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Review Article

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A REVIEW: NOVEL IN- SITU GEL APPROACHES FOR DRUG DELIVERY SYSTEM

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ABSTRACT

The 'in-situ gel' system has emerged as one of the most creative drug delivery technologies, thanks to its unique 'sol to gel' transition, which aids in the continuous and regulated release of medications. Before entering the body, a formulation is in solution form, but under certain physiological conditions, it transforms into a gel form**.** This is referred to as an in-situ gelling mechanism. In situ gel formation is applied to a range of polymers, which could be used for some drug administration routes. The in-situ gelling method has a wide range of applications and benefits in today's society. The purpose of this work is to provide an overview of in situ gels, including their mechanism, the numerous polymers used, and their applications.

KEYWORDS: In-situ gel, Polymers, oral disease.

INTRODUCTION

The "in-situ gel" is one of the most effective novel medication delivery systems, with sustained and regulated drug releases, increased patient compliance, and comfort support sexuality.[1] The in-situ gelling system is a formulation that begins as a solution before entering the body but turns into a gel under various physiological conditions. The presence of certain molecules or ions, as well as temperature, changes, solvent exchange, UV light, and the presence of certain molecules or ions, are just a few of the factors that affect the transition from sol to gel. "Sol-to-gel transfer" The above property can be leveraged to make vehicles that release bioactive chemicals for a long time. The "in-situ gelling" technique has various benefits, including simplicity of dosing application, reduced dosage frequency, and even drug protection from environmental changes. In-situ gelation of natural and synthetic polymers It can be used for oral, ophthalmic, transdermal, and other applications. Cheek, intraperitoneal, parenteral, injection rectal, and veginal routes.[2] Changes in the physiological identity of[3,4] enhance drug absorption in diverse parts of the gastrointestinal system, enhancing patients' c is a medication delivery strategy made possible by recent breakthroughs in situ gels. Natural polymers employed in the in-situ gelation technique include Carbopol, xyloglucan, xanthan gum, HPMC, poloxamer, pectin gellan gum, chitosan, alginic acid, guar gum, Carbopol, xyloglucan, xanthan gum, HPMC, poloxamer, and others. The in-situ gelling technique has various uses[5] benefits in modern living. The purpose of this paper is to introduce in-situ gels, their mechanics, the numerous polymers utilized, and their applications. The oral cavity provides a diverse environment for colorization by a variety of microorganisms. Oral disorders are complex pathologies that result from the intersection of various components. Including the oral microbiota[6] environmental and behavioral factors, lifestyle factors human genetic makeup(genome), and their transcription and translation, and oral Diseases from tooth decay to All of these diseases pose a major threat to oral health. When oral health is neglected, it can lead to hidden oral health concerns such as periodontal disease, caries and infections, and oral cancer, causing significant discomfort, tooth loss, and catastrophic health consequences. Oral candidiasis, often known as oral thrush, is a candida species mycosis (yeast or fungal infection) of the mouth's mucous membrane. Gum disease is one of the most frequent dental issues among people. Confront, although it can strike at any age.

The significance of an in-situ gelling system[7,8]

- The frequency with which Through its unique "sol-gel transfer," it allows for a controlled, long-term release of the medicine. Reduces the number of drugs in the body**.**
- Low dose drug required, no drug build-up or side effects.
- The bioavailability of the drug is higher.
- Gelation increases the residence time of the drug.
- The in-situ gel method lowers drug waste. A liquid dosage form that keeps medication releases consistent and can stay in touch with the cornea of the eye for long periods is ideal.

- Reduced system adsorption of the medicine discharged through the nasolacrimal duct can have several unfavorable consequences.

Advantages[9-11]

- The drug is released in a controlled, long-term method.
- Easy drug delivery
- It's possible to use it on patients who are not asleep.
- Improved patient compliance and convenience.
- Minimize dosing frequency and drug toxicity
- Improved bioavailability
- Biocompatibility and biodegradation are guaranteed by the use of natural polymers
- Natural macromolecules are biocompatible, biodegradable, and biometric substances that promote cell activity.
- Synthetic polymers have a well-defined structure that can be changed to obtain appropriate degradability and usefulness
- In-situ gels can be developed to have bio-adhesion for non-invasive drug delivery, particularly for drug targeting through the mucosa.
- Because of their hydrophilicity, in-situ gels provide crucial "stealth" qualities in vivo.
- It extends the delivery device's in-vivo circulation period by evading the host's immunological reaction and minimizing phagocytosis.

Limitations of the in-situ gel system[12,13]

- The sol form of the drug is prone to decomposition.
- Possible stability problems due to chemical decomposition.
- Consumption of food and water was found to be restricted for up to several hours after drug administration.
- Especially for the hydrophobic drug, you can limit the amount and uniformity of the drug load on the hydrogel.
- Only low dose requirement medications can be administrated.
- Due to its low mechanical strength, the hydrogel may dissolve or be expelled prematurely from certain local areas.

Ideal polymer characteristics for in situ gel preparation[14,15]

- The polymer must be able to adhere to the mucous membranes.
- Must be well tolerated and free of toxic effects.
- Pseudo-plastic behaviour is necessary.
- The polymer can reduce the of as the viscous shear rate increases.
- Preferred pseudoplastic behaviour of the polymer
- Good compatibility and optical transparency are preferred.
- Must affect tearing behaviour.

Mechanism

The formation of the in-situ gel system occurs through two mechanisms, including the physical mechanism and the chemical mechanism.

Physical mechanism

The following are the components of in-situ formation based on the physical mechanism.

Dispersion

In-situ gel compositions employ diffusion as a sort of physical method.[17] The solvent from the polymer solution diffuses into the surrounding tissue, causing the polymer matrix to precipitate or solidify. N-Meth pyrrolidone (NMP) is a popular polymer for in-situ gelation.

Abrasion

In-situ formulations use swelling, which is a type of physical technique. The polymer that surrounds the polymer is ingested, and the fluid in the external environment swells from the outside to the inside, slowly releasing the medicine. Mineral (glycerol monooleate) is a polarized lipid that forms a lyotropic liquid crystal phase structure when exposed to water. This material exhibits a variety of bioadhesive characteristics and can be destroyed in vivo through enzymatic action.

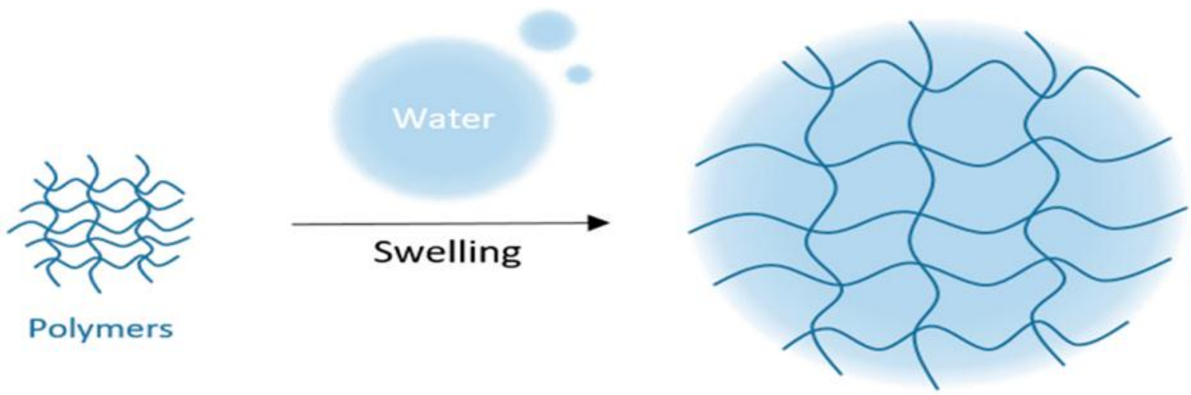

Figure 1: Swelling.

Chemical mechanism[18]
The following processes may be involved in in-situ gelation depending on chemical reaction mechanisms.

Enzymatic cross-linking
The most suitable way for generating the in-situ gelling system is enzymatic cross-linking. In this method, the gel is formed by cross-linking with enzymes present in body fluids. The in-situ formation is induced by the less widely studied natural enzyme but appears to have certain superiority over synthetic and convection techniques. For example, the enzymatic procedure guarantee potency under a physiological state, and the dose do not require potentially destructive chemical such as monomers or initiators. The intelligent stimuli-responsive delivery system may release insulin by use of hydrogels. The amount of enzyme is also changed to maintain the proper mechanism for controlling the rate of gelation, allowing the mixture to be injected before gelation.

Photopolymerization
The photopolymerization process[19] uses electromagnetic radiation during the in-situ gelling system is created. Reactive solution macromer to produce a gel, a monomer, and intruders may be introduced into the tissue location, followed by electromagnetic radiation. The most suitable polymer is In the presence of acrylate or a comparable compound, polymerizable functional groups dissociate. Monomers and photoinitiation such as macromers, are usually long-wave UV and visible wavelengths. Is high-frequency UV light rarely used. because it is physiologically toxic and has limited penetration into tissues in this method, a ketone, such as 2,2-dimethoxy-2-phenyl acetophenone, functions as an initiator for UV photopolymerization. Camphorquninone and ethyl eosin initiators are used in common visible light system.

Ion cross-linking
An ion-sensitive polymer is used for this approach. In the presence of different ions such as Na+, K+, Ca+, and Mg+, ion-sensitive polymers can go through a phase change. polysaccharides are also present in certain polysaccharides belonging to the ion-sensitive is a brittle gel that is hard and a small amount of K+, whereas elastic gels are mainly formed with carrageenan Ca2+ is present. Gellan gum is commonly known as Gel rite. In the presence of monovalent and divalent cations, it is an anionic polysaccharide that gels in situ.[20,21]

Various approaches to in situ gelation
The in-situ gelling system is obtained using a variety of methods.

Temperature Controlled
In the environmentally sensitive polymer system of in-situ gelled formulations, the temperature is the most widely employed stimulus. The temperature changes used are simple to manage and apply in both in vitro and in vivo situations. Body temperature induces gelation in this system, which does not require external heat. These hydrogels are liquids at room temperature (20-25 C) and change from gels when they come into contact with body fluids (35-25 C, 37 C). There are three different types of temperature control systems. They are an example of a negative heat sensitive type: Polygonal (N-isopropylacrmide) Polyacrylic acid heat reversible type example: Poloxamer, Pluronic, Tectonics. Positive heat sensitive type example: Polyacrylic acid heat reversible type example: Poloxamer, Pluronic, Tectonics. Thermal or temperature-reactive polymers are used in this system, and their physical properties vary rapidly or abruptly with temperature. These polymers show a miscibility gap at high or low temperature in the presence of high or low critical solution temperature exists.

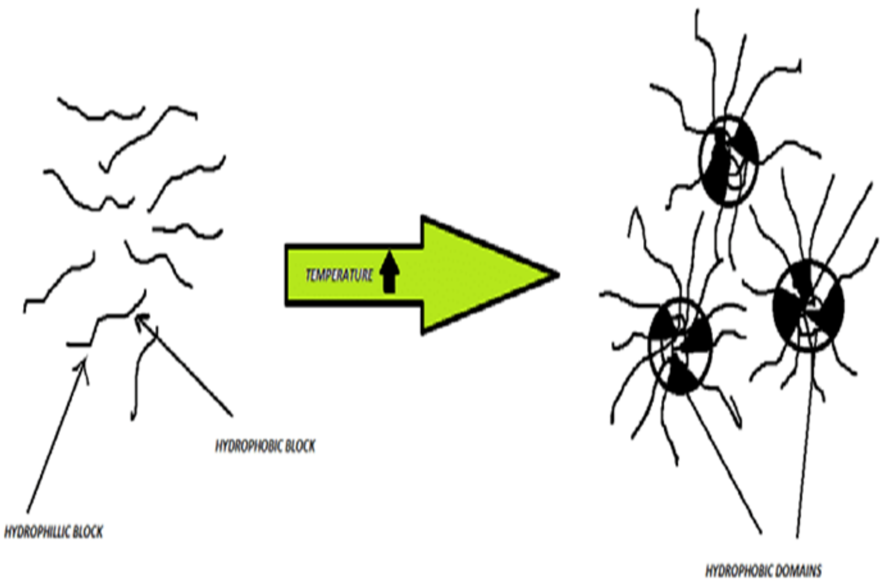

Figure 2: Mechanism of temperature sensitive system.

In-situ gelation triggered by pH

In this system, changes in pH form gels. This method uses a pH-sensitive or pH-responsive polymer. The pH-sensitive polymer contains acidic or basic side groups capable of accepting or releasing protons in response to changes in the pH in the environment.[22] Numerous polymers with Polyelectrolytes are ionizable groups that can be ionized. Because of the polyelectrolytes in the formulation, the external pH rises, causing the in-situ gelling hydrogel to swell. Polymers containing anionic groups are good candidates for this method. Coir acetate phthalate (CAP), carbomer and its derivatives, polyethylene glycol (PEG), pseudolatex, and polyacrylic acid (PMC) are a few examples.

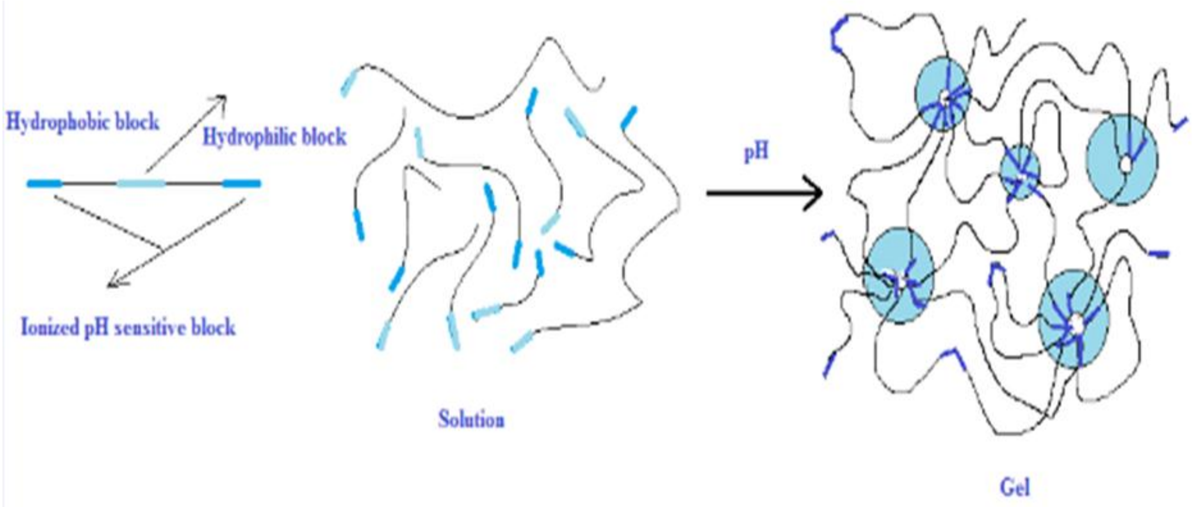

Figure 3: Mechanism of pH triggered in situ gel system.

Ion activation in-situ gelation

In this method, the gelation of the infused solution is triggered by varying the ionic strength.[23,24] The gelation rate is believed to depend on the osmotic pressure gradient across the surface of the gel. Polymer's exhibition osmatic induction gelation includes Gel rite or Gellan gum hyaluronic acid alginate etc.

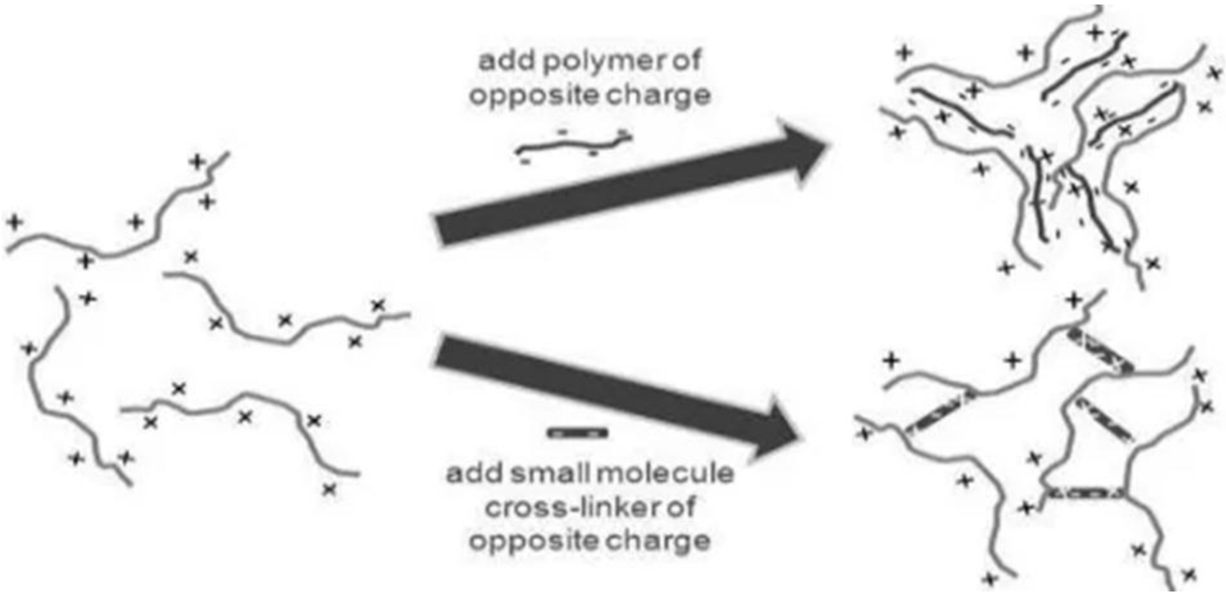

Figure 4: Mechanism of temperature sensitive system.

Polymers used as in situ gelling agents

Gellan gum

Gellan gum is an anionic substance. heteropolysaccharide produced by Micro be sphingomona elody. It consists of glucose, lamp north, gluconic acid and is interconnected with to give a tetracharcharide unit. Gel rite[25] Can be used by treating the alkali rubber to which is gelongmas that can remove acetyl groups in the molecule. Upon injection of, Gelrit is present in the presence of calcium ions, thus forming a gel. Gelation refers to the process of forming a solid substance. The Helix double transition followed by a zone the aggregation of the helix segment, forming a by[26] a three-dimensional network complexing with hydrogen bonding and cations water increase Gellan is used as a suspension and stabilizer in the food business.

Xanthium gum
Xanthan gum is an extracellular polymer with a high molecular weight generated by the Gram-negative bacterium Xanthomonas campestris. The cellulose skeleton (-D-glucose residues) is the basic structure of this naturally occurring cellulose derivative. Xanthan gum dissolves in cold and hot water, as well as alkaline and acidic conditions, due to the trisaccharide side chain of -D mannose -D glucuronic acid D mannose bound to alternating glucose residues in the backbone[27] Xanthan gum dissolves in cold and hot water, as well as alkaline and acidic conditions. Under alkaline circumstances, it demonstrates good stability. Shows good stability under alkaline conditions.

Guar gum
Guar gum is a type of gum manufactured from the endosperm of seeds. Hydrocarbons, facts, esters, alcohols, and ketones are insoluble in guar gum, although it is water soluble. In both cold and hot water they disperse easily and dissolve in both cold and hot water to form a small amount of colloidal solution. Guar gum has a derivative used a target distribution system in the creation of coated Hydrogels, nano microparticles, and matrix systems Polyacrylamide grated graft girls is a derivative of guar gum with good colorectal targeting[28] and polymer, among others. It's also employed as an a-polymer in matrix tablets that have a regulated release.

Alginic Acid
It's a polysaccharide made up of D-mannuronic acid and L-glucuronic acid residues connected by a 1,4-glycosidic bond. The arrangement of the block along the molecule in each block is determined by the source of the algae. With the addition of divalent and trivalent metal ions, a dilute aqueous solution of alginate forms a hard gel. The four successive glucuronic acid residues within the alginate chain's L- glucuronic acid block.[29] For ophthalmic preparations, acid[30] is used as the carrier. due to its favorable biological features such as biodegradability and non-toxicity.

Carbopol
Carbopol is a polyacrylic acid (PAA) polymer that gels when the pH goes above 4.0. At acidic pH, Carbopol is still dissolved in water. whereas at alkaline pH, it transforms into a low viscosity gel. Carbopol is used in conjunction with HPMC. This will raise the viscosity of the Carbopol solution while lowering its acidity. We discovered that the Carbopol 940 had superior[31] appearance and transparency when compared to other types of poly (acrylic acid) (Carbopol 940-934-941 and 910) 47.

Chitosan
Chitosan gelation is induced by two changes: chitosan is a natural substance found in shrimp and crab shells, and it is made up of a biodegradable, heat-sensitive, polycationic polymer made from chitin after it has been alkaline deacetylated. Chitosan is a biocompatible cationic polymer with a pH of 6.2 that may stay dissolved in an aqueous solution. Neutralizing an aqueous solution of chitosan to a Ph above 6.2 forms and precipitates a hydrated gel.[32,33]

Xyloglucan
The polysaccharide xyloglucan, often known as tamarind gum, is derived from the endosperm of seeds. Xyloglucan is made up of three different oligomers, including seven sugars, octa saccharides, and non-sugars, with different numbers of side chains galactose Because of its non-toxic, biodegradable, and biocompatible properties, it is mostly employed in medication delivery via oral, rectal, and ophthalmic routes. When heated to refrigerator temperature or cooled from a higher temperature, it gels[34] similarly to poloxamer.

Sodium Alginate
Sodium alginate is a salt of alginic acid, a linear block copolymer polysaccharide composed of βD-mannuronic acid and αL-glucuronic acid residues linked by 1,4-glycosidic linkages.[35]

EVALUATION AND CHARACTERIZATION OF THE GEL SYSTEM IN-SITU
The formulation and treatment of in situ gels for specific purposes is characterized by ensuring predictable performance in vitro and in vivo. The characteristic parameters for evaluation are,

- Visual appearance and clarity
- Determination of pH
- Gelling Capacity
- Gel strength
- Drug release
- Viscosity Studies
- Gelation time
- Gelation temperature
- Syringe ability
- Spreadability[36]

Determination of visual appearance, clarity, and pH
The appearance was influenced in a variety of ways. The first way is to visually check the product in the good cabinets against a block and white background using fluorescent lighting. The second method checks the pH with a pH meter. 2.5 g of each formulation was dispersed in 25 ml of filtered water and evaluated. Before using, the pH meter should be calibrated using buffers of pH 4 and 7.[37] Finally, the formulation's gelling capacity was tested to determine whether it was suitable for use as an in-situ gelling solution. By combining formulation 25:7 with fake tears and physically inspecting it, the gelling ability was measured.[38]

Capacity for Gelling
A visual method was used to assess gelling potential. A 100l sample was added to a vial containing 2 ml of

freshly manufactured artificial tears that had been equilibrated to 39% 350. The gelation is then visually inspected and the hours of gelation are recorded (Qi et al., 2007).

Drug release

Evaluation of a drug product is the release of the drug in the body. By knowing the time of destruction and the polymer components used, it is possible to design the drug according to the needs of drug therapy.[40]

Gel strength

Based on research, the strength of the gel depends on the gelling agent for using the mechanism in the formulation of the material. Gel strength can be measured with a geometer. Place in a water-based gel or container and gently pressurize to immerse the tool in the gel. The change in load on the tool can be measured as the thickness of the gel.[41,42]

Viscosity

The purpose of this study was to prescribe an in-situ gel that was previously known to exhibit thixotropic behaviour. Therefore, a rheology study should be performed.[43]

Eye drops or eye drops that use a polymer to increase the viscosity of can improve the bioavailability of the undiluted solution. The purpose of increasing the viscosity is to show down the sedimentation of the particles while maintaining the viscosity in order to maintain the suspension of the particles.[44]

Applications of in situ polymeric drug delivery system[45,46]

Oral drug delivery system

The pH-sensitive hydrogel could be used for site-specific delivery of drugs to specific areas of the gastrointestinal tract. Hydrogels constructed from various ratios of crosslinked PEG and PAA derivatives have enabled the preparation of silicone microspheres that produce prednisolone in gastric medium or exhibit gastric protective properties. Showed gastric medium or gastric protective properties. The cross-linked dextran hydrogel showed fast swelling under high pH conditions but investigated another polysaccharide such as amidated pectin, inulin, and guar gum to reveal a potential colon-specific drug delivery system. It has improved. Both gallan and sodium alginate formulations contain complex calcium ions and undergo a gelling process by releasing these ions in the acidic environment of the stomach.

Ocular drug delivery system

Natural macromolecules such as alginate, inulin, the overcome xyloglucan, and inulin are most commonly used in eye delivery system. The topical ophthalmic delivery system uses a variety of compounds, including autonomic drugs, anti-inflammatory and antibacterial agents, to relive intraocular pressure in glaucoma. Traditional delivery system often has a high tear turnover of and dynamics of, which reduces the availability and therapeutic response of, resulting in rapid removal of the drug from the eye. An ophthalmic in-situ gel, a bioavailability issue, was developed. To improve bioavailability, thickeners such as carboxymethyl cellulose, hydroxypropyl methyl cellulose, Carbopol, polyvinyl alcohol were used to increase the precorneal residence duration by increasing the viscosity of the formulation and bioavailability is also increased. Preservatives, chelators, surfactants and penetration enhancers help the medicine enter into the cornea.

Nasal drug delivery system

Xanthan gum and gallan gum are used as in-situ gel producing polymers in the nasal gel system. The effectiveness of mometasone folate in the treatment of allergic rhinitis is studied. An allergic rhinitis model was preformed using animal experiments and the effect of in-situ gel on antigen-induced nasal symptoms in sensitized rats was observed. In-situ gel has been shown to suppress the increase in nasal symptoms compared to over-the-counter formulations.

Rectal and vaginal drug delivery system

Many different types of drugs can be administered via the rectal route, including liquid, semi-solid (ointment, creams, and foams), and solid dose forms (suppositories). In-situ rectal gel made with acetaminophen, polycarbophil, and poloxamer F188 and poloxamer 407 as synthetic polymer-forming gel – creating liquid synthetic polymer considered in-situ use a gelled liquid suppository It's thought to be a good method because it increases bioavailability.

CONCLUSION

According to the current study, "In-situ gel" is one of the most innovative drug delivery methods. The in-situ gelling technology allow for a more controlled and extended delivery of drugs and improved patient compliance and comfort. For oral, ocular, transdermal, buccal, intraperotonial, parenteral, injectable, rectal, and vaginal routes a variety of natural and synthetic polymers are used. Advancements in innovative medication delivery systems are assisting in overcoming the limitations that traditional systems present.

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