REVIEW ARTICLE

# Liquid Oral Floating *In Situ* GELS: A Review

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## Abstract

The oral route technique is the most common technique for the oral administration of drugs into the body. It overcomes that the problems like drug targeting to organs can cause problems for administration through the oral route. The ideal solution to solve the issues of the quick release and brief gastrointestinal residence of liquids is to design a unique strategy, which is an *in situ* drug delivery system. It also prolongs the gastric residence time and controls the rate of drug release which can improve oral bioavailability and reduce the frequency of dosing. It is a particular variety of hydrogel that can hold a significant quantity of water and biological fluids without swelling. In *in situ* gelling systems, polymers such as guar gum, gellan gum, xanthan gum, carrageenan, xyloglucan, pectin, chitosan, and thiolate chitosan are used. The gel produced by the *in situ* gelling technique is thinner than the duration of gastric retention. The main aim of this review is to focus on the *in situ* gel principle, classification, advantages, disadvantages, and its application as a floating *in situ* gel system.

**Key words:** Floating drug delivery system, gastroretentive drug delivery system, *in situ* gel, novel drug delivery system

## INTRODUCTION

A floating drug delivery system is one of the novel drug delivery systems. In the form of gastro retentive floating systems, many dosage forms are created, including microspheres, microbeads, pills, capsules, and films. A recent development in floating medication delivery systems is an *in situ* gelling device. Applications for *in situ* gelling devices include oral, nasal, ocular, peroral, rectal, vaginal, and parenteral modes of delivery. Davis described the first description of a floating medicine delivery device in 1968. A low-density polymeric gel barrier is formed at the outer surface of floating systems, which are controlled or sustained-release dosage forms with characteristics such as hydrophilic matrices and so-called hydrodynamically balanced systems. Drug delivery dosage forms that float make use of several polymer systems.

Due to liquid oral medications are swiftly passed through the stomach, they have limited bioavailability. The issues of the quick release and brief gastrointestinal residence of liquids can be resolved by the oral *in situ* gel. When liquid orals come into touch with bodily fluids, they begin to gel due to the rise in temperature. This method takes use of phase shift caused by temperature. In comparison to current drug delivery systems, the formulation of the floating *in situ* gelling solution may maintain and prolong drug activity, enhance patient compliance, and decrease the frequency of administration of the medication.[1,2]

### Gastroretentive drug delivery system (GRDDS)

GRDDS has experienced tremendous growth in the field of oral medication administration recently. It is a frequently used strategy to overcome numerous issues with conventional oral administration, including poor bioavailability, by keeping the dose form in the stomach for a longer length of time and releasing the medication gradually. Many drug molecules

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whose primary sites of adsorption are the stomach or the proximal portion of the intestine, or whose absorption issues are in the distal part of the intestine, are affected by fast gastric emptying associated with typical oral drugs.

It is desirable to achieve a prolonged gastric residence time by the drug delivery to formulate a site-specific oral administration-controlled release dosage form. Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract for local or systemic effects.

A few of the gastroretentive drug delivery strategies under development include high-density (sinking) systems that are retained in the stomach's bottom, low-density (floating) systems that cause buoyancy in gastric fluid and mucoadhesive systems that cause adhesion to the stomach mucosa. Recently, several gastroretentive techniques have emerged as top strategies for site-specific oral controlled-release drug delivery systems. Floating drug delivery systems are comes under GRDDSs.[3,4]

### Floating drug delivery system

It is one of the important approaches to achieving gastric retention to obtain sufficient drug bioavailability; for medications that have an absorption window in the stomach or upper small intestine, this administration method is preferable. Since floating drug delivery devices are buoyant in the stomach for an extended length of time without changing the gastric emptying rate, the medication is released from the system slowly and at the appropriate pace. The stomach's residual system is emptied once the medication has been released.

As a result, the stomach retention period is lengthened and the fluctuations in plasma drug concentration are better managed. Figure 1 shows a floating medication delivery system. Air can be trapped or low-density materials can be used to provide the inherent low density. The design of floating dosage forms for single-and multi-unit systems has utilized the following strategies.

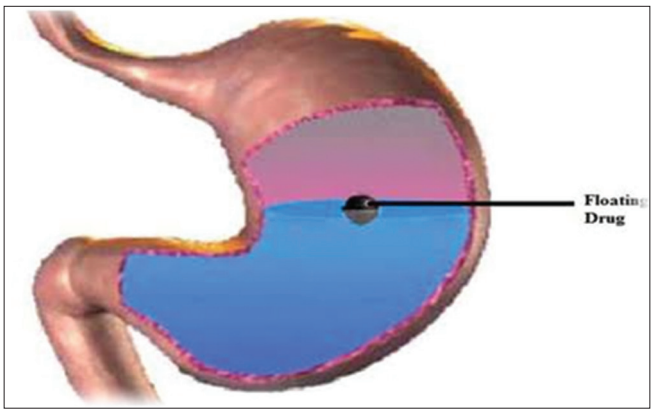


**Figure 1:** Floating drug delivery system

Figure 1 depicts a schematic illustration of a floating medicine delivery system. Accurate control of the ensuing drug release patterns might be effectively integrated with the system's good floating behavior. Effervescent and non-effervescent systems are two totally different technologies that are based on the principle of buoyancy.[3,4]

## EFFERVESCENT SYSTEMS

The floatability can be produced by the generation of gas bubbles. These buoyant systems utilize matrices prepared with swellable polymers such as polysaccharides (E.g., chitosan) and effervescent components (E.g., sodium bicarbonate, citric acid, or tartaric acid). In this system, carbon dioxide is released and causes the formulation to float in the stomach.

The design of a multilayer or bilayer system also allows for the incorporation of gas-generating material into any layer. The further modification involves the coating of a matrix with a polymer that is permeable to water but not to carbon dioxide. The main difficulty of these formulations is finding a good comprise between elasticity, plasticity, and permeability of polymers.[5]

### Gas-generating systems

These are formulated into two types which are single layer intragastric floating tablets and bilayer intragastric floating tablets. The residual system is expelled from the stomach once the medication has been properly and fully released from the floating system. This has the effect of extending stomach retention time and improving control of changes in plasma medication concentration.[6]

### Volatile liquid-containing systems

The floating chamber, which may be a vacuum, filled with air, or filled with innocuous gas, allows volatile liquid-containing systems to float in the stomach while the drug reservoir is enclosed inside a microporous compartment.[2,3]

### Inflatable gastrointestinal delivery systems

These devices have an inflatable chamber with liquid inside that evaporates at body temperature to induce the chamber to expand within the stomach. The medication constantly leaks into the stomach juice from the reservoir.[7]

### Intragastric osmotically controlled drug delivery

Osmotically regulated intragastric medication administration is made up of a biodegradable capsule, inflatable floating support, and a medication delivery system with osmotic pressure control. The drug reservoir compartment and

the osmotically active compartment make up the two compartments of the osmotic pressure-controlled drug delivery system. To initiate the drug release from the delivery orifice of the drug solution compartment, an osmotic pressure is produced and works on a collapsible bag, which causes the drug reservoir compartment to lower its capacity.[8]

### Non-effervescent systems

Non-effervescent floating drug delivery systems are normally prepared from highly swellable cellulose-type hydrocolloids, polysaccharides or matrix-forming polymers such as polyacrylate, polycarbonate, and polystyrene. A schematic representation of the mechanism of floating *in situ* gel is shown in Figure 2. After being taken orally, a medication that has been mixed with a gel-forming hydrocolloid comes into touch with stomach fluid and maintains some shape integrity and a bulk density below unity. The excipients utilized in this system the most frequently include polycarbonate, agar, sodium alginate, polyvinyl acetate, and HPMC. This system may be separated into other sub-types.[9]

### Colloidal gel barrier systems

These systems are prepared by using gel forming hydrocolloids including high amount of one or more cellulose type of hydrocolloids which are capable to produce gels and are highly swellable, for example, HPMC and Na CMC. When in touch with stomach contents, the system develops a viscous core, absorbs water, and traps air, causing the density to drop below 1 g/cm$^3$. Then, it begins to float.[10]

### Microporous compartment system

Based on encapsulation of drug reservoir inside a microporous compartment, the drug reservoir's peripheral walls are totally sealed thanks to its encapsulation inside a microporous compartment, preventing any undissolved medication from coming into direct touch with the stomach mucosa. Entrapped air in the flotation chamber causes the delivery system to float over the contents of the stomach. Gastric fluid enters through holes, dissolving the medication, and transporting it for absorption.[11]

### Alginate beads

These can be prepared by adding a sodium alginate solution to aqueous calcium chloride solutions, calcium alginate will precipitate and form spherical beads that are about 2.5 mm in diameter. The separation of these beads, their freezing in liquid nitrogen, and subsequent freeze-drying at −40°C for 24 h causes a porous system to develop, which maintains a floating force for more than 12 h.[7]

### Hollow microspheres

These are loaded with drugs and are prepared by a simple solvent evaporation method. Polymers used to develop these systems are polycarbonate, cellulose acetate, calcium alginate, agar, and pectin.[11]

## NEED FOR THE STUDY

Finding effective treatment alternatives that both doctors and patients can comfortably accept are one of the issues that the pharmaceutical business now faces. One of the difficult medication delivery techniques is *in situ* gel formulations. Delivery systems must also contribute to a better therapeutic outcome if they are going to provide viable alternatives to pharmaceuticals currently delivered by other routes.

Drugs with limited solubility and low stability in intestinal fluids can use floating drug delivery devices, which were developed to keep the medication in the stomach. To enable it to float on the stomach fluids, the floating drug delivery method makes the dose form less dense than the fluids. In comparison to conventional drug delivery systems with higher density, the formulation of the floating *in situ* gelling solution may sustain and prolong drug action, improve patient

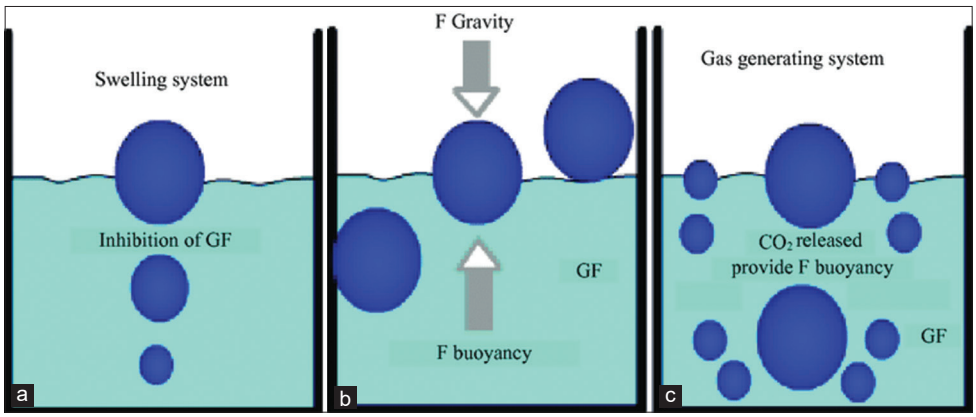


**Figure 2:** (a-c) Mechanism of the floating system

compliance, and reduce the frequency of administration of the drug. These systems initially settle down in the stomach and absorb water, swell, and float due to a decrease in system density. It effectively extends the release time to boost medication bioavailability.[12]

## POLYMERS

A polymer is any of a class of natural or synthetic substances composed of very large molecules called macromolecules which are multiples of simpler chemical units called monomers. Polymers are classified into two types based on the source that they are natural polymers and synthetic polymers.

### Natural polymers

It is widely used in oral, rectal, and ocular drug delivery due to its toxicity, biodegradability, and biocompatible property. Numerous biological applications, including medicines, tissue regeneration, scaffolds, drug delivery systems, and imaging agents, frequently employ natural polymers. All living things create naturally occurring polymers. Do not have any negative environmental consequences.

### Synthetic polymers

Engineers and scientists use petroleum oil to create synthetic polymers. It is a flexible substance having a variety of mechanical, thermal, and degrading characteristics that may be made into biomedical foams.

#### *Gellan gum*

Gellan gum when taken orally, calcium ions were released in the stomach's acidic environment, causing Magellan to gel, and creating an *in situ* gel. Gellan gum has the tendency of gelation, which is de temperature dependent water-soluble polymer that acts as a potential carrier for different oral floating sustained delivery dosage forms.[13]

#### *Pectin*

Pectin Divalent cations present in the stomach carry the transition of pectin to a gel state when it is administered orally. In general, calcium ions are required to produce gels that are suitable as vehicles for drug delivery. Hence, there is no need for organic solvents in the formulation. The clumps can be solubilized by mixing the pectin powder with a water-soluble carrier. The fluid state is maintained until the breakdown of the complex in the acid environment in the stomach, where the release of calcium ions.[14]

#### *Xyloglucan*

The prospective use of xyloglucan for oral medication delivery takes advantage of its delayed gelation period, which would enable *in situ* gelation in the stomach after oral administration of the xyloglucan solution. Xyloglucan has a similar gelation behavior as pluronic; however, it does so at considerably lower concentrations. There are four ways to make xyloglucan gel, including enzymatic breakdown with beta-galactosidase, adding alcohols, adding polyphenols, and adding an iodine solution. In the presence of 40–55% sugar over a broad pH range, it gels.[15]

#### *Xanthan gum*

Xanthan gum can form a strong gel when mixed with positively charged polymers. It is a long-chain polysaccharide with a large number of tri-saccharide side chains. Xanthan gum is soluble in hot water and cold water as well as in acidic and alkaline conditions. It is also used as a polymer in the formulation of an *in situ* gelling system. The bacteria *Xanthomonas campestris* produces xanthan gum, an extracellular polymer that appears as a gel as a result of the creation of a homogeneous solution.[13]

#### *Alginate*

Alginate is an anionic polymer that is primarily derived from brown seaweed. A naturally occurring hydrophilic polymer obtained from sea brown algae is sodium alginate. Alginates are black copolymer of L-guluronic and D-mannuronic acid residues connected by 1:4 glycosidic linkages in the acid environment of the stomach, both alginate salts and alginate acids precipitate to form a low density, but viscous gel sodium alginate is mostly used for the preparation of the gel-forming solution, for delivery of the drugs, peptides, and proteins.[16]

#### *HPMC*

It is a partly o-methylated and o-cellulose conforming to the limits for the various types of HPMC. It is widely used in oral and topical pharmaceutical formulations as, a controlled release agent, dissolution enhancer, solubilizing agent, sustained release agent, and viscosity-increasing agent. They are known beneficial in improving the residence time and drug release characteristics. At low temperatures, the solution is in liquid form and when temperature increases and gelation occurs.[17]

#### *Poloxamer*

Poloxamer is a series of commercially available dysfunctional tri-block copolymers of non-ionic nature. Pluronic or poloxamers also undergo *in situ* gelation by temperature change. Poloxamer-127 gives colorless transparent gels which are the most commonly used polymer in pharmaceutical technology. It is mainly used in gelling agent, emulsifying agent, and solubilizing agent. It depends on the ratio and distribution of hydrophilic and hydrophobic chains several molecular weights available having different gelling properties.[18]

### *Carbopol*

It is a pH-dependent polymer that forms a low viscosity get at alkaline pH but stays in solution form at acidic pH. At body temperature, a 25 to 40% aqueous solution of this substance will gel, and the release of the medication from such a gel can take up to a week. Carbopol is appropriate for gel production since it is non-toxic and non-irritating. An aqueous solution of carbopol is a low-viscosity acid solution that transforms into a gel on an increase in the pH and, therefore, may be used as *in situ* gelling.[19]

## *IN SITU* GELS[20]

*In situ* forming polymeric drug delivery systems have many advantages such as ease of administration, increased bioavailability, reduced dose frequency, and improved patient compliance. A schematic representation of floating *in situ* gel is shown in Figure 3. *In situ* gel-forming systems have been widely investigated as a vehicle for sustained drug delivery.

### Advantages of *in situ* gels

1. Improve patient compliance
2. Production is easy
3. Ease of administration
4. Improve therapeutic efficiency
5. Reduction in plasma level fluctuation.

### Disadvantages of *in situ* gels

1. It requires a high level of fluids
2. Change in pH may prompt degradation
3. Exposure in certain polymer to radiations (E.g., UV, visible, and electromagnetic). Hence, it induces the formation of gel within the package
4. It leads to degradation due to storage problems
5. Only a small dose is administered.

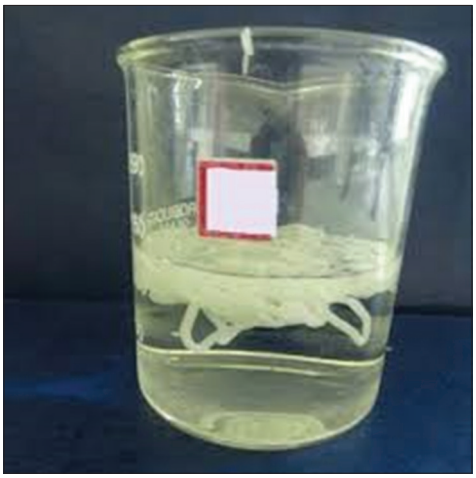

**Figure 3:** Schematic representation of floating *in situ* gels

## APPROACHES OF DESIGNING *IN SITU* GELS

### Physically induced *in situ* gel systems[13]

### *Swelling*

The formation of *in situ* gel occurs when lipid polymeric absorbs coater from the surrounding environment and expands to give desired space. For instance, Myverol 18-99 (glycerol mono-oleate), which is a polar lipid that swells into the water, generates a crystalline phase structure. It has some bioadhesive qualities and is susceptible to enzymatic degradation *in vivo*.

### *Diffusion*

In this process, the polymer matrix precipitates or solidifies as a result of the solvent from the polymer solution diffusing into the surrounding tissues. The solvent of N-methyl pyrrolidone is a useful solvent for diffusion.

### Chemically induced *in situ* gel systems[21]

### *Ionic cross-linking*

Polymers may undergo a phase transition in presence of various ions. Certain ion-sensitive polysaccharides such as carrageenan, pectin, gellan gum, and sodium alginate undergo phase transition ions such as calcium, potassium, magnesium, and sodium. While carrageenan forms rigid, a small amount of potassium is replied in brittle gels, elastic gels are the formed by carrageenan in presence of calcium. The use of a gelling agent, which may create a system including dispersed medicines and excipients, is required for *in situ* gel formation. The creation of twin helical junction zones occurs in the *in situ* gel. The medicine that is floating in the stomach is slowly and at the desired pace removed from the system. Natural enzymes have not been extensively studied; yet, they have certain benefits over chemical or photochemical methods for *in situ* gel system production.

### *Enzymatic cross-linking*

It is the most suitable method in which *In situ* gel formation is catalyzed by natural enzymes. In this approach, the gel is formed by cross-linking with the enzyme present in body fluids. Hydrogels are used in intelligent stimuli-responsive delivery systems that can release insulin. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase swell in response to blood glucose level release. A schematic representation of chemically induced *in situ* gels is shown in Figure 4. Modify the amount of enzyme also maintains a suitable mechanism for controlling the role of gel formation and confesses the mixture to be before gel formation.

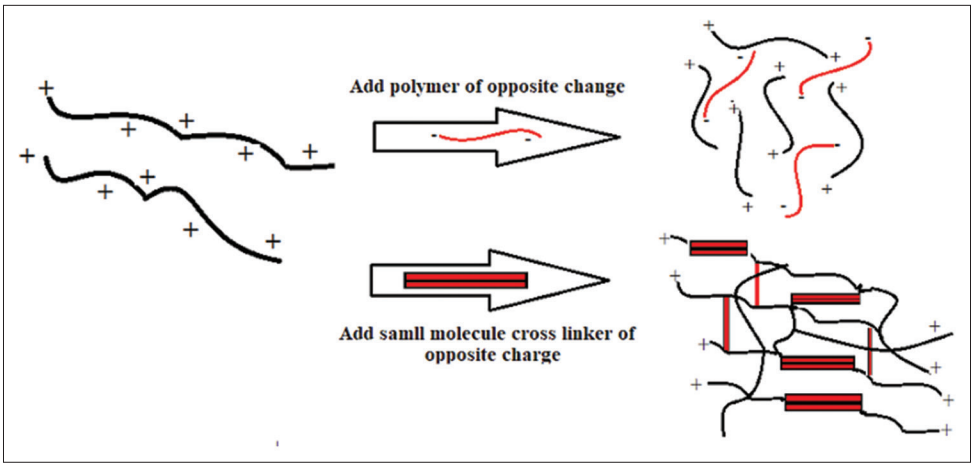


**Figure 4:** Chemically induced *in situ* gels

### *Photo-polymerization*

It is commonly used for the *in situ* formation of biomaterials, in which a solution of monomers such as acrylate or other polymerizable functional group initiators can be injected into the tissue site. The application of electromagnetic radiation is used to form a gel. The most suitable polymer for photo polymerization undergoes polymer dissociation by polymerizable functional groups in presence of photoinitiators like monomers or macromers. The log wavelength of UV and visible wavelength is used. A ketone such as 2,2-dimethoxy-2-phenylacetophenone is used as an initiator for UV photo-polymerization. Camphor, quinone, and ethyl eosin initiators are used in visible light systems.

## *In situ* gel formation based on physiological stimuli

### *Temperature-dependent in situ gelling*

These hydrogels are liquid at room temperature and undergo gelation when contact with body fluids due to temperature increases. The most extensively researched group of environmental-sensitive polymer systems in drug delivery research is likely the temperature-sensitive hydrogels. These polymers are two types based on the temperature. One is Negative thermosensitive type, for example, poly (N-isopropyl acrylamide) and another one is Positively thermosensitive type, for example, polyacrylic acid. In these systems, thermoresponsive or temperature-responsive polymers are used. The negative temperature-sensitive hydrogels compress on heating over critical solution temperature (LCST) and have a lower LSCT. A schematic representation of the formation of the solution to gel on basis of temperature is shown in Figure 5. Polymers with LCST transition between ambient and physiological temperature are used. One of the most LCST transitions is poly [N-isopropyl acrylamide] [PNIPAAM]. PNIPAAM is a water-soluble polymer at low LCST, but hydrophobic above LSCT. A positive temperature hydrogel is an upper critical solution temperature (UCST) such hydrogels contract cooling below UCST. Polymer networks of polyacrylic acid (PAA) and polyacrylamide (PAAM) have positive temperatures depending on swelling.[21]

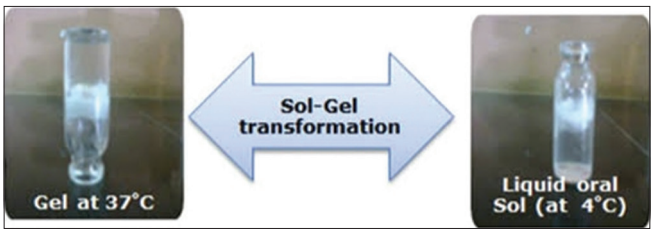


**Figure 5:** Liquid oral solution to gel

### *pH in situ gelation*

In this system, the gel is formed due to pH changes. In this approach, pH sensitive polymers or pH responses are used. Acidic or basic polymers that are pH-sensitive receive or release protons in response to pH variations in the surrounding environment. The polymers include a huge number of polyelectrolytes, or ionizable groups. The swelling hydrogels increase with external pH increases in weak acidic of polymer but decreases polymer in weak base groups, for example, carbomer and its derivatives. Liquid drug formulations have a number of drawbacks, such as low bioavailability and a tendency to be removed readily. PAA can be used to formulate this type of system in order to minimize these drawbacks and to maximize the drug delivery. Figure 6 illustrates a schematic diagram of a pH-dependent *in situ* gel. At a pH of 7.4, the solution is a gel. Before lacrimal fluid could neutralize the low pH of the PAA solution, it would harm the surface of the eye.[13]

## PRINCIPLE

The main step in creating an *in situ* gel system is using gelling agents to create a stable suspension system that includes the medicine that has been disseminated and additional excipients. A change in pH will cause this solution/suspension mixture to gel in the stomach environment. The formulation used is a sodium alginate or gellan gum solution that releases calcium chloride exclusively in the stomach's acidic environment. Gellan gum, also known as sodium alginate, serves as a gelling agent and traps free calcium ions in its polymeric

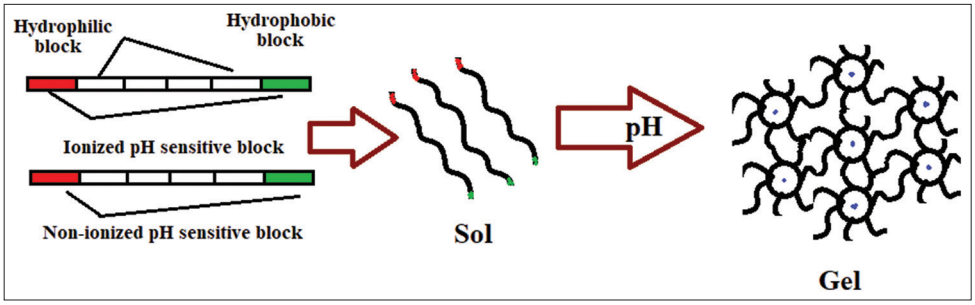


**Figure 6:** pH-dependent gel formation

chains. To build a three-dimensional network, this gelation entails the development of a double helical junction and then the reassembly of double helical segments. By complexing with cations and forming a hydrogen bond with water, double helical segments are created during the gelation process, which results in the construction of a three-dimensional network. The gelling agents serve as a dispersion medium in the form of the aqueous solution to contain the drug in dispersed form along cross-linking.[22]

## MECHANISM OF DRUG RELEASE FROM *IN SITU* GEL SYSTEM[2]

### Diffusion-controlled mechanism

#### *Matrix system*

The active agents present in the drug are equally dispersed as a solid and then converted into a hydrogel-inert biodegradable polymer matrix. Water enters the matrix at a constant pace, then the medication dissolves and leaves the matrix at a constant rate. The medicine is released after interacting with the biodegradable polymers. The length of the drug's diffusional pathe is exactly proportional to the thickness of the hydrated matrix. If the polymer matrix is inert and the drug release is diffusion-controlled, then the rate of release of the drug is can be described by the Higuchi equation.

#### *Reservoir devices*

In reservoir devices, the drug is enclosed by a core also known as a reservoir. This, in return, is enclosed by a rate-controlling polymeric membrane of hydrogel which allows the diffusion of the drug. If these systems contact with water, the water will diffuse into the system contact with water, the water will diffuse into the system and dissolution of the drug. The way of transport of drugs can be described by Fick's first law if the drug activity in the reservoir is kept constant and if they are infinite sink conditions then the rate of release of drugs is kept constant since it depends on membrane permeability and it is independent of time. Thus, zero order of kinetics can be achieved. Once a drug is exhausted, the release becomes concentration-dependent following first-order kinetics. These kinds of drug delivery systems are mainly used to deliver the active by oral routes.

### Swelling-controlled mechanism

#### *Solvent-activated system*

It occurs by diffusion of the drug which is faster than hydrogel swelling. When a hydrogel is kept in an aqueous solution, the water molecule enters into a polymer network which occupies some space and then the meshes of the network will start expanding which allows other water molecules into the network. However, the hydrogel swelling is not a continuous process. The elasticity at the covalently or physically cross-linked network will counterbalance the infinite stretching of the network to prevent its destruction. For example, the release of drugs from hydrogel is a frequently used mechanism.

#### *Osmotic swelling*

For hydrogels, the total swelling pressure is depending on volume fraction, the relaxed volume of the network, and cross-link density independent of gel pH and swelling time.

### Chemically controlled mechanism

It is divided based on the chemical reaction occurring during drug release into:

#### *Pendant chain system*

It is the most common reaction where the drug is covalently attached to a polymer backbone. The bond between drug and polymer can be broken by enzymatic degradation and release.

#### *An erodible drug delivery system*

The release of the drug is controlled by the dissolution during surface erosion or bulk degradation of the polymer backbone than the drug diffusion from the erodible system. The rate of release of the drug depends on the diffusion of polymer degradation. The drug is released by different mechanisms that they are erosion of the polymer which is much slaver than the diffusion of the drug through the polymer, and then drug release can be treated as a diffusion-controlled release.

## EVALUATION OF *IN SITU* GELLING SYSTEM

### Clarity

Under a black-and-white background, it is possible to visually assess the clarity of the created solution. One of the most important aspects of preparation is the solution's clarity.[23]

### Viscosity

The viscosity of all formulations was determined using a Brookfield digital viscometer before using spindle number 2 at 50 rpm. A volume of 50 mL of the sample was measured and taken into Nessler's cylinder and sheared at a rate of 50 and 60 rpm using spindle numbers. The formulation should have an optimum viscosity that allows easy swallowing as a liquid and then undergoes a rapid sol-gel transition due to ionic interactions. The shear thinning's behavior provides an advantage for the administration process. Gellan was attributed as a consequence of increasing the chain interaction with polymer concentration.[24,25]

### The solution to gel time

*In vitro* gelation time was determined using USP dissolution apparatus containing 500 mL of 0.1N HCl at 37°C. It converts from sol to gel. The formulation was coming in contact with 0.1N HCl and time was measured. Figure 7 illustrates the schematic transition of *in situ* gel from solution to gel form. Gelling time is required for the first gelation of the *in situ* gelling system.[26]

### Gel strength

This parameter is evaluated using a remoter with a specific amount of solution from the gel prepared. A beaker is raised at a certain rate, so pushing a probe of rheometer slowly through the gel. It can be measured by changes in load on the probe can be measured as a function depth of immersion of the probe.

**Figure 7:** Solution to *in situ* gel

The solution, the colored solution of the formulation is prepared and in a test tube, 15 mL gelation medium [0.1N HCL pH 1.2] is taken. After that, 1 mL of the colored formulation is added. As the solution encounters the gelation medium, a stiff gel is produced. A gelling capacity is determined based on stiffness and the period of gel constant. Evaluation of gelling capacity is measured by visualization method.[23]

### *In vitro* floating study

The floating ability of the gel is determined in a 500 mL stimulated dissolution apparatus, after the prepared formulation is introduced in the dissolution vessel. Then, the duration of the formulation is constant. *In vitro* gelling capacity was categorized based on FLT and DOF as follows.

a. Low gelling capacity [+]: FLT [immediate gelation] and DOF<12 h
b. Intermediate gelling capacity [++]: FLTC [immediate gelation] and 24 h>DOF>12 h
c. High gelling capacity [+++]: FLT [immediate gelation] and DOF>24 h.[27]

### *In vitro* drug release

The release rate of the drug from *in situ gel* can be determined using up dissolution rate testing apparatus. At 50 rpm, 900 mL of 0.1N HCL can be used as a dissolution medium and a temperature of 37°C can be maintained. A schematic representation of gel formation by increasing temperature is shown in Figure 8. The 5 mL samples can be withdrawn at various time points for estimating the drug release UV visible spectrophotometer. The same volume of medium is to be replaced every time.[28]

### Stability studies

The room temperature storage condition was 298 K and 65% RH and the condition for accelerated stability studies was 313 K temperature at a relative humidity of 348 K stability to be tested for 30 days.[29]

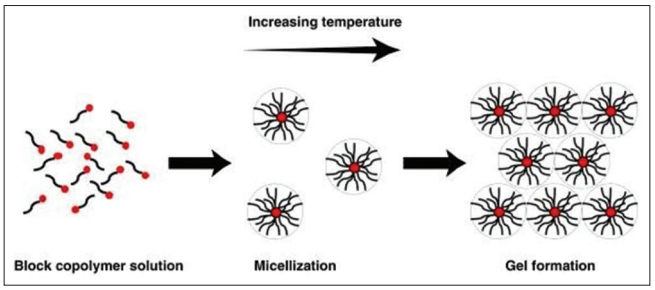


**Figure 8:** Example of gel formation by increasing temperature

### Swelling index

The gel swelling index of the selected formulation is determined by a simple method. The *in situ* gel formed in 40 mL of 0.1N HCL was used separate the 0.1N HCL gel fraction from each formulation and removes the excess HCL solution with paper towels. The initial weight of gel at 12 h was calculated and determined the weight difference.[30]

### pH determination

The pH of the solution can be determined using a digital pH meter and favorable conditions that facilitate *in situ* gelling can be identified. Using medium of different pH values can help determine the impact of pH on the gelation of solution.[31,32]

## RECENT ADVANCES

The recent advancement of biotechnologies has led to the development of labeled macromolecular therapeutic agents that require complex formulations. *In situ* gel formulations are one of the challenging drug delivery systems that various biodegradable polymers are used for the formulation of *in situ* gel. Natural polymers satisfy the characteristics of an ideal polymer, but batch-to-batch reproducibility is difficult synthetic polymers are used. Patel *et al*., described that a sodium alginate based floating in situ gelling system of famotidine was prepared by dissolving varying concentrations of alginate in deionized water containing sodium citrate; in which varying concentrations of drug and calcium chloride was added and dissolved by stirring. When this mixture was mixed with vegetable oil and a biocompatible hydrophilic solvent led to the formation of injectable *in situ* forming organogel. The loaded organogel degraded and released gradually leuprolide for 14–25 days.[29]

## CONCLUSION

The gastroretentive floating drug delivery is challenging for prolonging gastric retention and physiological compatibility with the stomach. Through local drug release, FDDS will significantly enhance the pharmacotherapy of the stomach itself and result in high drug concentrations in the gastric mucosa that are sustained over an extended length of time. The goal of developing the *in situ* gel formulation was to increase patient compliance and decrease dose frequency. Utilizing polymeric *in situ* gels for the controlled release of different medications has a number of benefits over traditional dosing forms. The development of liquid orals for their prolonged drug release has a lot of potential in conjunction with *in situ* drug administration. Gels show site-specific drug delivery may be local or systemic delivery as it returns to the stomach for a long period by floating on gastric fluid. Since they may be supplied in drop form and greatly lessen visual issues, *in situ* activated gel-forming devices appear to be preferable.

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