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A Review on Concept of In Situ Gel and Its Applications

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ABSTRACT

Today, controlled and sustained drug delivery has become the standard in modern drug design. Intensive research is being conducted to significantly improve the efficacy, reliability, and safety of medicines. This interest was evoked by the benefits exhibited by the in-situ formed polymer delivery system such as improved patient compliance, ease of administration, and reduced frequency of administration. Gel formation depends on factors such as temperature modulation, pH changes, the presence of ions, and UV light. In-situ formed gel then releases a drug in a sustained and controlled manner. Both natural and synthetic biodegradable polymers are used for the formulation of in-situ gels such as pectin, alginic acid, gellan gum, xyloglucan, etc. In-situ gels are evaluated for their physical strength, appearance, and performance both *in vitro* and *in vivo*. Recent developments in the field of polymer science and technology allow in-situ gels to be used in different drug delivery systems like ocular, nasal, buccal, vaginal, and rectal, etc. This review mainly focuses on the introduction to in-situ gel, various approaches utilized, various polymers used, its evaluation, and applications.

INTRODUCTION:

The "in-situ gel" system has emerged as one of the best new drug delivery systems. The in-situ gelling system helps to improve the sustained and controlled release of the drug, patient compliance, and comfort due to the special features of the "Sol to Gel" transition (1). An in-situ gelling system is a formulation that is in the form of a solution before it enters the body, but it transforms into a gel under one or combinations of a variety of physiological conditions. The sol-to-gel transition depends on a variety of factors, including temperature, pH changes, solvent exchange, UV radiation, and the presence of specific molecules or ions (2). Drug delivery systems with the above "sol-to-gel" properties can be widely used in the preparation of sustained delivery vehicles for bioactive molecules. The "in-situ gelling system" has several advantages, including ease of dose application, reduced dosing frequency, and protection of the drug from changing environmental conditions.

A variety of natural and synthetic polymers undergo in-situ gel formation and may be used in the oral, ocular, transdermal, buccal, intraperitoneal, parenteral, injection, rectal, and vaginal routes (3). Recent advances in in-situ gels have made it possible to take advantage of changes in physiological uniqueness and in different areas of the gastrointestinal tract to improve drug absorption and improve patient convenience and compliance (4). Pectin, gellan gum, chitosan, alginic acid, guar gum, carbopol, xyloglucan, xanthan gum, HPMC, poloxamer, etc. are some of the natural polymers used in the in-situ gelling systems (5). This review focuses primarily on the introduction of in-situ gels, different approaches, the evaluation of the various polymers used, and their applications.

IMPORTANCE OF IN-SITU GELLING SYSTEM: (6-8)

- In-situ gels promote the controlled and sustained release of the drug because of its special ‘Sol-Gel transition.’ after administration.
- Because of the sustained release of drug frequency of drug administration and the dose of a drug can be reduced.
- Accuracy of dosing and controlled release of drugs from in-situ gels results in no drug accumulation and no side effects.
- Significant increases in bioavailability and reduction in dose of a drug.

- The increased residence time of the drug and increased contact of the drug with tissue due to gel formation.

- Accurate and reproducible doses delivery is possible with in situ gels unlike conventional gel formulations.

- In-situ gel systems show ease of administration because of their physical form which results in improving patient compliance and comfort.

APPROACHES OF IN-SITU GEL DRUG DELIVERY

There are three broadly defined mechanisms used for triggering the in-situ gel formation: Physiological stimuli, physical changes in biomaterials, and chemical reactions.

In-situ formation based on physical mechanism:

Diffusion: Diffusion is the type of physical approach used in in-situ gel formulations. This method involves the release/ diffusion of solvent from a polymer solution to surrounding tissue resulting in Precipitation or Coagulation of polymer matrix (9).

Swelling: In-situ formation can also occur when a material absorbs water from the surrounding environment and expand to occur desired space. In this method, the polymer absorbs surrounding fluids that are present in the exterior environment and swell to release the drug slowly (10).

In-situ formation based on physiological stimuli:

Thermally trigged system: Temperature-sensitive hydrogels are probably the foremost commonly studied class of environment-sensitive polymer systems in drug formulation development. The use of polymers, where the transition from sol-gel is caused by increased temperature, is an attractive way to approach in-situ formation. The ideal critical temperature range for such systems is ambient and physiological temperatures, facilitating clinical manipulation and requiring no external heat source other than the body to gel the trigger. The useful system must be adjustable to account for small differences in local temperature that may be encountered on the surface of the skin or the appendages in the oral cavity (11).

There are three main strategies for the formation of temperature-responsive sol-gel polymer systems. For convenience, temperature-sensitive hydrogels are classified into negative heat-sensitive, positive heat-sensitive, and heat-reversible gels (1, 3). Negative temperature-

sensitive hydrogels have a low critical solution temperature (LCST) and shrink when heated above the LCST. Polymers with a low critical temperature (LCST) transition between ambient and physiological temperatures are used for this purpose. One of the most widely studied polymers showing useful LCST transitions is poly N-isopropyl acrylamide (PNIPAAm) (12). Positive temperature-sensitive hydrogels have an upper critical solution temperature (UCST) and such hydrogels shrink when cooled below UCST. The polymer network of polyacrylic acid (PAA) and polyacrylamide (PAAm) or poly acrylamide-co-butyl methacrylate has a positive temperature dependence of swelling (13, 14). These polymers exhibit miscibility gaps at high or low temperatures and have upper or lower critical solution temperatures (15).

pH triggered systems: In these systems solution to gel transition is triggered by pH change. All pH-sensitive polymers contain additional acidic or basic groups that accept or release protons in response to changes in environmental pH. Polymers with many ionizable groups are known as polymer electrolytes. The polyelectrolytes are present in the formulation causes an increase in external pH that leads to swelling of hydrogel that forms in-situ gel(16). Swelling is dependent upon the external pH and functional group present on the hydrogel. For weakly acidic (anionic) groups hydrogel swelling increases with increasing external pH on the other hand it decreases with weakly basic (cationic) groups. Most anionic pH-sensitive polymers are based on PAA (Carbopol®, carbomer) or its derivatives (17). Similarly, a low viscosity polyvinylacetal diethylaminoacetate (AEA) solution at pH 4 forms a hydrogel at neutral pH conditions (18).

Drugs prescribed in liquid solutions have some limitations, including limited bioavailability and a tendency to be easily removed by tears. Low pH of the PAA solution was found to damage the surface of the eye before it was neutralized by tears. This problem was partially resolved by combining PAA with the viscosity-enhancing polymer HPMC, resulting in a sol at pH 4 and a pH-responsive polymer mixture gelled at pH 7.4 (19). A mixture of polymethacrylic acid (PMA) and polyethylene glycol (PEG) has also been used as a pH sensitive system to achieve gelation (20).

In-situ formation based on chemical reactions:

Chemical reactions that result in in-situ gelation may include enzymatic processes, precipitation of inorganic solids from supersaturated ionic solutions, and photo-initiation processes.

Ionic crosslinking: Polymers can undergo a phase transition in the presence of various ions like Na^+, K^+, Ca^+, and Mg^+. Some of the polysaccharides fall into the ion-sensitive class (21). While k-carrageenan forms a hard and brittle gel in response to small amounts of K^+, i-carrageenan mainly forms elastic gels in the presence of Ca^{2+}. Gellan gum is an anionic polysaccharide that gels in-situ in the presence of monovalent and divalent cations such as Ca^{2+}, Mg^{2+}, K^+, and Na^+. Gelation of low methoxy pectin can be caused by divalent cations, especially Ca^{2+}. Similarly, alginic acid gels in the presence of divalent/polyvalent cations eg. Ca^{2+} by the interaction of the alginate chain with the glucuronic acid block (22).

Enzymatic cross-linking: In this method, a gel is made by cross-linking with the enzymes which are present in body fluids. In-situ formation catalyzed by natural enzymes has not been extensively studied but appears to possess several advantages over chemical and photochemical approaches. For instance, enzymatic processes operate efficiently under physiological conditions without the necessity for potentially harmful chemicals like monomers or initiators. Intelligent stimulus-responsive delivery systems using hydrogels capable of releasing insulin are studied. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to blood sugar levels and the pulsatile release of trapped insulin. The quantity of enzyme can also be adjusted to control the rate of gel formation, which allows the mixture to be injected before gel formation (23).

Photo-polymerization: Photo-polymerization method of in-situ gel formation involves the use of electromagnetic radiation. A solution of monomer or reactive macromer and initiator can be injected into the tissue site and electromagnetic radiation can be applied to form a gel. The most suitable polymers for photo-polymerization are polymers that undergo dissociation by functional groups that are polymerizable in the presence of photoinitiators such as acrylates or similar monomers and macromers. Long wavelengths of UV light and visible wavelengths are generally used. Short-wavelength UV light, however, is rarely used because of its limited penetration into tissues as well as its biologically harmful effects. Ketones such as 2, 2 dimethoxy-2-phenylacetophenone are often used as initiators for UV photo-polymerization, while camphorquinone and ethyl eosin initiators are often used in visible light systems. These systems can be easily designed to be degraded by chemical or enzymatic processes, or for long-term persistence *in vivo* (24). The photoreaction provides a rapid polymerization rate at physiological temperatures. Also, the system can be easily placed in volumes of complex shapes, leading to the formation of implants (25).

POLYMERS USED AS IN-SITU GELLING AGENTS:

Pectin: Pectins are a family of polysaccharides, with a polymer backbone mainly containing α- (1-4) –D galacturonic acid residues. Low methoxy pectin (esterification <50%) easily forms a gel in an aqueous solution in the presence of free calcium ions and crosslinks the galacturonic acid chain as described in the egg-box model. Pectin gelation occurs in the presence of H^+ ions, the source of divalent ions, calcium ions are generally required to produce a gel suitable as a vehicle for drug delivery (26). The main advantage of using pectin in these formulations is that it is water-soluble and does not require an organic solvent. The divalent cations present in the stomach perform a pectin-to-gel transition when orally administered. Complex forms of calcium ions can be included in formulations to induce pectin gelation (27). Sodium citrate can be added to the pectin solution to form a complex with most of the calcium ions added to the formulation. This allows the formulation to remain in a fluid state (sol) until the complex is degraded in the acidic environment of the stomach where the release of calcium ions causes gelation. The amount of calcium and citrate ions can be optimized to maintain the fluidity of the formulation and result in gelation before administration when the formulation is administered to the stomach (28).

Xyloglucan: Xyloglucan is also called tamarind gum because it is a polysaccharide derived from the endosperm of tamarind seeds. The polysaccharide is composed of a (1-4)-β-D-glucan backbone chain, which has (1-6)-α-D xylose branches that are partially substituted by (1-2)-β-D-galactoxylose (104). Xyloglucan is composed of three different oligomers, such as heptasaccharide, octasaccharide, and non-saccharide, with different numbers of galactose side chains. When xyloglucan is partially degraded by β-galactosidase, the resulting product exhibits thermally reversible gelation due to the lateral stacking of rod-like chains. The sol-gel transition temperature depends on the degree of galactose elimination. When warmed to body temperature, it forms a thermoreversible gel. Its potential use in oral delivery utilizes the proposed slow gelation time (minutes) that allows in-situ gelation in the stomach after oral administration of a chilled xyloglucan solution (29). Due to its non-toxicity, biodegradability, and biocompatibility, xyloglucan gels are potentially used for oral, intraperitoneal, ocular, and rectal drug delivery (30,31).

Gellan gum: Gellan gum is an anionic deacetylated extracellular polysaccharide secreted by *Pseudomonas elodea*, with one α-L-rhamnose, one β-D-glucuronic acid, and two β-D-glucuronic acid residue as tetrasaccharide repeating units. It is commercially available as

GelriteTM and kelcogel TM obtained by treating gellan gum with an alkali to remove acetyl groups in the molecule. It tends to temperature-dependent or cation-induced gelation. This gelation involves the formation of a double helix junction zone followed by agglomeration of the double helix segments to form a three-dimensional network by complexation with cations and hydrogen bonding with water (32).

Gellan gum produces cation-induced in-situ gelations (Ca^{2+}, Mg^{2+}) by cross-linking between negatively charged helices and monovalent or divalent cations (Na^{+}, Ca^{+}, Mg^{+}, K^{+}). Divalent ions are superior to monovalent cations in promoting gelation. Gelation prolongs the residence time of the drug at the absorption site and increases the bioavailability of the drug (33).

Alginic acid: Alginic acid is a gum extracted from brown algae. This is a linear block copolymer polysaccharide in which β-D-mannuronic acid and α-L-glucuronic acid residues are linked by 1, 4-glycosidic linkages. The proportion of each block and the placement of the blocks along the molecule depends on the source of the algae. A dilute aqueous solution of alginate forms a hard gel by the addition of divalent and trivalent metal ions by a coordinated process containing consecutive glucuronic acid residues within the α-L glucuronic acid block of the alginate chain (34). A L-glucuronic acid (G) is placed as an alternating sequence (MG) block with the MM or GG block, and the interaction of the G block with the calcium moiety of the polymer forms a homogeneous gel. The mechanical strength and porosity of the hydrogel depend on the G: M ratio, the type of crosslinker used, and the concentration of the alginate solution (35). Alginic acid has favorable properties such as biodegradability and non-toxicity, making it a vehicle of choice for ophthalmic formulations. Long-term precorneal retention of alginic acid-containing formulations was sought not only for their ability to gel in the eye but also for their good mucosal adhesion properties due to the presence of carboxylic acid groups (36).

Xanthan gum: Xanthan gum is a high molecular weight extracellular polysaccharide produced by fermentation of the gram-negative bacterium *Xanthomonas campestris*. The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone (βD-glucose residues) and a trisaccharide side chain of β-D-mannose-β-D-glucuronic acid-α-D-mannose attached with alternate glucose residues of the main chain (37). The anionic property of this polymer is due to the presence of both glucuronic acid and

pyruvate groups in the side chains (38). Xanthan gum is soluble in cold and hot water, as well as alkaline and acidic conditions. Shows good stability under alkaline conditions.

Chitosan: Chitosan is a natural component of shrimp and crab shells consisting of biodegradable, heat-sensitive, and polycationic polymers obtained by the alkaline deacetylation of chitin. It is a polysaccharide consisting of a copolymer of glucosamine and N-acetylglucosamine. Chitosan is a biocompatible pH-dependent cationic polymer that can remain dissolved in an aqueous solution up to pH 6.2. Neutralizing an aqueous solution of chitosan to a pH exceeding 6.2 forms a hydrated gel (39,40). The pH gelling cationic polysaccharides solution are transformed into thermally sensitive pH-dependent gel forming aqueous solutions, without chemical modification or cross-linking by adding a polyol salt with a single anionic head, such as glycerin, sorbitol, fructose, or glucose phosphate salt, to the chitosan aqueous solution (41).

Carbopol: Carbopol is a high molecular weight cross-linked polyacrylic acid derivative. It is a water-soluble vinyl polymer. When the pH rises above a pKa value of about 5.5, it indicates a sol-to-gel transition in an aqueous solution. Carbopol remains in solution at acidic pH but turns into a low-viscosity gel at alkaline pH. HPMC is used in combination with Carbopol, which increases the viscosity of the Carbopol solution while reducing the acidity of the solution. Various water-soluble polymers such as carbopol system-hydroxyl propyl methylcellulose system, polymethacrylic acid, polyethylene glycol fall into the category of pH-induced in-situ precipitation polymer systems (42).

Carbopol molecules are tightly coiled acidic molecules. When dispersed in water, the carboxyl groups of the molecule are partially dissociated to form a flexible coil. Being a pH-sensitive polymer, the polymer swells as the pH of the solution rises. In acidic media, hydrogen bonds cause the gel to collapse, and when the pH rises, electrostatic repulsion occurs between the anionic groups, causing the gel to swell. The gelling effect is activated in two stages: dispersion and hydration of carbopol and neutralization of the solution by the addition of sodium hydroxide, triethanolamine, or potassium hydroxide (43).

Poloxamer: Poloxamer is a water-soluble triblock copolymer. It consists of two polyethylene oxide (PEO) and a polypropylene oxide (PPO) core in the ABA configuration 37. Polypropylene oxide is a hydrophobic central part surrounded on both sides by hydrophilic polyethylene oxide. Poloxamer is marketed as Pluronic and has excellent thermosetting properties and increased drug residence time. Poloxamer produces a clear, colorless, and

transparent gel. It depends on the proportion and distribution of hydrophilic and hydrophobic chains of several molecular weights available with different gelling properties (44).

At room temperature (25ºC), poloxamer behaves as a viscous liquid, and as the temperature rises (37ºC), it turns into a clear gel. At low temperatures, it forms small micelle subunits in solution, and as the temperature rises, it increases in viscosity and swells to form a large micellar cross-linked network. It is mainly used as a gelling agent, emulsifier, and solubilizing agent (45).

HPMC: Hydroxypropyl methylcellulose is composed of glucan chains with repeating β- (1, 4) -D-glucopyranose units. Methylcellulose is a natural polymer composed of native cellulose with alternating methyl substituents on the chain. Cellulose materials have shown viscosity inversely proportional to temperature, except for HPMC and MC. It is a water-soluble cellulosic ether and is widely accepted due to its dissolving properties in both organic and aqueous solvent systems. Also, its flexibility and lack of taste and odor, and its stability in the presence of heat, light, air, or moderate levels of moisture make it a good candidate for drug delivery systems. At low temperatures (30°C) the solution is in liquid form and as the temperature rises (40-50 ° C) gelation occurs (46).

The gelation of HPMC solutions is mainly caused by hydrophobic interactions between molecules, containing methoxy substitutions. At low temperatures, the polymer hydrates and there is little polymer-polymer interaction other than simple entanglement. As the temperature rises, the polymer gradually loses hydration water. This is reflected in the decrease in relative viscosity. Eventually, when sufficient but not complete dehydration of the polymer occurs, the polymer-polymer association occurs and the system approaches an infinite network structure, as experimentally reflected by a sharp rise in relative viscosity. This sol-gel conversion is used in the design of in-situ gelation systems (47).

Guar gum: Guar gum is also called guaran, a natural gum obtained from the endosperm of seeds. Guar gum is insoluble in hydrocarbons, fats, esters, alcohols, and ketones, but soluble in water. They are dispersible in both cold and hot water and form colloidal solutions in small amounts. Guar gum has derivatives used in coating matrix systems, nanoparticles, and hydrogels in the formation of targeted delivery systems. Guar gum also has derivatives such as graft polymers such as polyacrylamide grafted guar gum, which has good colon targeting properties. It can also be used as a polymer for sustained-release matrix tablets (48).

EVALUATION AND CHARACTERIZATION OF IN-SITU GELLING SYSTEM:

Clarity: The clarity of the formulations before and after gelling is often determined by visual examination of the formulations under light alternatively against white and black backgrounds (49). Additionally, the contents are often set in motion with a swirling action. Also, it is observed for the formation of turbidity or any unwanted particles dispersed within the solution (50).

pH: pH affects both the solubility and stability of the drug in the formulation. The formulation should remain stable at its pH and at the same time be non-irritating to the patient at the time of administration. The pH is measured by a digital pH meter (51). It should be pre-calibrated using standard buffers of pH 4 and pH 7 according to established procedures (52).

Texture analysis: Formulation hardness, consistency, and cohesion are assessed primarily using a texture analyzer that demonstrates the injectability of the sol, making the formulation easy to administer *in vivo*. To maintain close contact with surfaces such as tissue, the gel's adhesiveness value should be high.

Texture analysis provides information about the mechanical properties of a sample: hardness, compressibility, and adhesion. These properties can directly correlate with sensory parameters *in vivo*, helping to develop products with desirable attributes that contribute to patient acceptability and compliance (53).

Gelling capacity: Gelling capacity is determined for in-situ gels for ophthalmic formulations. The in-situ gel is mixed with simulated tear fluid to examine the gelling ability of ophthalmic products. This is determined by visual observation of a drop of formulation during a vial containing 2.0 ml of freshly prepared simulated tear fluid. Gelation was visually assessed by recording the time and time it took for the formed gel to dissolve (54, 55).

Gel-Strength: This parameter can be evaluated using a rheometer. Depending on the gelation mechanism of the gelling agent used, a specific amount of gel is prepared from the form of the sol in the beaker. This gel, in the beaker, rises at a constant rate, so slowly push the probe into the gel. Changes in the load on the probe can be measured as a function of the probe immersion depth below the gel surface (56).

Rheological studies: Rheology studies should be performed on in-situ gels, as we know from our previous knowledge that gels exhibit thixotropic behaviour (57). Viscosity and

rheological properties of polymer formulations in solution or gel can be measured with Brookfield rheometers or other types of viscometers such as research rotators and Oscillatory rheometers. The viscosity of these formulations should be such that no problems are expected during administration by the patient, especially during parenteral and intraocular administration (58).

Gelation pH: Gelation pH is determined by an in-situ gel formation system incorporating a pH-sensitive polymer. The formulation is then placed in a beaker and 1M NaOH was added dropwise with continuous stirring. Use a pH meter (Equiptronics digital pH meter) to check the pH and while the viscosity is also measured. Changes in viscosity at each pH are recorded. The pH at which a rapid change in viscosity is observed is referred to as gelation pH (17).

Gelation temperature: The gelation temperature or sol-gel transition temperature is the temperature at which the liquid-to-gel phase transition occurs. Gelation temperature is determined for an in-situ gel formation system incorporating a thermoreversible polymer and was described by Miller & Donovan technology (59). In this 2 ml in-situ gel is transferred to a test tube and placed into a water bath then the temperature of the water bath is increased slowly and constantly. After equilibrating the gel for 5 minutes at each setting, the gelation of the formulation is examined. The formation of the gel is indicated by the lack of movement of the meniscus when the tube is tilted. This is known as the gelation temperature when the meniscus would no longer move upon tilting to 90° (60).

Drug-polymer interaction study and thermal analysis: Interaction studies should be performed with Fourier Transform Infrared (FTIR) spectroscopy. During the gelation process, the nature of the interacting forces can be evaluated using techniques that employ the KBr pellet method. Thermogravimetric analysis (TGA) can be performed on in-situ polymer systems to quantify the proportion of water in hydrogels. Differential scanning calorimetry (DSC) was performed to observe if there was a change in the thermogram compared to the pure active ingredient used for gelation (61).

***In vitro* drug release studies:** For in-situ gel formulations intended to be administered by the oral, ocular, or rectal route, evaluation studies must be performed to determine drug release from the formulation *in vitro*. The study is performed using a plastic dialysis cell or Franz diffusion cell (62). The cell consists of two half-cells, a donor compartment, and a receptor compartment. Both half-cells are separated with the help of semipermeable

cellophane/dialysis membrane /cellulose membranes. The formulation is placed in the donor compartment and a newly prepared simulated buffer is placed in the receptor compartment. The entire assembly is placed on a thermostat-controlled magnetic stirrer. The temperature of the medium is maintained at 37ºC ± 0.5ºC. The total amount of receptor solution can be removed at intervals and replaced with a new medium. This receptor solution can be diluted with the respective solvent as needed and the drug release can be analyzed at each nm using analytical techniques such as UV spectrophotometer using reagent blanks. For injectable in-situ gels, the formulation is placed in a vial containing the receptor medium and placed on a shaker water bath at the required temperature and vibration rate. Samples are taken and analyzed regularly (63). The drug content is then calculated using the formula generated from the standard calibration curve. Calculate the percentage of cumulative drug release (% CDR). The data obtained is further subjected to curve fitting of drug release data (64).

Accelerated stability studies: The sterile formulations are subjected to stability testing to assess shelf life. The sterile formulation is replaced in amber-coloured glass vials, closed with grey butyl rubber closures, and sealed with aluminum foils. The vials containing formulation are kept in a stability chamber, maintained at 40 ± 2°C, and 75 ± 5 % RH for one month as per the International Conference of Harmonization (ICH) State Guidelines. Samples could be withdrawn weekly and analyzed for drug content, pH, visual appearance, gelling capacity, and in vitro drug release (65).

APPLICABILITY OF IN-SITU POLYMERIC DRUG DELIVERY SYSTEM

According to the route of administration, these in-situ polymeric systems may be classified as illustrated in the following sections. Furthermore, some of the patents on an in-situ gel for delivery systems have been issued in the two decades, and are being summarized in Table No. 1.

Ocular drug delivery system:

The unique properties of the ocular cavity and its effective clearance mechanism make ocular administration of the drug a difficult target with low therapeutic response. New generation ophthalmic formulations are tasked with improving the availability of drugs administered by the ocular route and thus improving their therapeutic efficacy. This can be achieved by using in-situ gelling formulations that increase pre-corneal retention time and achieve optimal drug concentrations at the target site (66). Such in-situ gelation systems receive a phase transition-

forming viscoelastic gel in response to one or more environmental stimuli such as temperature, ions present in tears, and pH (67).

Following topical application, gel formation in the conjunctival cul-de-sac provides sustained release of the loaded drug to ensure long-term therapeutic effects, reduce dosing regimens, and thus improve patient compliance. Polymers commonly used in the manufacture of such systems are biocompatible, well-tolerated, and preferably mucosal adherent. Further, pseudoplastic behaviour is desirable. Painful blinking can be avoided by ensuring that the viscosity of the polymer solution administered decreases with an increasing shear rate (68). The in-situ gelation system can also be used as a vehicle for drug-filled nanoparticles and is involved in improving both drug solubility and corneal permeability, which is characterized by the low bioavailability of the eye. Incorporation of low-viscosity colloids into semi-solid formulations results in longer retention on the ocular surface (69).

Nasal drug delivery system:

The nasal cavity has emerged as an attractive route for multi-site targeting for the administration of a wide variety of drugs, from small compounds to biopolymers such as peptides, proteins, and vaccines (70). The nasal route is a natural choice for topical administration of drugs aimed at treating local disorders affecting the nose and sinuses, such as allergic or infectious rhinitis, sinusitis, nasal sinusitis, and nasal sinus lesions(71). Also, the nasal mucosa represents a non-invasive alternative route for the systemic delivery of drugs with low bioavailability. The highly vascularized nasal epithelium has been utilized to achieve rapid absorption of drugs that normally undergo extensive first-pass metabolism and/or gastric degradation after oral administration (72). Furthermore nasal pathway has been proven beneficial for brain drug delivery because of bypassing of blood-brain barrier (BBB). Delivery from the nose to the brain ensures direct and rapid delivery of the drug from the nasal cavity to the central nervous system (CNS) via the olfactory epithelium (73).

Even though the intranasal pathway offers several advantages in terms of accessibility, efficacy, tolerability, and patient compliance, mucous fimbria clearance is primarily responsible for reducing drug residence time in the nasal environment. Represents the physiological factors involved. Such a self-cleaning mechanism is responsible for attempts to prevent the rapid excretion of the drug from the nasal cavity, thereby treating the local disease of the nose or systemic blood flow or CNS. (74). The drug is administered as a simple aqueous solution and approaches to improve accessibility have been proposed to prolong the

residence time in the nasal cavity. The nasal in-situ gelling formula appears to be a more effective alternative than that of nasal fluid (75).

Such formulations are readily administered as low viscosity polymer solutions to ensure optimal nasal deposition and turn into gels upon contact with the mucosa. Sol-gel transitions can be triggered by a variety of physical or chemical stimuli, especially temperature, pH, and ionic strength. The *in vivo* formation of the polymer network increases the contact time between the drug and the site of action/absorption, resulting in sustained release of the drug component (76). Nasal administration of corticosteroids is a front-line therapeutic strategy for the topical treatment of nasal inflammatory diseases. Many research groups have identified the unique advantages of the in-situ gelling systems for topical drug delivery to the nasal cavity: rapid gel formation not only reduces the mucociliary clearance effect but also nasal mucosa. Through systemic absorption of locally acting drugs, thus blocking and thus limiting their systemic absorption (77).

Buccal drug delivery system:

Over the last decade, administration of the intraoral in-situ gelation system has been used primarily for the topical treatment of oral mucositis, controlling pain, regulating the inflammatory response, enhancing the wound healing process, and treating bacterial infections. It has emerged as a valuable strategy to prevent fungal infections. Oral mucositis represents the most common and clinically significant complication of systemic chemotherapy and/or radiation therapy in patients with head and neck cancer. Such pathological conditions are generally characterized by thinning of the oral epithelium leading to mucosal inflammation and ulceration, mainly associated with severe pain and bleeding (78).

Oral mucositis has a profound effect on a patient's nutritional status and quality of life, and sometimes increases the risk of oral infections. Under the most severe conditions, clinicians are forced to reduce chemotherapeutic/radiation doses or temporarily discontinue treatment (79). In an attempt to prevent or reduce the discomfort caused by ulcerative lesions of the mucosa, the current first-line treatment in most US hospitals consists of oral rinsing with a solution containing a local anesthetic (eg, lidocaine). However, the analgesic effect is moderate and short-term (less than 30 minutes), probably due to limited contact between the anesthetic and the damaged mucous membrane. Also, repeated rinsing throughout the day leads to paralysis of the entire oral mucosa, including healthy areas. Other traditional

formulations such as mouthwashes and polymer gels have also been used for topical delivery of anti-inflammatory, cure-promoting, or antifungal agents. Anyway, their short residence time in the oral cavity due to the flushing effect of saliva and the cleaning action of the tongue results in treatment failure (80).

In this context, the use of mucosal adherent in-situ gelation systems represents an effective approach to overcome the shortcomings of conventional therapies. After topical application to the damaged mucosa, the polymer solution turns into a mucosal adhesive gel in response to various stimuli (ie, temperature changes, the presence of divalent ions, etc.), providing a protective layer on ulcerative lesions. The unique design and configuration of such a system ensure both extended residence time at the site of injury and sustained release of the drug, avoiding repeated doses, and improving patient compliance (81).

Gastrointestinal drug delivery system:

The pH-sensitive hydrogels have the potential to be used for site-specific delivery of drugs to specific areas of the gastrointestinal tract (81). Studies dealing with the development of in-situ gelling formulations for topical administration of the drug to the rectal colon site have been reported. Various approaches are used, including the sol-gel transition caused by an increase in ion concentration or temperature or a change in pH. Some studies have taken multiple approaches, leading to the development of formulations based on a mixture of ionic, temperature, and/or pH-sensitive polymers. Pectin, xyloglucan, and gellan gum are natural polymers used to form oral drug delivery systems in-situ. The possibility of orally administered in-situ gelling pectin preparations for sustained drug delivery has been reported (82). The main advantage of using pectins in these formulations is that they are water soluble and therefore do not require organic solvents. Both gellan gum and sodium alginate formulations contain complex calcium ions that undergo a gelation process by releasing these ions in the acidic environment of the stomach (83).

Vaginal drug delivery system:

In addition to being an important organ of the reproductive pathway, the vagina is also a suitable pathway for the administration of drugs with local and systemic effects. Antibiotics, hormones, spermicides, and anti-inflammatory drugs have traditionally been administered topically via the vaginal pathway. Besides, the vagina exhibits several features such as abundant blood supply, large surface area, and the potential to bypass the first-pass

metabolism, creating a vaginal pathway suitable for systemic administration of drugs such as calcitonin (84). On the other hand, the self-cleaning effect of vaginal fluid is responsible for the leakage of many dosage forms, resulting in reduced therapeutic effectiveness. The adoption of mucoadhesive and in-situ gelling formulations represents a strategy proposed over the last few decades to increase the residence time of liquid vaginal formulations at the site of action/absorption. Over the last decade, two approaches have been proposed to increase the viscosity of the formulation upon administration. This allows the use of a mixture of (i) heat-sensitive polymers and (ii) mucoadhesive polymers that can interact with proteins present in the vaginal cavity (85).

Rectal drug delivery system:

The rectal route can be used to deliver many types of drugs prescribed as liquids, semi-solids (ointments, creams, and foams), and solid dosage forms (suppositories). Traditional suppositories often cause discomfort when inserted. Also, the suppository cannot be adequately held in a particular location in the rectum and can sometimes move upwards into the colon, allowing the drug to undergo the first-pass effect. Choi has developed a new in-situ gelling liquid suppository with a gelling temperature of 30-36°C. Poloxamer 407 and/or poloxamer 188 were used to confer temperature-sensitive gelling properties. In-situ gels have the potential to be applied to the rectal pathways. Miyazaki et al. investigated the use of xyloglucan-based thermoreversible gels for rectal drug delivery of indomethacin (86,87).

Intravesical drug delivery system:

In-situ gelling formulations have attracted some interest as an ideal topical and sustained delivery system for chemotherapeutic agents. After intratumoral or peritumor injection, such a system, in the sol state before administration, turns into a hydrogel in response to a particular stimulus and releases the drug locally in a controlled manner. Increased drug levels at the target site (tumor) maximize anticancer activity and at the same time minimize systemic toxicity. Also, the three-dimensional structure of hydrogel ensures sustained drug release that prolongs tumor exposure to chemotherapeutic agents (88). In particular, a detailed review of the literature has suggested that a certain number of published papers focus on the use of the in-situ gelation system in the topical treatment of cancer.

Today, gold standard treatments include surgical resection followed by intravesical injection of chemotherapeutic agents to prevent recurrence and/or progression of the tumor.

Postoperative treatment consisting of oral or direct drug administration to cancer cells. Nevertheless, the effectiveness of chemotherapeutic agents can be compromised by both limited permeabilities that prevent the drug from spreading to cancerous tissues and short drug residence times in the affected area. (89). The use of complex drug delivery systems, especially nanoparticle-loaded in-situ gelling formulations, improves (i) the solubility of lipophilic drugs (ie, paclitaxel) and (ii) permeability through the hydrophilic urothelium. Compounds appear as a valuable strategy for enhancing, and finally (iii) prolong drug residence time in cancerous tissues (90).

Table No. 1: List of some patents of in-situ gelling system.

Patent Number	Title of the patent	Year of publication	Reference
US 20020119941	In-situ gel formation of pectin	2001	91
US 2002/0114778 A1	Reversible gelling system for ocular drug delivery	2002	92
US 20050063980	Gastric raft composition	2002	93
US 6511660 B1	Ophthalmic drug delivery formulations and method for preparing the same	2003	94
US 6703039 B2	Reversible gelling system for ocular drug delivery	2004	95
US 2011/0082128 A1	In-situ gel ophthalmic drug delivery system of estradiol or other estrogen for prevention of cataracts	2011	96
WO 2011018800 A3	In-situ gel forming solution for ocular drug delivery	2011	97
US 20120009275	In-situ forming hydrogel wound dressing containing antimicrobial agents	2011	98
US 2011/0082221 A2	In-situ gelling system as sustained delivery for front of eye	2011	99

US 8343471 B2	Nanoparticulate in-situ gels of TPGS, gellan and PVA as vitreous humor substitutes	2013	100
US 6777000 B2	In-situ gel formation of pectin	2014	101
US 9757330 B2	Recipe for in-situ gel, and implant, drug delivery system formed thereby	2017	102
EP 3173067 A1	Mucoadhesive buccal in-situ gel formulation	2017	103

CONCLUSIONAND FUTURE PROSPECT:

The major portion of pharmaceutical research focuses on the controlled and targeted delivery of a drug. Over the last decade, In-situ gels have proved to be reliable, safe, and efficient dosage form for controlled and targeted delivery of drugs. The use of various polymeric systems has afforded various advantages over conventional drug delivery systems. In-situ formulations show the ease of administration as these are in solution form, while shows controlled release after administration because of gel formation. Ease of administration, reduced dosing frequency, and good stability and biocompatibility characteristics have resulted in increased patient compliance and comfort.

The research studies performed so far, have demonstrated the efficacy of in-situ gels as a potential therapeutic platform for the administration of bioactive agents for the treatment of various diseases. However, the in-situ gel system has been facing some challenges with drug delivery, such as enzymatic degradation of the drug molecule, low membrane permeability, initial drug burst, and extensive clearance. As well as challenges associated with their development that are related to drug stability, drug release kinetics, and the conditions under which the system is delivered to the body. Lastly, in the future, we expect the innovation of new and more reliable in-situ gel systems consisting of multiple ingredients, involving a multi-target approach, and which could be responsive to some biochemical markers associated with the disease conditions for gel formation. With the extensive toxicodynamic studies of excipients and polymers used in the preparation of the gels and by using novel polymers and solvent systems, it is possible to develop an optimum controlled and site-specific delivery system in near future.

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