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A New Approach to Drug Delivery Using In-Situ Gel for Stomach-Specific Sustained Absorption

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ABSTRACT

Floating in-situ forming polymeric formulations are drug delivery systems that are in sol form before being supplied to the body, but then gel in-situ to form a gel after being injected. Temperature modulation, pH alteration, presence of ions and ultraviolet irradiation, electrical sensitivity, and enzyme sensitivity are all elements that influence the creation of gels, from which the medication is released in a controlled and sustained manner. Controlled and sustained drug administration has recently become a popular strategy in modern pharmaceutical design, with extensive research being conducted to improve medicinal product performance, reliability, and safety. The in-situ gel forming polymeric formulations have various advantages over conventional drug delivery systems, including sustained and prolonged action, strong patient compliance, and good durability and biocompatibility features, making in situ gel dosage forms very trustworthy. Gellan gum, sodium alginate, HPMC (hydroxypropyl methylcellulose), xyloglucan, pectin, chitosan, poly (DL lactic acid), poly (DL-lactide-co-glycolide), and poly-caprolactone are some of the biodegradable polymers used to make in situ gels. Sol-gel transition temperature and floating lag time of gel, in-vitro drug release tests, gel strength, viscosity & rheology, and clarity are all factors to consider when evaluating in-situ gel systems. Recent advances in polymer science and technology have resulted in the development of a variety of stimuli-sensitive hydrogels, such as pH and temperature-sensitive hydrogels that are employed for the targeted delivery of proteins to the colon and chemotherapeutic drugs to cancers. The in-situ gel dosage forms are particularly reliable due to the drug's sustained and prolonged release, as well as its good stability and biocompatibility.

Keywords: In-situ gels, polymers, polymeric gel, sustained release, photo-polymerization, pH, carbopol, gellan gum, floating

INTRODUCTION

The Floating Drug Delivery System (FDDS) is a successful device for increasing drug bioavailability by prolonging the stomach residence time. Davis was the first to describe FDDS in 1968. FDDS are low-density systems with sufficient buoyancy to float above gastric contents and stay in the stomach for an extended period. Floating drug delivery devices for gastric retention float on the surface of gastric fluids and have a controlled release, resulting in a long-lasting impact [1]. A ton of elements impact the medication bioavailability of helpful portion plans. The stomach home time (GRT) of various portion plans is a significant thought. The stomach can purge into the small digestive tract in as little as a couple of moments or up to 12 hours [2]. Drug retention in the gastrointestinal plot is a profound factor process that is impacted by variables, for example, stomach purging, gastrointestinal travel span of measurement structures, drug discharge from the dose structure, and medication retention area. Drugs with a short half-life and simple ingestion from the gastrointestinal parcel (GIT) are quickly taken out from the fundamental flaw. To get sufficient helpful adequacy, these drugs should be dosed frequently [3]. Several strategies are now used to build an effective stomach-specific or gastro retentive drug delivery system, including hydrodynamically balanced systems (HBS) / floating drug delivery system, and low-density raft systems utilizing alginate gels, and low-density systems. A combination of hydrophilic polymers (hydroxypropyl, methylcellulose) and floating agents are used to create swellable, floating, and sustained release gels (calcium carbonate). It's also useful for medications that enter the stomach at an acidic pH. Higher density delivery systems settle down in the stomach first, then absorb water, expand, and float as the density of the system decreases [4].

In-Situ Gelling System

The in-situ gelling framework has become one of the most noticeable among novel medication conveyance frameworks because of many benefits like superior patient consistency and decreased recurrence of medication organization. 'In-situ' is a Latin word that signifies 'in position'. There are many setting-off instruments for in-situ gel development some of them are pH change, temperature change, and dissolvable trade [5]. Because the gel generated by the in situ gelling technology is lighter than gastric fluids, it floats over the stomach contents or adheres to the gastric mucosa due to the bio-adhesive nature of the polymer, resulting in dosage form retention and an increase in gastric volume [6].

Importance of In-Situ Gelling System

- **i.** In comparison to already formed gels, the ability to provide correct and repeatable quantities is critical [7].
- **ii.** In-situ forming polymeric delivery system with advantages such as simplicity of administration and reduced administration frequency [8].

iii. Due to buoyancy, the gastric retention period is prolonged [9].

iv. Reduces dosage frequency, which improves patient compliance.

v. Bioavailability improves despite the first-pass effect because variations in plasma drug concentration are minimized and a desired plasma drug concentration is maintained through continuous drug release.

vi. Short-half-life medicines can have a better therapeutic effect.

vii. Controlled drug release over a long time.

viii. Drug distribution to the stomach can be site-specific.

ix. Floating in-situ dosage forms are superior to single unit floating dosage forms because they release medicine uniformly and there is no chance of dose dumping.

x. It can be used with both hydrophilic and hydrophobic medicines, as well as different solutes.

xi. Controlling water swelling and cross-linking density can help manage therapeutic agent release. [10].

Approaches to *In-Situ* Gelling Drug Delivery

There are four broadly defined mechanisms used for triggering the *in-situ* gel formation of biomaterials: Physiological stimuli (e.g., temperature and pH), physical changes in biomaterials (e.g., solvent exchange and swelling), and chemical reactions (e.g., enzymatic, chemical and photo-initiated polymerization).

In-situ formation based on physiological stimuli

Thermally trigged system–

Temperature touchy hydrogels are presumably the most regularly concentrated class of climate delicate polymer frameworks in drug conveyance research [11]. The utilization of biomaterial whose advances from sol-gel are set off by expansion in temperature is an appealing method for drawing closer to in-situ development. The ideal basic temperature range for such a framework is surrounding and physiologic temperature, to such an extent that clinical control is facilitated and no outside wellspring of intensity other than that of the body is expected to trigger gelation. A valuable framework ought to be tailorable to represent little contrasts in nearby temperature, for example, maybe experienced in limbs at the outer layer of skin or in the oral pit. Three fundamental procedures exist in designing the thermo-responsive sol-gel polymeric framework. For comfort, temperature-touchy hydrogels are grouped into adversely thermosensitive, decidedly thermosensitive, and thermally reversible gels. Negative temperature-delicate

hydrogels have a lower basic arrangement temperature (LCST) and contract after warming over the LCST. Polymers with low basic temperature (LCST) change among encompassing and physiologic temperature is utilized for this reason. One of the most widely examined polymers that display helpful LCST change is poly [(N-isopropyl acrylamide) (PNIPAAm)]. PNIPAAm is a water solvent polymer at its low LCST, however hydrophobic above LCST, which result in precipitation of PNIPAAm from the arrangement at the LCST. Pluronics are poly (ethylene oxide)- poly (propylene oxide)- poly (ethylene oxide) (PEO-PPO PEO) triblock co-polymer that is liquid at low temperature, yet frames dependable gel when warmed as an outcome of a problem request change in micelle pressing which makes these polymers reasonable for in situ gelation [12]. A positive temperature delicate hydrogel has an upper basic arrangement temperature (UCST), such hydrogel contracts after cooling beneath the UCST. Polymer organizations of poly (acrylic corrosive) (PAA) and polyacrylamide (PAAm) or poly (acrylamide-co-butyl methacrylate) have positive temperature reliance on enlarging [13]. The most normally utilized thermo-reversible gels are arranged from poly (ethylene oxide)-b-poly (propylene oxide)-b-poly (ethylene oxide) (Pluronics®, Tetronics®, poloxamer). Polymer arrangement is a free streaming fluid at encompassing temperature and gels at internal heat level [14]. Cappello et al. created novel "protein polymers" ProLastins, which go through irreversible sol-gel progress. At the point when infused as an answer into the body, the material structures into a firm, stable gel in practically no time. It stays at the site of infusion giving ingestion times from short of what multi-week to numerous months. Such a framework would be not difficult to direct into wanted body depression [15].

pH triggered systems –

Another in situ gel formation based on physiologic cues is gel formation triggered by pH variations. In reaction to variations in environmental pH, all pH-sensitive polymers include pendant acidic or basic groups that receive or release protons. Polyelectrolytes are polymers that have a large number of ionizable groups. If the hydrogel contains weakly acidic (anionic) groups, swelling increases as the external pH rises, but decreases if the polymer contains weakly basic (cationic) groups. PAA (Carbopol®, carbomer) or its derivatives are used in the majority of anionic pH-sensitive polymers. Similarly, low viscosity polyvinyl acetal diethyl amino acetate (AEA) solutions at pH 4 create hydrogel at neutral pH [16]. One of the limitations of pharmaceuticals generated in liquid solutions is that a small amount of PAA solution will cause damage to the eye's surface before being neutralized by the lacrimal fluid. This problem was partly solved by combining PAA with HPMC, a viscous-enhancing polymer, which resulted in pH-responsive bioavailability and easy tear fluid evacuation. To decrease these factors and maximize medicine administration, Kumar and Himmelstein developed a poly (acrylic acid) (PAA) solution that would gel at pH 7.4. The author discovered that low pH polymer combinations that were solution at pH 4 and gel at pH 7.4 were soluble at concentrations high enough to trigger gelation [17].

***The In-situ* formation is based on the physical mechanism**

Swelling –

When the material absorbs water from the surrounding environment and expands to fill the appropriate space, this is known as in situ formation. Myverol 18-99(glycerol mono-oleate), a polar lipid that expands in water to produce lyotropic liquid crystalline phase structures, is one such chemical. It has some bioadhesive qualities and can be destroyed in the body by enzymes [18].

Diffusion-

The diffusion of solvent from the polymer solution into the surrounding tissue results in the precipitation or solidification of the polymer matrix in this approach. The solvent N-methyl pyrrolidone (NMP) has been proven to be effective in such systems [19].

***In-situ* formation based on chemical reactions**

Chemical reactions that result from *in-situ* gelation may involve precipitation of inorganic solids from supersaturated ionic solutions, enzymatic processes, and photo-initiated processes:

Ionic crosslinking –

In the presence of different ions, polymers may undergo a phase change. Ion-sensitive polysaccharides are among the polysaccharides. In the presence of a modest amount of K+, k-carrageenan forms hard, brittle gels, whereas i-carrageenan creates elastic gels. Gellan gum, also known as Gelrite®, is an anionic polysaccharide that gels in situ when exposed to monovalent and divalent cations such as Ca2+, Mg2+, K+, and Na+. Divalent cations, particularly Ca2+, can cause gelation of low-methoxy pectins. In the presence of divalent/polyvalent cations, such as Ca2+, alginic acid gels due to interaction with the guluronic acid block in alginate chains [20].

Enzymatic cross-linking-

Natural enzyme-catalyzed in-situ production has not been extensively studied, but it appears to offer some advantages over chemical and photochemical techniques. An enzymatic process, for example, works effectively under physiological settings without the need for potentially dangerous substances like monomers and initiators. The use of hydrogels in intelligent stimuli-responsive delivery systems that can release insulin has been researched. Cationic pH-sensitive polymers with immobilized insulin and glucose oxidase can swell in response to blood glucose levels, pulsatile releasing the entrapped insulin. Adjusting the amount of enzyme also gives you a simple way to control the rate of gel formation, allowing you to inject the mixes before they form [21].

Photo-polymerization-

In-situ biomaterial creation is frequently achieved using photo-polymerization. A monomer or reactive macromer solution with an initiator can be injected into a tissue location, and electromagnetic radiation can be utilized to generate a gel. Because they photo-polymerize quickly in the presence of a suitable photo-initiator, acrylate or similar polymerizable functional groups are commonly utilized as polymerizable groups on individual monomers and macromers [22]. Long-wavelength ultraviolet and visible wavelengths are most commonly used. Short wavelength ultraviolet is rarely employed since it penetrates tissue poorly and is biologically damaging. In ultraviolet photo-polymerization, a ketone, such as 2, 2 dimethoxy-2-phenyl aceto-phenone, is frequently employed as the initiator, but in visible light systems, camphor quinone and ethyl eosin are frequently used [23]. These systems can be easily damaged by chemical or enzymatic processes, or they can be constructed to last in vivo for a long time. When photo-polymerizable materials are injected into the appropriate place, they are photo cured in situ using fiber optic cables and then release the medicine for a long time. At physiological temperatures, photoreactions generate rapid polymerization rates. Furthermore, the systems are simple to insert in complex-shaped volumes, resulting in the construction of an implant. Sawhney et al. describe a photopolymerizable, biodegradable hydrogel as a tissue contacting material and controlled release carrier [24].

Polymers used in the development of *in-situ* drug delivery systems

Natural and synthetic polymers are used, but biopolymers are safe and effective in oral medication delivery systems.

Ideal Characteristics of Polymers

A polymer used in in-situ gels should have the following properties: biocompatibility.

- It should have the ability to attach to mucous.
- It should behave in a pseudo-plastic manner.
- It should have a high level of tolerance and optical activity.
- It should have an impact on tear production.
- The polymer should be able to decrease viscosity as the shear rate increases, resulting in lower viscosity during blinking and tear film stability during fixation [25].

Pectin

Pectins are a type of polysaccharide with a backbone primarily made up of - (1-4)-D galacturonic acid residues. In the presence of free calcium ions, low methoxy pectins (degree of esterification 50%) rapidly form gels in an aqueous solution, which crosslink the galacturonic acid chains in the egg-box model. Although pectin gels in the presence of H + ions, a source of divalent ions, calcium ions are usually required to generate gels that are appropriate as drug delivery vehicles

[26]. The fundamental benefit of utilizing pectin in these formulations is that it is water-soluble, eliminating the need for organic solvents. When pectin is taken orally, divalent cations found in the stomach help it transition to a gel state. To induce pectin gelation, calcium ions in their complex state may be incorporated into the formulation. To build a compound with the majority of calcium ions in the formulation, sodium citrate can be added to the pectin solution. The formulation can be kept in a liquid state (sol) until the complex breaks down in the stomach's acidic environment, causing the release of calcium ions, which induces gelation [27]. The amounts of calcium and citrate ions in the formulation can be adjusted to keep it fluid before delivery and prevent it from gelling in the stomach. The potential for sustained delivery of paracetamol using an orally administered in situ gelling pectin formulation has been reported [28].

Xyloglucan

Xyloglucan is a polysaccharide produced from tamarind seeds, consisting of a (1-4)—D-glucan backbone chain with (1-6)—D xylose branches partially replaced by (1-2)—D-galactoxylose. The lateral stacking of the rod-like chains causes thermally reversible gelation when xyloglucan is partially degraded by - galactosidase. The temperature of the sol-gel transition varies depending on how much galactose has been removed. When heated to body temperature, it generates thermally reversible gels. Its potential for oral delivery is based on the projected delayed gelation period (a few minutes), which would allow in-situ gelation in the stomach after the oral administration of cold xyloglucan solution. Oral, intraperitoneal, ophthalmic, and rectal medication administration could all be possible with xyloglucan gels [29].

Gellan gum

Gellan gum (also known as Gelrite TM or Kelcogel TM) is an anionic deacetylated exocellular polysaccharide secreted by Pseudomonas elodea, consisting of one -L-rhamnose, one -D-glucuronic acid, and two -D-glucuronic acid residues in a tetrasaccharide repeating unit. It has a tendency to gel, which is temperature-dependent or triggered by cations. The creation of double-helical junction zones is followed by the aggregation of the double-helical segments into a three-dimensional network by cation complexation and hydrogen bonding with water. Gellan solution with calcium chloride and sodium citrate complex made up the composition. When calcium ions are given orally, they are discharged into the stomach's acidic environment, causing gellan to gel and form a gel in situ [30].

Alginic acid

Alginic acid is a polysaccharide that is made up of -D-mannuronic acid and -L-glucuronic acid residues linked together by 1, 4-glycosidic connections. Depending on the algal source, the quantity of each block and the placement of blocks along the molecule differ. When di and trivalent metal ions are added to dilute aqueous alginate solutions, a cooperative mechanism

involving sequential glucuronic residues in the L glucuronic acid blocks of the alginate chain forms solid gels. Because of its advantageous biological features, including biodegradability and nontoxicity, alginic acid can be used as a carrier for ocular formulations. Alginic acid formulations were studied for a prolonged precorneal stay, not only because of their capacity to gel in the eye but also because of their muco-adhesive qualities [31].

Xanthan gum

The gram-negative bacterium Xanthomonas campestris produces xanthan gum, which is a high molecular weight extracellular polysaccharide. This naturally occurring cellulose derivative has a cellulosic backbone (-D-glucose residues) and a trisaccharide side chain of -D-mannose—D-glucuronic acid—D-mannose connected to the main chain's alternate glucose residues. The inclusion of both glucuronic acid and pyruvic acid groups in the side chain gives this polymer an anionic property [32].

Chitosan

Chitosan is a biodegradable, thermosensitive, polycationic polymer made from the basic deacetylation of chitin, which is found in shrimp and crab shells. Chitosan is a pH-subordinate cationic polymer that remains disintegrated in aqueous solutions up to a pH of 6.2. The formation of a hydrated gel-like encourage is prompted by the balance of Chitosan fluid answer for a pH greater than 6.2. The pH gelling cationic polysaccharides arrangement is changed into thermally delicate pH subordinate gel shaping watery arrangements, with no synthetic adjustments or cross-connecting by the expansion of polyol salts bearing a single anionic head, such as glycerol, sorbitol, fructose, or glucose phosphate salts to chitosan fluid arrangement [33].

Carbopol

Carbopol is a notable pH subordinate polymer, which stays in arrangement structure at acidic pH yet frames a low consistency gel at soluble pH. HPMC is utilized in mix with carbopol to give consistency to carbopol arrangement while lessening the acridity of the solution. Various water dissolvable polymers, for example, carbopol framework hydroxyl propyl methyl cellulose framework, poly (methacrylic corrosive)-poly (ethylene glycol) go under the classification of pH-incited in-situ hastening polymeric frameworks. In light of this idea, the definition and assessment of an ophthalmic conveyance framework for indomethacin for the treatment of uveitis were done. A supported arrival of indomethacin was noticed for a time of 8 h in-vitro accordingly thinking about this framework as an incredible contender for visual conveyance. A pH-incited in-situ accelerating polymeric framework (a watery arrangement of the carbopol-HPMC framework) was planned and created by Ismail et al. for plasmid DNA conveyance [34].

Pluronic F-127

Poloxamers or pluronic (showcased by BASF Corporation) is a series of monetarily accessible difunctional triblock copolymers of non-ionic nature. They involve a focal square of moderately hydrophobic polypropylene oxide encompassed on the two sides by the squares of somewhat hydrophilic polyethylene oxide. Because of the PEO/PPO apportion of 2:1, when these particles are inundated into the watery solvents, they structure micellar structures above basic micellar fixation. They are viewed as PEO-PPO-PEO copolymers. Artificially they are Oxirane, methyl-polymer with oxirane or α-Hydro-ω-hydroxypoly(oxyethylene) a poly(oxypropylene) poly(oxyethylene)a block copolymer [35]. The pluronic triblock copolymers are accessible in different grades contrasting in atomic loads and actual structures. Contingent on the actual assignment for the grades is appointed, like F for chips, P for glue, and L for fluid. Pluronics or Poloxamers additionally go through in situ gelations by temperature change. They are triblock copolymers comprising poly (oxyethylene) and poly (oxypropylene) units that go through changes in dissolvability with changes in climate temperature Pluronic F 127. A 25-40% watery arrangement of this material will gel at about internal heat level, and medication discharge from such a gel happens over a time of as long as multi-week. Pluronic F-127 was utilized as an in-situ gel framing polymer along with muco-adhesive polymers, for example, Carbopol 934 and hydroxyl propyl methylcellulose to guarantee long home time at the application site. Controlled arrival of medication was accomplished in-vitro demonstrating antimycotic adequacy of created definition for a more extended timeframe [36].

Synthetic polymers

Synthetic polymers are frequently used in parenteral formulations. The trend in drug delivery technology has been toward biodegradable polymers that don't need to be removed surgically once the drug supply has run out. The most recent investigations have focused on aliphatic polyesters such as poly (lactic acid), poly (glycolic acid), poly (lactide-coglycolide), poly (de-acetone), and poly-caprolactone. Synthetic polymers are frequently used in parenteral formulations [37]. The trend in drug delivery technology has been toward biodegradable polymers that don't need to be removed surgically once the drug supply has run out. The most recent investigations have focused on aliphatic polyesters such as poly (lactic acid), poly (glycolic acid), poly (lactide-coglycolide), poly (de-acetone), and poly-caprolactone [38]. Different polymers like triblock polymer frameworks made out of poly (D, L-lactide)-block-poly (ethylene glycol)-block-poly (DL-lactide), mixes of low atomic weight poly (D, L-lactide) and poly (ε-caprolactone) are additionally being used. These polymers are fundamentally utilized for the injectable in-situ definitions. The practicality of lactide/glycolide polymers as excipients for the controlled arrival of bioactive specialists is all around demonstrated. These materials have been exposed to the broad creature and human preliminaries without proof of any hurtful incidental effects. When appropriately ready under GMP conditions from purged monomers, the polymers show no proof of fiery reaction or other antagonistic impacts upon implantation.

Thermosetting frameworks are in the sol structure when at first comprised, yet after warming, they set into their last shape. This sol-gel change is known as restoring [39]. Yet, assuming this restored polymer is warmed further, it might prompt corruption of the polymer. Restoring mostly includes the development of covalent cross-connections between polymer chains to shape a macromolecular organization. Dunn et al. planned a thermosetting framework utilizing biodegradable copolymers of DL-lactide or L-lactide with ε-caprolactone for prosthetic embed and slow delivery drug conveyance frameworks. This framework is fluid external to the body and is equipped for being infused by a needle and once inside the body, it gets. In-situ accelerating polymeric frameworks, the polymer precipitation from arrangement might prompt gel development in-situ and this precipitation can be actuated by a change in temperature (thermosensitive frameworks), dissolvable expulsion, or by change in pH [40].

A significant illustration of thermosensitive polymer is poly-(N-isopropyl acrylamide), [poly (NIPAAM)], which is utilized for the arrangement of in-situ gels. It has a lower basic arrangement temperature stage detachment at around 32. The polymers, for example, poly (DL-lactide), poly (DL-lactide-glycolide) and poly (DL-lactide-co-ε-caprolactone) structure dissolvable evacuation encouraging polymeric frameworks [41].

Floating In-Situ Gelling Drug Delivery System

Prolonging the time a dose form spends in the stomach may have therapeutic benefits. For the site-specific regulated administration of pharmaceuticals for both local and systemic effects, gastro-retentive in-situ gelling devices can be developed. Aqueous solutions of various anionic hydrocolloids and effervescent agents are typically used in these systems. Gel formation occurs in the stomach due to cation induced gelation, as well as gas production due to the reaction between gastric acid and the effervescent ingredient. Because the gas is trapped in the gel structure, its density is less than unity [42].

Recent Research on in-situ gelling system

Demonstrated that oral administration of aqueous solutions containing either gellan gum or sodium alginate and calcium in complexed form results in the formation of gels in rabbits and rat stomachs, which function as depots for the release of paracetamol over a period of 6 h [43].

Similar bio-availabilities in rabbit to those of a commercial suspension for the oral administration of paracetamol can be achieved with these in situ gelling formulations, with the advantage that such formulations are homogeneous liquids when administered orally and do not have the problems that may be associated with the formulation and administration of suspensions [44].

Developed and evaluated floating *in-situ* gelling systems based on pectin for the site-specific delivery of Ambroxol. Their study has shown that 1.5% (w/v) solutions of pectin with a degree

of methoxylation of 9% containing a source of calcium in complexed form have potential use as *in-situ* gelling vehicles for oral administration [45].

Developed a gellan gum-based in-situ gelling formulation bearing amoxicillin for the treatment of stomach-specific *Helicobacter pylori* infection. Various formulations were prepared by dissolving gellan gum in deionized water to which varying concentration of drug and calcium carbonate was added [46]. Their results showed that these formulations have the feasibility of forming gels in the sustaining the drug release from the gels over the period of at least 8 h. Further, the prepared in situ gels were effective in clearing *H. pylori* in infected gerbil's stomach at a dose level, which was 10-fold less than the amoxicillin suspension, which is important from the viewpoint of reducing adverse effects during the therapy [47].

Developed an *in-situ* gelling drug delivery system consisting of Chitosan and glyceryl monooleate (GMO) in 0.33M citric acid-containing paclitaxel for sustained and targeted drug delivery for chemotherapy to mucin-producing cancerous cells. The amount of paclitaxel transported across cell lines was much lower in the case of the gel as compared with paclitaxel in solution indicating that this gel delivery system can be used to sustain the release of paclitaxel [48].

Evaluation and Characterization of Floating In-Situ Gel

The following parameters can be examined and characterized on in situ gels:

1. Clarity

Visual assessment of prepared solutions against a black and white background determines their clarity. [49].

2. Texture analysis

The texture analyzer is used to measure the firmness, consistency, and cohesiveness of the formulation, which primarily determines the syringe ability of the sol, indicating that the formulation may be easily delivered in-vivo. Gels with higher adhesiveness are required to sustain close contact with surfaces such as tissues [50].

3. Sol-Gel transition temperature and gelling time

The sol-gel transition temperature can be defined as the temperature at which the phase transition of sol meniscus is first detected when held in a sample tube at a certain temperature and then heated at a specified rate for in-situ gel-forming systems comprising thermo reversible polymers. The absence of movement of the meniscus when tilting the tube indicates gel formation. Gelling time is the time it takes to detect gelation for the first time, as mentioned above [51].

4. pH measurement

The pH was measured in each of the solutions of sodium alginate-based *In situ* solutions, using a calibrated digital pH meter at 27°C [43].

5. *In-vitro* floating ability

900 cc of 0.1N HCl (pH 1.2) were used in the in-vitro floating research. The mean temperature was maintained at 37 degrees Celsius. Without much disturbance, a ten milliliter formulation was added to the dissolution tank holding medium. The time it took the formulation to emerge on the medium surface (floating lag time) and the time it floated on the dissolution medium surface continuously (duration of floating) were recorded [52].

6. Measurement of rheological properties of sols

The viscosity of drug-free sols synthesized in water was measured using a Brookfield cone and plate rheometer with a cone angle of 0.80 (DV-III ULTRA) and spindle cp 40 (see Fig. 1.2). Changing the angular velocity from 0.5 to 100 rpm at a regulated ramp speed was a typical run. The velocity was increased to 100 rpm after 6 seconds at 0.5 rpm, with a comparable pause at each level. With a 6-second delay, the angular velocity hierarchy was reversed (100 rpm to 0.5 rpm). The viscosity was calculated using the average of two observations. The evaluations were done three times [53].

7. *In vitro* gelation study

The gelation cells were made of Teflon® at the Banaras Hindu University's Instrumentation Centre in Varanasi, India. The cells were cylindrical reservoirs that could hold 3mL of gelation solution, or simulated stomach fluid (SGF, pH 1.2). A 250-l translucent plastic cup was contained within the bottom cells to hold the gel sample in place when it was formed. Then, using a micropipette gently inserts 100 l of the preparation into the cup's cavity, and slowly add 2ml of the gelation solution (SGF) [54].

8. Measurement of *in vitro* drug release

The release rate of Piroxicam from in-situ gelling formulations was measured using a USP dissolving test device (USP 24) with a paddle stirrer at 50 rpm, as described by Mishra and Rajnikanth (2008) [55]. The temperature was kept at 370.5 °C and the dissolution medium was 500 cc of 0.1M HCl (pH 1.2). Using a disposable syringe, ten milliliters of formulation were drawn up, the needle was cleaned, and the surplus formulation was removed from the needle end. Ten milliliters of in situ gel solution were deposited in a Petri dish, which was then placed in a dissolving vessel containing a dissolution medium [56]. A precisely measured sample of the dissolution medium was taken at each time interval and replaced with pre-warmed (37°C) fresh medium. At predefined intervals, samples were taken and evaluated UV spectrophotometrically at 333nm. The tests were carried out three times [57].

9. Preliminary *In-Situ* Evaluation of Gel formation in Stomach

For in-vivo evaluations such as bioavailability tests of new formulations, man is the ideal model. Animal models should be employed initially during the product development stage to tune the formulation to the desired parameters, as no superfluous human testing should be done. The use of animal models has several benefits, including the ability to conduct early in vivo research during preclinical drug development [58]. These experiments are less expensive and faster than those conducted on humans. Furthermore, animal models can be employed not only as a screening tool before human investigations but also for later mechanistic analyses of findings from human studies. The dose is usually given in animal research as the amount of medication in relation to body weight. While evaluating dosage forms, it is recommended to deliver the dose intended for people to avoid the development of specific low-dose formulations for animal studies [59]. The purpose of this study was to use rats as animal models to evaluate the behavior of the best prototype gel in situ. The goal of the study was to see how the stomach environment affected the formation of the gel structure after a dosage of the sample was given [60]. Following oral administration of 1 ml of the tested sample to the rats for 30 minutes, visual inspection of the stomach contents revealed the formation of well-defined gel-matrix blocks with appropriate integrity in both samples. This finding indicates that the gel matrix formed quickly after injection. This is consistent with the findings of the in-vitro portion of the study [61].

Marketed products of in-situ polymeric systems at a glance

Topalkan - Al-Mg antacid

Liquid Gaviscon - Al-hydroxide (95mg), Mg carbonate (385mg)

Conviron - Ferrous sulphate

Table 1: Marketed products of in-situ polymeric systems

S. No	US Patent	Formulations
1.	US20120009275	In situ forming hydrogel wound dressing containing antimicrobial agents [62]
2.	US20050063980	Gastric raft composition 63]
3.	US5360793	Rafting antacid formulation [63]
4.	US20020119941	In situ gel formation of pectin [64]
5.	US20110082221	In situ gelling system as sustained delivery for eye [65]

Development of in-situ gel of various drugs by different researchers

CONCLUSION

Finally, the constructed in-situ gelling system has the potential to generate gels in the stomach while also sustaining medication release from the gels over time. This reduces the number of doses required and enhances patient compliance. Because the drug is imprisoned in the gel

network, these in-situ gelling systems may reduce the occurrence of gastric side effects by preventing the drug from coming into direct touch with the gastric mucosa. Our findings suggest that these in-situ gelling systems could be used as a site-specific drug delivery system for medications suitable to the pediatric and geriatric populations, with fewer stomach side effects and better patient compliance. Several biodegradable polymers having in situ gelling activity are available. We can increase stomach retention and thus bioavailability of medicinal drugs by fully understanding the floating behavior of biodegradable polymers. In situ gels have improved stability and biocompatibility, as well as better drug release, making them more reliable dosage forms than traditional ones.

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