelling that has proven to be an ideal candidate in drug delivery as compared to oral dosage forms because of higher bioavailability, bypass of hepatic metabolism, direct entry into the systemic circulation and uniform dosage forms. Among the most crucial characteristics present by in situ gelling system is the trans-sol phase in which there is the transition from liquid state into solid phase upon getting in contact with physical as

well as chemical parameters like pH, temperature, presence and concentration of ions. Due to their unique property there is much research and development in the formulation of in situ gelling system that has led to the rise of much more efficient systems that makes them ideal for drug delivery in the therapy for treating diseases most notably ocular diseases like eye infection. Formulation of in situ gelling system is easy and there are numerous approaches to prepare them like cross linking, suspension polymerisation, irradiation assisted polymerisation, physical as well as chemical cross linking of hydrogels. There is variety of routes from which they can be administered to patient like oral, ocular, vaginal and nasal. The mechanism by which they release drug is usually classified into three categories like swelling in which there is the absorption of water by the polymer that leads to their expansion of volume with subsequent delivery of the drug, second one is diffusion in which the drug permeates the surrounding physiological fluid after diffusing from the polymer and the last one is chemical reaction-based drug release. In situ gelling systems are usually evaluated for many parameters like visual clarity, texture, pH and gel strength etc. in order to assess their formulation uniformity and better drug release. In the upcoming future, there is a great scope of their inclusion among the best efficient drug delivery systems that will increase the efficiency of the therapy and management of diseases.

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