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IN SITU GELLING DRUG DELIVERY SYSTEMS- A REVIEW ON RECENT DEVELOPMENTS

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ABSTRACT

There has been an increased focus on developing novel drug delivery systems during the last thirty years. Polymeric drug delivery methods have been formulated based on substantial research and development. Interest in in situ gel systems has grown in recent years. A number of patents for new in situ gel forming technologies have been issued in recent years, with each patent typically referring to a variety of biological applications. This interest is because in situ systems have advantages such as reduced administration frequency and improved patient adherence. Focused systemic pharmacological effects can be acquired through in situ drug delivery systems. Compared to parenteral and oral routes, these are far more convenient and provide greater bioavailability. Various routes, including oral, ophthalmic, rectal, vaginal, intravenous, and intraperitoneal, are capable of delivering in situ gel formulations. They are in a solution state prior to administration and are capable of producing gels in response to certain endogenous stimuli, including temperature increase, pH shift, and the presence of ions. Drug loaded nano and micro particles are transported in these vehicles. Natural, synthetic, and semi-synthetic polymers with in situ gelling activity may be used alone or in combination to develop such drug delivery systems. It is highly desirable to associate it with mucoadhesive polymers in order to extend the duration of action or to increase the absorption of drugs. Furthermore, in situ gelling systems include solid polymeric formulations, which are typically created by freeze-drying and rapidly hydrate when body fluids come into contact with them, forming a gel capable of controlled drug release. This review discusses the benefits and drawbacks,

mechanism of drug release, drug characteristics to be employed, types of polymer used, evaluation, and recent breakthroughs in in situ drug delivery systems.

KEYWORDS: In situ, gelling, cross linking, polymers.

INTRODUCTION

During the past decade, increasing attention has been given by the scientific community to the development of in situ gel drug delivery systems. A vast majority of these systems are distinct in that they are sol-state prior to administration and then converted to gel in the body. They are characterized by ease of administration, prolonged residence time, and maintaining drug release in a controlled fashion after administration, resulting in decreased administration frequency and increased patient convenience and compliance. The ability of these drug delivery systems to be administered via a variety of routes to achieve a local or systemic effect of the drug contained within is the driving force behind their enormous success. Additionally, they are also effective as vehicles for nano- and micro-drug delivery systems. The sol–gel transition can be induced by a number of conditions, including a temperature increase, a change in pH, or the presence of ions. At room temperature, in situ gelling systems which are thermosensitive in nature are in the sol state and transition to the gel state occur at temperatures close to body temperatures (32°C–37° C, depending on administration site). The phase transition process is brought about by a significant change in the solubility of polymers in water, which is defined by the presence of hydrophobic and hydrophilic groups in their structure. Increased temperature causes a reorganization of polymer–water interactions, resulting in rapid dehydration and precipitation of solvated polymer chains. When the temperature is increased, amphiphilic polymers that assemble themselves into micelles in water at concentrations above the critical micellar concentration form gel. When the critical temperature for micellar packing is exceeded, an orderly packing of the micelles occurs, culminating in gelation. The thermosensitive polymers poly N-isopropylacrylamide (PNIPAM), poloxamers (Pluronic ®), and cellulose derivatives are the most frequently used polymers in drug delivery. Gellan gum (GG), pec (pectin) and anionic polysaccharide compounds like alginates (ALG), which are ion sensitive polymers, can be cross-linked by a monovalent cation (Na+) and or a divalent cation (Ca+). In a variety of physiological fluids, including saliva, tears, and nasal fluid, divalent cations (Mg2+ and Ca2+) are present. As a result of the cross-linking mechanism, a sol–gel transition occurs, forming a strong gel in their presence. The type and concentration of cations are related to the viscosity and rate of

sol–gel transition of the cross-linked polymer. Ionizable carboxylic or phosphoric (weakly acidic) or ammonium groups (weakly basic) within the structure of pH-sensitive polyelectrolyte polymers determines them. A pH change, depending on the polymer's *pka*, results in changes in the polymer's ionization state and, consequently, in its conformation and solubility, resulting in gelation. Not only can the molecular weight of the polymer have a significant effect, but also the temperature and ionic strength of the physiological medium. Polyacrylic acid (PAA) and chitosan are the most extensively investigated pH-sensitive polymers.[1]

Insitu gel benefits

The following are the major benefits of in situ gel drug delivery systems.

1. It is possible to reduce the frequency of administration.
2. The time period during which a drug is available at its maximum absorption site.
3. Drugs possessing a narrow absorption range in the small intestinal region can be delivered.
4. The in situ gastro retentive drug delivery systems (GRDDS) are useful for drugs that are absorbed through the stomach region, such as ferrous salts, for treating peptic ulcers.
5. In conventional ophthalmic solutions, where bioavailability is the key issue, in situ gel is a perfect solution.
6. By resisting ocular drainage, an in-situ gelling technique increases bioavailability and results in a longer residence time.

Drug candidates for in situ gel

1. Locally effective drugs in the stomach. like antacid compounds, misoprostol etc.
2. Drugs possess a narrow absorption window in the GI region, e.g., Vitamin B2 (riboflavin) and levodopa.
3. Drugs which are absorbed primarily through the stomach and upper GI tract, like cinnerazine.
4. Drugs which disintegrate in the colon, like ranitidine HCl and metronidazole.
5. Medications which can disrupt normal colonic bacteria, like amoxicillin trihydrate.

Polymers employed in the in-situ gelling systems

The following polymers are widely used in the formulation of in situ drug delivery systems.

1. **Chitosan:** Chitosan, a thermosensitive, polycationic polymer derived from chitin found in shrimp and crab shells, is a biodegradable and biocompatible polymer. Chitosan is a pH-

dependent cationic polymer that is soluble in water up to a pH of 6. Pregel formation, which occurs when chitosan aqueous solution is neutralized to a pH greater than 6.2, results in a gel-like precipitate. To cause thermally sensitive pH dependent gelation, polyol salts with a single anionic head, such as glycerol, sorbitol, fructose, or glucose phosphate salts, are added to the chitosan aqueous solution.

2. **Gellan gum:** This is an anionic polysaccharide which is water soluble in nature, found in the Sphingomonas elodea bacterium. Gelation may be caused by temperature or in the presence of cations. The Gellan solution is mixed with sodium citrate and calcium chloride to form the gel. It has been reported that gellan has successfully been used as a vehicle for oral delivery of theophylline, amoxicillin, and other medications.
3. **Xyloglucan:** This polysaccharide is a 1-4-β-D-glucan-based polymer, which has (1-6) α-D-xylose branches and (1-2) β-D-galactoxylose. The degraded product of this molecule reacts with β-galactosidase to form a thermally reversible gel. Galactose elimination yields a difference in the gel transition temperature. Reversible gels are formed when the temperature is raised to body temperature. The potential in-vivo use of xyloglucan in the stomach allows for gelation following oral administration. Xyloglucan gels have potentially been used for oral, intraperitoneal, ocular, and rectal drug delivery.[2]
4. **Alginic acid**: Alginic acid is a polysaccharide obtained from brown algae that is a linear block copolymer of -D-mannuronic acid and -L-glucuronic acid with 1,4-glycosidic linkages. The number of blocks and their distribution differ depending on the algae source. The addition of consecutive glucuronic residues in the -Lglucuronic acid blocks of the alginate chain gradually causes aqueous alginates solutions to form firm gels when di and trivalent metal ions are added. Because of its favorable biological properties, such as biodegradability and nontoxicity and muco adhesion, alginic acid is an excellent vehicle for ophthalmic formulations.
5. **Carbopol:** Carbopol remains in solution at acidic pH levels. At alkaline pH, however, it forms a gel. HPMC is used in conjunction with carbopol to provide viscosity to the solution while reducing the acidity of the solution. They can be used as pH-induced in-situ precipitating polymeric systems. Based on this concept, Indomethacin eye drops for the treatment of uveitis were developed and tested. Ismail et al. designed and developed an in-situ precipitating polymeric system to deliver plasmid DNA using aqueous carbopol-HPMC solutions.[3]

5. **Pectin**: The vast majority of pectins are polysaccharides composed of 1-4 D-galacturonic acid units, each with a D-galactosyl group at one end. Only about half of the methoxy pectins have more than 50% esterification. Methoxy pectins gel into a liquid in the presence of free calcium ions, forming crosslinks. Pectin gelation will produce gels in the presence of H+ ions, but in order to produce these gels, a source of divalent ions, typically calcium ions, is required. Pectin is extremely useful in these formulations because it is soluble in water and thus eliminates the need for organic solvents. Ions present in the stomach aid in the transition of pectin to a gel state when taken orally. The complex form of calcium, when combined with calcium ions, can be used to induce pectin gelation. Sodium citrate may be used in the formulation to create a complex containing the majority of the calcium ions. To keep the formulation in water with a low pH until the complex breaks down in the acidic environment of the stomach, where the release of calcium ions causes gelation. The calcium and citrate concentrations are optimized to maintain the formulation's fluidity while in the stomach. According to research, a simple orally administered in situ gelling pectin formulation can deliver Paracetamol for extended periods of time.[3]
6. **Pluronics**: Difunctional triblock copolymers are a series of commercially available non-ionic poloxamers, such as pluronic (marketed by BASF Corporation). The blocks of polypropylene oxide (PPO) surround the blocks of polyethylene oxide (PEO), which is arranged so that the hydrophobic central block is surrounded on both sides by the hydrophilic blocks. The PEO/PPO ratio of 2:1 result in micellar structures that form above the critical micellar concentration when these molecules are placed in aqueous solvents. Polymer grades vary in molecular weight and physical form, making the plutonic triblock copolymers readily available. The final application solution contained Pluronic F-127 as a gelling polymer, alongside mucoadhesive polymers such as Carbopol 934 and hydroxyl propyl methylcellulose, which ensured that the solution remained on the skin for an extended period of time. The antimycotic efficacy of a developed formulation was demonstrated in-vitro, which has shown a longer duration of drug release.[4]

Synthetic polymers

Preparations intended for parenteral use are frequently made using synthetic polymers. Due to new drug delivery technologies favouring biodegradable polymers, there is a reduced demand for surgical removal, because once the drug supply is depleted, it no longer needs to

be removed. Extensive research on aliphatic polyesters has been conducted in recent years, with a focus on poly (lactic acid), poly (glycolic acid), poly (lactide coglycolide), poly (decalactone), and poly ε-caprolactone. The use of synthetic polymers for parenteral products is popular. As a trend, it has been in the past few years for drug delivery techniques to use biodegradable polymers, eliminating the need for surgical removal once the drug supply is depleted.[5]

Approaches

In situ formation based on physical mechanism

Swelling and Diffusion

Stomach floating in situ gel systems exhibits the tendency to remain longer at the pyloric sphincter. Swelling of the polymer happens after absorption of water causes formation of gel. Certain biodegradable lipid substances such as myverol (glycerol mono-oleate) form in situ gel under such a phenomenon. Swelling is maintained by the degree of cross-linking between the polymeric chains. On coming in contact with gastric fluid, the polymer absorbs water and swells. The extensive swelling of these polymers is due to the presence of physical and chemical cross-linkers in the hydrophilic polymer network. A solution of a polymer such as N-methyl pyrrolidone (NMP) involves diffusion of solvent from the polymer solution into the surrounding tissue and results in solidification of the polymer matrix. These cross links minimize the dissolution of the polymer and hence maintain the physical integrity of the dosage form.

In situ gelling based on chemical stimuli

Ionic crosslinking

Gelrite (Gellan gum), pectin, sodium alginate, and carrageenan are typical examples of ion pH sensitive poly saccharides. They form a gel in the presence of divalent or polyvalent cations. such as Ca2+, Mg2+ and Na2+. For example, alginic acid gels in the presence of Ca2+.

Enzymatic cross linking

Certain natural enzymes that function efficiently under physiological conditions without the use of potentially harmful chemicals such as monomers and initiators, provide a convenient mechanism for controlling the rate of gel formation, allowing the mixtures to be injected before gel formation in situ.

Temperature dependent in situ gelling

In this method, a temperature-dependent phase transition from a less viscous solution to a relatively high viscosity gel is observed. Polymers react with one another to form a solvated solution. Changes in temperature cause a rapid shift in the solubility of hydrophobic macromolecules within a system. Polyacrylic acid, polyacrylamide, and other temperature-sensitive polymers are the most studied for developing in situ gel properties, such as a gel that hardens as it cools. Before administration, they are present in liquid form, which is then transferred into gel at body temperature. Following body fluid exposure, these in situ gels transition to a gel state between 35^{o}C and 37^{o}C due to a temperature-induced phase transition. When the temperature in the environment rises, the polymers' solubility rises rapidly (at a lower critical solution temperature, LCST). One of the most extensively investigated polymers that exhibit useful LCST transition is poly (N isopropylacrylamide), commonly abbreviated as PNIPAAm. At the LCST, hydrogen bonding between the polymer and water is an unfavorable interaction, whereas polymer-polymer and water-water interactions produce a more hydrophobic, stable structure. At ambient temperature, the polymer solution is a liquid, but when heated, it transforms into a gel. Cooling below their upper critical solution temperature (UCST) causes in situ gels to contract.

pH Triggered In situ gelation

As the pH of the system changes, a gel develops. This approach makes use of pH sensitive or pH responsive polymers. pH sensitive polymers have pendant acidic or basic groups that can receive or release protons in reaction to pH variations in the environment. Poly electrolytes are polymers having a high concentration of ionizable groups. The presence of poly electrolytes in the formulation causes the hydrogel to expand and form an in situ gel by raising the external pH. Polymers containing anionic groups are particularly well suited to this method. Examples are cellulose acetate phthalate (CAP), carbomer and its derivatives, polyethylene glycol (PEG), pseudo latexes, and poly methacrylic acid (PMC).[4]

In situ gel formation principle in gastroprotective in situ gel system

The principle of formulation of the gastroprotective in situ gel system may be explained as follows. After being combined with a gelling agent, the drug and other excipients are encapsulated in such a gel. The gelation of this sol system would occur in the human stomach as a result of ionic complexation caused by a rise in pH. This formulation contains sodium alginate, which binds to Ca2+ and releases it only in the stomach's acidic environment.

Sodium alginate is used as a gelling agent. The free Ca2+ ions become entangled in the sodium alginate polymeric chains, causing the polymer chains to cross link and create a matrix structure. Following the creation of double helical junction zones, the double helical segments reaggregate to create a three-dimensional network by complexation with cations and hydrogen bonding with water. As a result, the formulation stays liquid until it reaches the stomach, where the sodium alginate gelation happens instantaneously.[3]

Applications of Insitu gel DDS

1. Ocular drug delivery system

Natural polymers such as gallan gum, alginic acid, and xyloglucan are widely used in ocular delivery systems. In local ophthalmic delivery systems, various compounds such as antimicrobial agents, anti-inflammatory agents, and autonomic drugs are used to relieve intraocular tension in glaucoma. In the presence of high tear amounts and eye dynamics, rapid drug elimination from the eye is caused. Hence, conventional delivery systems frequently result in poor availability and therapeutic response. Viscosity enhancers such as Hydroxy Propyl Methyl Cellulose, Carboxy Methyl Cellulose, Carbomers, and Poly Vinyl Alcohol are used to raise the viscosity of the formulation to extend the precorneal residence period and improve bioavailability. To enhance ocular drug penetration, chelating agents and surfactants are employed in addition to preservatives.

2. Nasal drug delivery system

Gallan gum and xanthan gum are frequently utilized as in-situ gel formation polymers in nasal in-situ gel systems. Researchers tested Momethasone Furoate for the treatment of allergic rhinitis and found it to be highly effective.[1] The impact of in-situ gel on antigen-induced nasal symptoms in sensitized rats was studied. When in-situ gel was shown to suppress the rise in nasal symptoms, compared to the formulation of nosonex (market formulation), which is normethadone furoate suspension 0.05 %.

3. Rectal drug delivery system

Insitu gel systems are highly appreciable as rectal drug delivery systems. They can deliver various liquids, semisolids like ointment, cream, and foams, and solid medications like suppositories to the rectum. In the past, suppository usage has commonly been associated with pain. In addition, suppositories are incapable of remaining in the rectum due to their tendency to go upward to the colon. Consequently, they pass through the first pass metabolism. A liquid suppository formulated with gelation temperatures between 30°C and

36°C was reported by Choi and colleagues.[6] The temperature-sensitive gelation characteristic was conferred by using Poloxamer 407 and Poloxamer 188.

4. Vaginal drug delivery system

The reproductive tract, vaginal canal can also be used as a route for medication delivery. In situ gelation formulations based on a thermo-plastic graft copolymer that undergoes in situ gelation have been developed to provide the prolonged release of active ingredients such as nonoxynol-9, progestins, estrogens, peptides, and proteins over a longer period of time. A new study by Chang et al. recently published shows a mucoadhesive thermo-sensitive gel which included poloxamers and polycarbophil exhibited enhanced and extended clotrimazole efficacy in fungal conditions than traditional PEG based dosage forms.[1]

5. Injectable drug delivery system

One of the most apparent methods of delivering sustained release medications is to place them in a delivery device and inject or implant them into human tissue. Thermo reversible gels based on poloxamers are commonly used for this purpose. The effectiveness of poloxamer gel alone or in combination with hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose (CMC), or dextran was also studied by researchers. Scientists investigated gels containing insulin or insulin-poly D, L-lactic-co-glycolic acid (PLGA) nanoparticles and found that these formulations might be beneficial in the creation of a controlled delivery system. Poloxamer gels were also investigated for intramuscular and subcutaneous human growth hormone delivery, as well as the creation of a long acting single dose lidocaine injection.[7]

6. Systems for delivering drugs to the skin

Pluronic F127, a thermally reversible gel, was evaluated as a vehicle for percutaneous Indomethacin delivery. According to an in-vivo research, a 20% w/w aqueous gel may be beneficial as a basis for topical medication delivery. Poloxamer 407 gel has been shown to be effective in the administration of insulin trans dermally. The use of chemical enhancers in conjunction with iontophoresis resulted in a synergistic increase in insulin permeability.[6]

7. Oral drug delivery system

Natural polymers such as pectin, xyloglucan, and gellan gum are used in the oral in situ gel delivery method. Because pectin is water soluble, there is no need for an organic solvent. Cross-linked dextran hydrogels with quicker swelling under high pH conditions were studied,

as were other polysaccharides such as amide pectins, guar gum, and insulin, in order to build a possible colon-specific drug delivery system. Hydrogels containing various amounts of PAA derivatives and crosslinked PEG enabled the creation of silicone microspheres that released prednisolone into the stomach media or displayed gastroprotective characteristics.

Evaluation and characterization of in situ gelling systems

The following are some of the commonly employed evaluation and characterization parameters of in situ drug delivery systems. Depending on the type of formulation, these parameters and evaluation procedures may be varied.

1. Clarity

Visual assessment against a black and white background helps determine the purity of the prepared solution. An illuminated background can also be used for this purpose.

2. Texture analysis

To evaluate the consistency, hardness, and cohesion of in situ gels, researchers use a texture profile analyzer that identifies gels' strength and ease of administration. In order to maintain an intimate touch with the mucus surface, greater adhesiveness is required in the gel.

3. pH of gel

The pH of the gel is an extremely important parameter and can be determined by using a calibrated pH meter.

4. Sol-Gel transition temperature and gelling time

The sol-gel transition temperature for in situ gel forming systems containing thermo reversible polymers may be defined as the temperature at which the phase transition of the sol meniscus is first seen when maintained in a sample tube at a certain temperature and subsequently heated at a specified pace. Gel formation is evidenced by a lack of movement of the meniscus when the tube is tilted. Gelling time is the time it takes to detect gelation for the first time, as stated above.

5. Gel-Strength

A rheometer can be used to assess gel strength. A certain amount of gel is taken in a beaker from the sol form. This gel-containing beaker is elevated at a certain rate, allowing a probe to move gently through the gel. The variations in load on the probe may be monitored as a function of the probe's depth of immersion below the gel surface.

6. Gelling capacity

In-situ gel can be treated with the simulated fluid with which it will come into contact. The gelation can be visually examined by observing the time required for the formulated gel to dissolve.

7. Rheological studies

The viscosity is determined using a Brookfield viscometer. In the sample tube, an in-situ gel formulation is inserted. The formulation should have a viscosity of 5-1000 millipascal-second (mPa.s) before gelling and a viscosity of 50-50,000 mPa.s following ion gel activation, particularly in ophthalmic preparations.

8. Isotonicity evaluation

Isotonicity is an essential property of ophthalmic preparations. Isotonicity is maintained to avoid tissue damage or eye discomfort. An isotonicity test is performed on all ophthalmic preparations, and the analysis indicated that they had acceptable release characteristics, gelling capacity, and the appropriate velocity. The formulation is combined with a few drops of blood and examined under a microscope at 45x magnification before being compared to a typical commercial ophthalmic preparation.

9. Swelling studies

Swelling experiments are carried out in a cell that is outfitted with a thermo jacket to keep the temperature constant. The cell contains artificial tear fluid (composition: 0.67g Nacl, 0.20g $NaHCO_3$, 0.008g $Cacl_2.2H_2O$, and distilled water). After attaining equilibrium at 37°C, 1 milliliter of the prepared solution is placed in the dialysis bag and immersed in the swelling medium. At certain intervals, the bag is withdrawn from the medium and its weight is recorded. The following relationship is used to calculate the swelling of the polymer gel as a function of time.

$\% St = (Wt - W_0)\ 100/W_0$

St = Swelling at time "t".

W_0=Initial weight of gelling solution.

Wt=Final weight of gel.

10. Statistical analysis

Using the SPSS statistical software, analysis of variance (ANOVA) is utilized to assess the difference between computed parameters. The statistical difference producing $P \leq 0.05$ is

taken into account. The Duncan multiple comparison is used when it is required to determine which of the distinct formulations differ considerably.

11. High performance liquid chromatography

In reversed phase mode, the HPLC system has usually been employed in the past. The analysis is usually carried out on a Nova pack C18 packed column (150 mm length X 3.9 mm id), which can be used for estimation purposes.

12. Fourier transformer infra red

FTIR investigations look into the likelihood of drug-excipient interactions. KBR pellets are used to record the FTIR graphs of pure drugs and drug-excipient combinations.

13. Thermal analysis

To quantify the proportion of water in a hydrogel, thermo gravimetric analysis (TGA) may be performed on an in situ formed polymeric system. Different scanning calorimetry techniques are used to determine if there are numerous changes in thermograms when compared to pure components, suggesting the presence of an interaction.

14. In vitro drug release studies

The Franz diffusion cell is used to conduct an in vitro release investigation of an in situ gel solution. In the donor compartment, the formulation is put in, and in the receptor compartment, newly produced simulated tear fluid is deposited. A dialysis membrane (0.22 m pore size) is put between the receptor and donor compartments. The entire system is put on a magnetic stirrer that is thermostatically regulated. The medium temperature is kept constant at $37^{o}C \pm 0.5^{o}C$ for 6 hours, a 1ml sample is extracted at predefined time intervals of 1hr, and the sample volume is replenished with new medium. The withdrawn sample is analyzed after dilution with a UV spectrophotometer at the appropriate nm using a reagent blank. The drug content is determined using a standard calibration curve. The collected data is then used to fit a curve for medication release data. The best fit model of their kinetics is tested for Krosmeyers peppas and Fickian diffusion mechanisms.

15. Ocular irritancy studies

Male albino rabbits weighing 1-2 kg are used in ocular irritancy tests. The modified Draize method is used to assess the risk of eye irritation in ophthalmic products. The formulation is placed in a lower cul-de-sac and irritancy is evaluated after 1 hour, 2 hours, 48 hours, 72

hours, and 1 week following administration. The rabbits' eyes are checked on a regular basis for redness, swelling, and watering.

16. Sterility testing

Sterility testing is performed in accordance with recent Pharmacopoeias. The formulation is incubated for at least 14 days at 30°C -35°C in the fluid thioglycolate medium to determine the growth of bacteria and at 20°C -25°C in the Soya bean casein digest medium to determine the growth of fungus in the formulation.

17. Accelerated stability studies

As per International Conference of Harmonization (ICH) Guidelines, the formulation is put into amber colored vials and sealed with aluminium foil for a short term accelerated stability assessment at 40 °C and 75 % RH. Every month, the sample is tested for clarity, pH, gelling capability, drug content, rheological assessment, and in vitro dissolution.

18. Histopathological studies

Two samples of mucosa tissue (3 cm^2) were placed on in vitro diffusion cells. One mucosa served as a control (0.6 ml water), while the other received 0.6 ml of tailored organogel (conditions similar to in vitro diffusion). The mucosa tissues were fixed in 10% neutral carbonate formalin for 24 hours, and the vertical slices were dehydrated using graded ethanol solutions. Hematoxylin and eosin are used to stain the subdivided tissues. The slices beneath the microscope were photographed at 100 times their original magnification. The microscopic findings are analyzed.

19. Antimicrobial activity

To determine the biological activity of the sol-gel-system against bacteria, antimicrobial efficacy tests are performed. This is determined using cup plate methods in agar diffusion media. The microbiological growth of bacteria is evaluated by the concentration of a standard antibiotic preparation and is carried out using the microbial assay serial dilution method.[1]

Advancements in recent years

One of the problems confronting today's pharmaceutical business is developing effective treatment choices that are acceptable to both physicians and patients. If delivery methods are to give viable alternatives to medicines now administered via other channels, they must also contribute to a superior therapeutic result. One of the most difficult drug delivery methods is

in situ gel formulations. Various biodegradable polymers are utilized in the formation of insitu gels. However, there are fabrication issues, challenging process abilities, and the usage of organic solvents in their production (particularly for synthetic polymer-based systems), burst effects, and irreproducible drug release kinetics. Natural polymers have the properties of a perfect polymer, but batch to batch repeatability is problematic, thus synthetic polymers are employed. The current improvement in biotechnologies has resulted in the creation of dependable macromolecular therapeutic medicines that necessitate complicated formulations for effective delivery.

Two in situ gel forming formulations were used to assess the sustained delivery of paracetamol. The formulation was essentially an aqueous solution of gellan gum (1.0 percent w/v) or sodium alginate (1.5 percent w/v) containing the calcium ion complex, which allows calcium ions to be released in an acidic environment. These calcium ions subsequently induced the gelling agents to gel (gellan gum or sodium alginate). Diffusion controlled release of paracetamol from in situ produced gels was performed in vitro over a 6-hour period. The bioavailability of paracetamol for in situ gel formulation was found to be excellent. The gelling property of cimetidine for oral administration also was investigated. The formulations were made from a dilute solution of enzyme-treated xyloglucan, which forms a thermosensitive gel at body temperature, as well as gellan gum and sodium alginate. In addition, complex calcium ions were added, which when released in an acidic environment create gel when they come into contact with the polymers gellan gum and sodium alginate. Cimetidine plasma levels following oral treatment of rabbits were compared to a commercially available cimetidine/alginate solution, and in vivo release characteristics were determined to be comparable.[8]

Marketed formulations of in-situ formulations

The following are some of the marketed products available as insitu formulations.

ReGel: depot-technology: Regel is a proprietary drug delivery system developed by Macromed that is based on triblock copolymers. It is a class of thermally reversible gelling polymers designed for parenteral administration, with varying gelation temperatures, breakdown rates, and release properties depending on molecular weight, degree of hydrophobicity, and polymer concentration. Following injection, the physical characteristics of the polymer change, resulting in the development of a water-insoluble, biodegradable gel depot. Regel Oncogel is a frozen formulation of paclitaxel. It is a free-flowing liquid below

room temperature that, when injected, creates an in-situ gel in reaction to body temperature. hGHD-1 is a new injectable depot formulation of human growth hormone (hGH) that employs Macromed's Regel drug delivery technology for the treatment of hGH deficient patients.

Cytoryn: This is one of Macromed's products, which is a new, peritumoral, injectable depot formulation of interleukin-2 (IL-2) for cancer immunotherapy that is being used with a Regel drug delivery system. An immiscible liquid at room temperature forms a gel depot upon injection and provides a controlled release of the medication. The Cytoryn immune-enhancing formulation safely delivers four times the highest dosage of IL-2 that may be safely administered according to current standards. Systemic antitumor immunity is also may be stimulated by cytoryn.

Timoptic-XE: A sterile, isotonic, buffered, aqueous gel forming solution of timolol maleate is offered by Merck and Co. Inc. under the brand name *Timoptic* (Timolol Maleate Ophthalmic Gel). Two dose levels are available: 0.25% and 0.5%. The solution's pH is around 7.0, and the osmolarity is approximately 260 to 330 milliosmoles. Timoptic-XE 0.25% includes 2.5 mg of timolol per milliliter (3.4 mg of timolol maleate). Ingredients that are inactive include gellan gum, tromethamine, mannitol, and water for injection, as well as benzododecinium bromide, which is employed as a preservative, at a concentration of 0.012 percent. Topical use of Timoptic XE on the eye decreases both high and normal intraocular pressure, regardless of whether glaucoma is present.[7]

CONCLUSION

In summary, the fundamental criterion of a successful novel controlled release product is to increase patient compliance. The use of polymeric in-situ gel for controlled release of different medicines offers a number of benefits over conventional dosage forms. Sustained and extended drug release, high stability properties and biocompatibility make in situ gel dosage shapes highly dependable. The use of in situ gel formulations of biodegradable and water-soluble polymers can enhance the acceptability and excellence of medicinal products. The choice of a hydrogel depends on its inherent characteristics and the therapeutic usage that has been researched in the past. Non-biodegradable gels might be helpful for methods other than parenteral delivery. Poloxamer hydrogel may be the most extensively investigated system. Particularly interesting systems include poly ethylene glycol - poly (lactic-co-glycolic acid) hydrogels for medicinal applications. Creating an appropriate gastro-retentive

dosage form for the delivery of stomach-specific drugs is still a big challenge. So, several techniques have been used in order to get the necessary gastro retention, of which a floating medication delivery system has been the most promising option. The Floating in situ gelling system is one technique in the floating system for the administration of medications that undergoes a gel transition under acidic stomach conditions and allows the special release of medicinal products for longer periods while floating on the gastric fluid surface. These methods give the benefit of greater drug absorption from the upper portion of the stomach. As the system remains in the stomach for a longer time, local pharmacological activity is boosted due to lengthy contact time with the gastric mucosa. This leads to lower doses and greater therapeutic efficiency.[9]

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