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ORAL FLOATING *IN SITU* GEL SYSTEM: A NOVEL PLATFORM FOR ORAL DRUG DELIVERY

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ABSTRACT

Floating *In situ* gel is a novel drug delivery system that maximizes the oral absorption of the drugs. Floating *In situ* gelling systems are liquid at room temperature but undergo gelation when in contact with the body fluids. Floating *In situ* gel-forming drug delivery is a kind of mucoadhesive drug delivery system. Different approaches involved in producing the floating *in-situ* gel formation are based on physical changes, chemical changes, and physiological stimuli. Floating *In situ* gel formulation is mainly prepared by the gelation method. Materials of floating *in situ* gels are drug, gelling polymer, cross-linking agent, buffering agent, and gas generating agent. Many natural, biodegradable, synthetic, and biocompatible polymers like sodium alginate, pectin, xyloglucan, Gellan gum, guar gum, etc are used in the preparation of floating *in situ* gelling systems. Gastro retentive floating *in situ* gel-forming system provides a suitable way for controlling drug delivery within the stomach where an environment-specific gel-forming solution, floats on the surface of gastric fluids. Floating *In situ* gelling system has several advantages over conventional drug delivery systems like the sustained and prolonged release of drugs, reduced administration frequency, improved patient compliance, ease of administration, and effective cost. It provides a more effective surface area than the tablet and it leads to an increased release and Improves availability. Floating *in situ* gels were used to treat the diseases like gastritis and other local infections related to GI the tract.

KEYWORDS: Floating *in situ* gel, stomach-specific drug delivery, gastro retention, Floating drug delivery system.

INTRODUCTION

Gastro retentive drug delivery is a site-specific drug delivery in the stomach. It retains the dosage form in the stomach and the drug is released in a sustained manner to a specific site. Oral drug delivery systems show fewer bioavailability problems due to their rapid gastric transit time from the stomach, mainly in drugs that are less soluble at the alkaline pH of the intestine. It increases the frequency of dose administrations. To avoid these drawbacks the gastro retentive drug delivery systems proposed to increase the gastric residence of drug delivery systems in the upper part of the GIT. Among GRDDS floating systems are the most suitable gastro retentive *in situ* gel-forming system that provides controlled drug delivery in a sustained manner. The floating *in situ* forming system is liquid at room temperature and converts into a gel when in contact with the gastric fluids of the stomach. These floating *in situ* forming systems floats over the gastric contents due to the low-density gel formation than gastric contents. This low-density gel formation provides gastric retention and prolongs the contact time along with producing continuous slow drug release. These floating *in situ gel*-forming systems utilize smart polymers like sodium alginate, Xyloglucan, etc. which act as gel-forming agents. The floating ability of the gel may be improved by the addition of gas-generating agents like calcium carbonate, and bicarbonates, etc., various approaches are involved in producing the floating *in situ* gel formulation based on physical, chemical, and physiological changes.[1]

To create an oral floating *in situ* gel system, it was necessary to comprehend three components of the system:

1. The physiochemical and pharmacological properties
2. GIT physiology and anatomy
3. A dose form feature.

Basic physiology of GIT

The fundus, body, and antrum are the three anatomical divisions of the stomach (pylorus). The proximal section, which is formed by the body and the fundus, acts as a storage area for undigested matter. While the antrum is

the main site for mixing movements and acts as a pump to empty the stomach by pushing motions. The stomach empties both after eating and after fasting. The patterns of mobility in the 2 states are different though. When a person is fasting, a series of electrical events that cycle through the stomach and intestine every two to three hours takes place. Wilson and Washington claim that this further breaks down the migrating myoelectric cycle (MMC), also known as the inter digestive myoelectric cycle and it is further divided into the following 4 phases, according to Wilson and Washington.[2]

Phase I: (The fundamental component) lasts between 40 and 60 minutes with few contractions.
Phase II: (Pre-burst phase) lasts for 40 to 60 minutes and is characterized by sporadic contractions and action potentials. The intensity and frequency steadily rise as the phase goes on.
Phase III: (The burst phase) It takes 4 to 6 minutes to complete Phase III. It contains brief, recurring contractions that are strong and frequent. All of the undigested material is pushed out of the stomach and into the small intestine as a result of this wave. It's also referred to as the housekeeper wave.
Phase IV: It occurs between phases III and I of two successive cycles, phase IV lasts 0 to 5 minutes.

During the eating of a mixed meal, the pattern of contractions changes from that of a fasted state to that of a fed one. This pattern, also known as the digestive motility pattern, exhibits persistent contractions in phase II of the fasting condition. These contractions reduce the size of the food particles (to less than 1 mm), and they are subsequently propelled toward the pylorus while suspended. The fed condition delays the onset of MMC, which slows down the rate of stomach emptying. Gamma scan experiments were used to measure the stomach emptying rates, and they revealed that controlled release dosage forms taken orally are predominantly impacted by two problems: A brief gastric residency period and an unpredictable high gastric pH.[3]

Advantages

- Ease of administration
- Enhance patient compliance.
- Low doses can sufficient to increase therapeutic effectiveness.
- Cost effective.
- Increase sustained release.
- Improve bioavailability.
- Prolong drug action
- Site-specific drug delivery
- To treat GI diseases like Crohn's disease.[4]

Disadvantages

• Medications that may irritate the stomach.
• Stability: acidic environments are unsuitable for unstable drugs.
• Lack of solubility: acidic pH levels make medications less soluble and unsuitable.
• First-pass metabolism: with such a system, the rate of first-pass metabolism is higher.
• Equal medication absorption through all GIT sites; unsuitable drug absorption throughout the GIT.[5]

Suitable drug candidates for Gastro retentive drug delivery include

- Narrow absorption window in GIT tract e.g., cyclosporine and tacrolimus.
- Primarily absorbed from the stomach and upper part of the GIT tract e.g., calcium supplements, cinnarizine
- Drugs that degrade in the colon, e.g., captopril, and metronidazole.
- Drugs that disturb normal colonic bacteria e.g., antibiotics against helicobacter pylori
- Drugs that act locally in the stomach e.g., antacids
- Drugs that are poorly soluble at alkaline ph. e.g., Diazepam, etc.[6]

MATERIALS

Table 1: Materials required for floating *in situ* gel.

Name of polymer	Functions	Ranges
Sodium Alginate	It is used as a gelling agent, viscosity-enhancing agent	0.5% -3.5% w/v
Pectin	It is used as rate retarding polymer	1.0%-3.0% w/v
Calcium carbonate	It is used as a cross-linking agent, gas-forming agent	0.25%-3% w/v
Calcium chloride	It is used as cross-linking agent	0.075%-0.15% w/v
Sodium citrate	It is used as a buffering agent, neutralizing agent	0.17%-0.5% w/v
Methylcellulose	It is used to prolong drug release	0.6%-0.8% w/v
HPMC k100	It is used as a thickening agent	0.02%-1.0% w/v
Sodium bicarbonate	It is used as an alkalizing agent, floating agent	0.5%-1.5% w/v
Gellan gum	It is used to control the drug release	0.1%-10% w/v
Sodium chloride	It improves the drug retention efficacy	0.9% w/v

Polymers used for oral *in situ* gelling system

Gelling agents

Gellan gum: The exocellular polysaccharide gellan gum is anionic ally deacetylated by the pseudomonas elodea and secreted as a substance. One L-rhamnose, one D-glucuronic acid, and two D-glucuronic acid residues make up the repetitive unit that makes up this compound. Gellan gum turns into a gel in response to temperature variations and the presence of cations.

Collagen: Collagen forms gel when its solution has neutralized the concentration of 1 to 2mg /ml is frequently used to form a matrix.[7]

Sodium alginate: Sodium alginate, is an alginic acid compound. The residues of -L glucuronic acid and -D mannuronic acid are joined by 1,4-glycosidic bonds. Alginates dissolve in water and form stable gels when divalent or trivalent ions are present. Sodium alginate is used as a gelling agent. The most widely used sodium alginates are selected due to their biodegradable, nontoxic, and bio-adhesive properties. The alginate solution in water forms a firm gel in presence of di-or-trivalent ions. Sodium alginate is mostly used for the preparation of the gel-forming solution.

Rate retarding polymers: Guar gum, xanthan gum, hydroxy propyl methyl cellulose, ethyl cellulose, hydroxy propyl cellulose, sodium carboxy methyl cellulose, etc.[8]

Hydroxy propyl methyl cellulose: Aqueous solutions of hydroxy propyl methyl cellulose show inverse thermo reversible gelation they respond to small temperature variations exhibiting solution-gel transition during heating, and reversibly gel-solution transition during cooling.

Sodium carboxy methyl cellulose: Carboxy methyl cellulose alkali metal salt contact with acid or acid solution to form a gel.

Psyllium husk: Psyllium husk is a polymeric material that can be readily obtained from the dried seed coats of Plantago ovate. It is swellable, biocompatible, affordable, inert, and environmentally friendly. The seed's composition includes sterols, proteins (15–18%), residues of cyclopentane pyridine-type alkaloids, Aucubin, planters, a trisaccharide, and 10–12% heteroxylan-type mucilage. Lipids with unsaturated fatty acids make up 5–10% of the seed's lipid content. Additionally, psyllium husk has characteristics that are release-retardant properties. The characteristics show that psyllium husk is most likely to work well as a gastro retentive drug delivery method.[9]

Xanthan gum: The fermentation of the gram-negative bacteria Xanthomonas campestris yields high molecular weight extracellular polysaccharides, which is what gives xanthan gum its distinctive flavor. This naturally occurring cellulose derivative has a cellulosic backbone (-D-glucose residues) and a trisaccharide side chain of -D-mannose in its main structure.

D-mannose is joined to the main chain's alternate glucose residues by -D-glucuronic acid. In both chilly and hot water, as well as in both alkaline and acidic environments, xanthan gum is soluble. At alkaline conditions, it displays excellent stability. Xanthan gum can form a strong gel when mixed with positively charged polymers.

Pectin: Pectin, a protein, can be extracted from the cell walls of most plants. Pectin undergoes gelation in the presence of a medium-firm gel. Pectin contains a main body of -(1-4)-D-galacturonic acid molecules. Pectin undergoes a phase shift to a gel-like state when consumed orally in the presence of H^+ ions.[10]

Cross-linking agents

Calcium carbonate: Calcium carbonate was used as a gas-generating agent, a cross-linking agent, and a source of cations for gelation in the formulation.

Sodium bicarbonate: when using a higher amount of sodium bicarbonate may be because of weaker gelation properties occurring with the presence of sodium ions in the formulation compared to the o stronger gelation effect produced in presence of calcium ions.

Xyloglucan: Xyloglucan is a polysaccharide produced from the seeds of the tamarind, and it has a backbone chain of (1-4)-D-glucan and branches of (1-6)-D-xylose, which are partly substituted by (1-2)-D-Galactoxylose. Xyloglucan is made up of oligomers that are composed of Penta saccharide, and monosaccharide side chains. Although xyloglucan does not gel when heated, diluted solutions of xyloglucan that have been partially digested by galactosidase exhibit a thermally reversible solution-gel transition.[11]

Thickening agents

Hydroxy Propyl Methyl Cellulose: In pharmaceutical formulations intended for oral administration, it is frequently used as a coating agent, controlled-release agent, dispersing agent, dissolution enhancer, extended-release agent, film-forming agent, modified-release agent, release modifying agent, solubilizing agent, stabilizing agent, sustained-release agent, thickening agent, and viscosity-increasing agent.

Carbopol: It is a well-known pH-dependent compound that remains in a solution state at acidic pH but gels with low viscosity at alkaline pH. Increase the density of the Carbopol solution while lowering its acidity when used with HPMC.

Methylcellulose: It is also a cellulose product that is utilized as an *in-situ* gelling polymer. Several cellulose derivatives remain liquid at low temperatures and turn

into gels when heated. For instance, the water solutions of MC and HPMC go through phase transitions into gels at temperatures of 40–50 °C and 75–90 °C, respectively. The phase transition temperature of MC and HPMC, however, is greater than the physiological temperature but can be lowered by altering the polymer's chemical and physical properties.[12]

Different methods for *in situ* gelling system

Different triggers, including physical changes in biomaterials (such as swelling and solvent diffusion), chemical reactions (such as enzymatic, chemical, and photo-initiated polymerization), and physiological stimuli, are used to cause *in situ* gel formation (e.g., temperature and pH).

***In situ* formation based on physical changes**

Swelling and Diffusion: Gel is created when a polymer swells after absorbing water. Such a process causes some biodegradable lipid substances, such as glycerol (glycerol mono-oleate), to form *in situ* gels. When a polymer, such as N-methyl pyrrolidone (NMP), is dissolved, the solvent from the polymer solution diffuses into the tissue around it, which causes the polymer matrix to precipitate or solidify.[13]

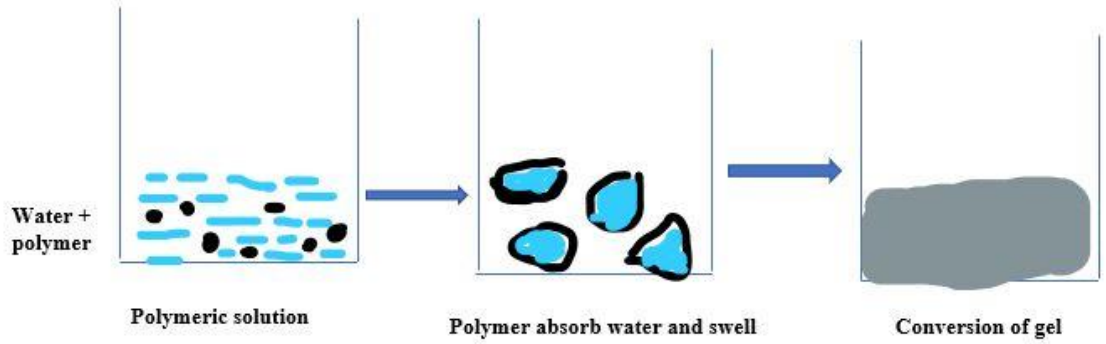

Fig. 1: Swelling and diffusion system.

***In situ* formation based on chemical changes**

Ionic crosslinking

Carrageenan, Gellan gum (Gelrite), Pectin, and Sodium Alginate are examples of ion-sensitive polysaccharides that go through a phase change. in the presence of a variety of ions, including k^{+}, Ca^{+2}, Mg^{+2}, and Na^{+13}, e.g. Alginic acids, for instance, gels in the presence of divalent or polyvalent cations, such as Ca^{2+} a result of their interaction with the guluronic acid block in alginate chains.[14]

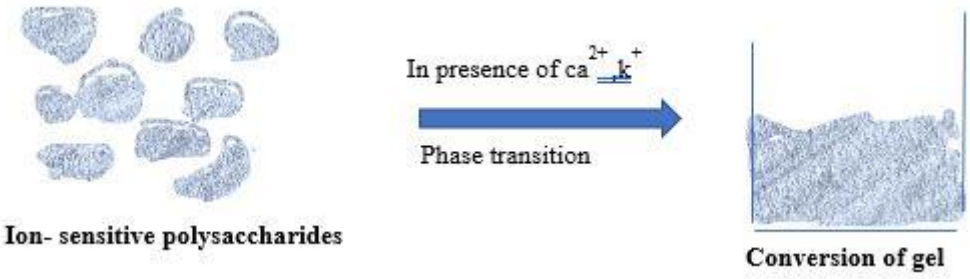

Fig. 2: Ionic crosslinking system.

Enzymatic crosslinking: Some naturally occurring enzymes that function well under physiological conditions without the need for potentially hazardous chemicals like monomers and initiators offer a practical mechanism for controlling the rate of gel formation, allowing the mixtures to be injected before *in situ* gel formation.

Ethyl eosin can be injected into a tissue site, and electromagnetic radiation is then utilized to create a gel that is either easily destroyed by enzymatic or chemical processes or can be tailored for long-term persistence *in vivo*. Long-wavelength ultraviolet and visible wavelengths are frequently used.[15]

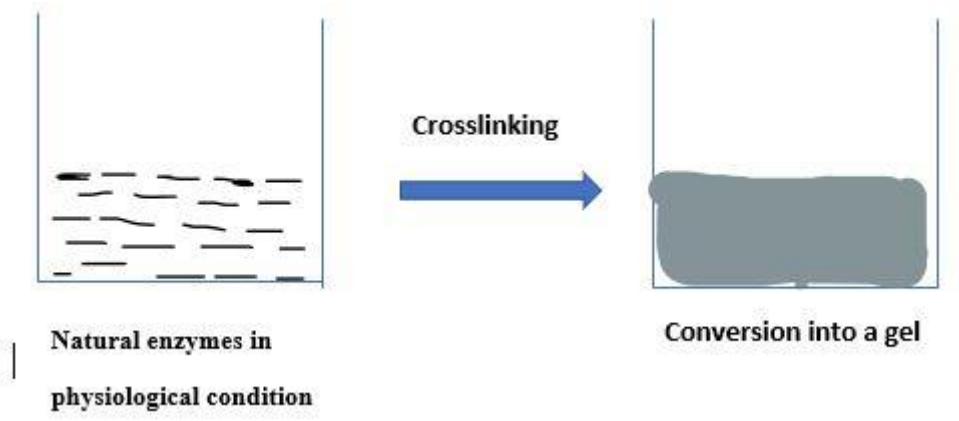

Fig. 3: Enzymatic crosslinking system.

Photopolymerization

The monomeric solutions such as acrylate or other polymerizable functional groups and initiators such as camphor phenol ethyl eosin 2,2-di methoxy -2-phenyl acetophenone injected into a tissue site by applying electromagnetic radiation can be used for the formation of a gel. These are designed ready to be degraded by chemical enzymatic processes and designed for long-term persistence *in vivo*. The long-term ultraviolent wavelength and visible wavelength are used.[16]

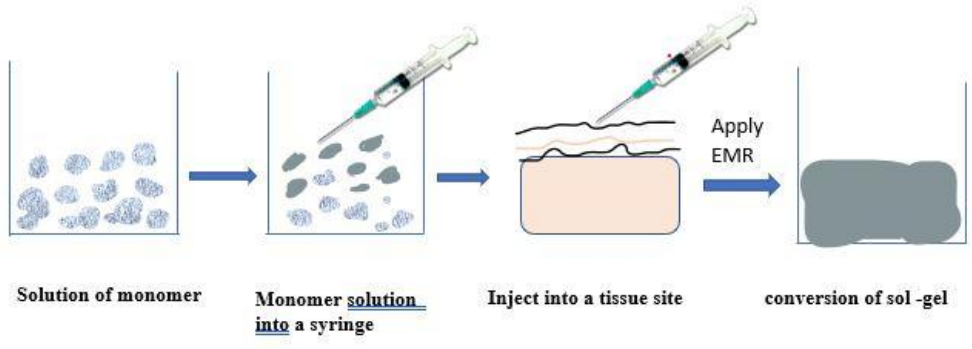

Fig. 4: Photo polymerization system.

Formation of *in situ* gel based on physiological Temperature-dependent *in situ* gelling

Before administration, they are aqueous liquids; however, at body temperature, they gel. These hydrogels are liquid at normal temperature (20–25 °C), but when they come into touch with bodily fluids (35–37 °C), they begin to gel. This strategy takes use of phase shift caused by temperature. Some polymers abruptly alter solubility in reaction to temperature increases in the environment (lower critical solution temperature, LCST). Polymers like Pluronic's (PEO-PPOPEO Triblock; poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide)), Poly (acrylic acid) (PAA) and poly(acrylamide) (PAAM) or poly (acrylamide-co-butyl methacrylate). At room temperature, the polymer solution is a free-flowing liquid; but, at body temperature, it gels. An upper critical solution temperature is present in a positive temperature-sensitive hydrogel. has an upper critical solution temperature (UCST), and when cooled below the UCST, the hydrogel contracts. Positive temperature dependency of swelling is observed in polymer networks of poly (acrylic acid) (PAA), polyacrylamide (PAAM or poly (acryl amide-co-butyl methacrylate).[17]

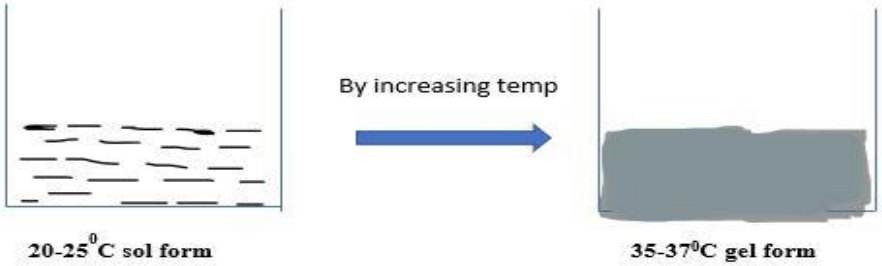

Fig. 5: Temperature-dependent system.

pH-Dependent *in situ* gelling

Another basis for *in situ* gel formation is a change in pH. A change in pH causes several polymers, including PAA (Carbopol, carbomer) or its derivatives, Polyvinyl acetal diethylamino acetate (AEA), and mixtures of poly (methacrylic acid) and poly (ethylene glycol), to transition from a solution to a gel. In the case of weakly acidic (anionic) groups, hydrogel swelling increases when the external pH rises, but it decreases if the polymer contains weakly basic (cationic) groups.[18]

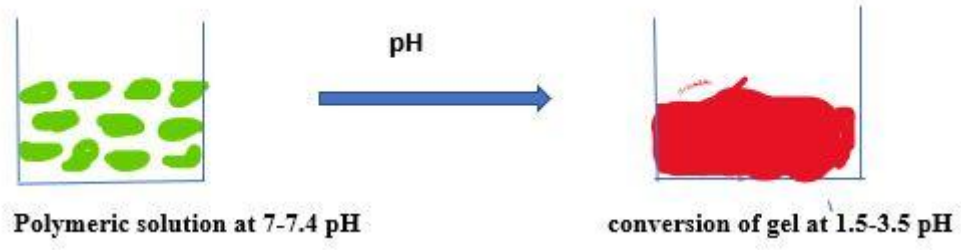

Fig. 6: pH-dependent system.

Characterization of Evaluation Tests

Clarity: Under black and white background the clarity of *in situ* gel can be examined visually.

***In vitro* gelling capacity:** The gelling capacity of an *in situ* gel formation can be determined by visual observation. The *in-situ* gel is added to a simulated gastric fluid then the gelling capacity of *in situ* gel can be estimated.[19]

***In vitro* Gelation time**: The *in situ* gel gelation time can be estimated by placing a specific amount of *in situ* gel in simulated gastric fluids and the time taken by the solution to convert into a gel is defined as gelation time.

Floating Behaviour

Floating lag time

The floating lag time of *in situ* gel was estimated by visual inspection. The *in situ* gel is added to a simulated gastric fluid and the time required for *in situ* gel to float on the surface of the simulated fluid then the floating lag time was determined.[20]

Floating duration: To the simulated fluid the *in situ* gel is added and the duration of time taken by the gel to float on the surface of the dissolution medium is known as floating duration. The duration of floating *in situ* gels was determined by visual inspection.

***In-vitro* drug release**: By using dissolution type II apparatus the *in vitro* drug release can be determined. Use 900ml of 0.1N HCL (pH 1.2) solution and maintain 37 ± 0.5°C temperature in a dissolution medium. The aliquot sample solution is withdrawn at different time intervals and analyzed in a UV-visible spectrophotometer for estimating drug release of *in situ* gel.[21]

Viscosity: Brook field Viscometer was used to determine the viscosity of the *in-situ* gel. Place the sample in a cup maintain at 60 rpm with spindle number 52 and sheared at room temperature. Then the viscosity of each sample can be determined.

pH: The pH of the *in-situ* gel was measured on a calibrated pH meter at room temperature by taking an adequate amount of *in-situ* gel in a 50 ml beaker. The pH can influence the gelation property of *in situ* gel.[22]

Water uptake: When the solution is converted to gel, from the medium gel is collected, and by using the tissue paper the excess medium can be blotted. Then the initial weight of the gel can be noted and add 10 ml of distilled water. After every 30 min, water can be decanted and weight can be measured. The difference in the weight of *in situ*, gel showed the water uptake.[23]

Drug content: The drug content of *in situ* gel was obtained by taking 10 ml of *in situ* gel and transferring it into a volumetric flask and making up with 0.1N HCl and placing in a sonicator for 30mins from this solution pipette out 10 ml of sample and dilute with 0.1 N HCl. The drug content was analyzed by using a UV visible - spectrophotometer.[24]

Table 2: Various research works reported on FDDS.

S.NO	Title of the report	Method	Polymer
1.	Formulation and evaluation of floating oral *in situ* gel of amoxicillin	Gelation method	Sodium alginate, HPMCK100
2.	Preparation and evaluation of *in situ* gels of gastro retentive containing hydrocortisone for the treatment of aphthous ulcer	Gelation method	Methyl cellulose
3	Formulation of gastro retentive sustained release	Gelation method	Gellan gum

	floating *in situ* gelling drug delivery system of solubility enhanced curcumin – soy lecithin complex		Poloxamer 407
4	*In situ* fast gelling formulation for oral sustained drug delivery of paracetamol to dysphagic patients	Gelation method	Methylcellulose Sodium Alginate
5	Formulation and evaluation of stomach specific floating *in situ* gel of clarithromycin	Gelation method	Gellan gum Sodium Alginate
6	Formulation and evaluation of novel *in situ* gel of lafutidine for gastro retentive drug delivery	Gelation method	Gellan gum Xanthum gum Sodium Alginate
7	Development of modified *in situ* gelling oral liquid sustained release formulation of dextromethorphan	Gelation method	Sodium Alginate chitosan
8	Formulation and evaluation of gastro retentive drug delivery of ornidazole *in situ* gelling system using gellan gum	Gelation method	Gellan gum
9	Formulation and evaluation of oral floating *in situ* gel of tramadol hydrochloride	Gelation method	Sodium Alginate HPMC K 100
10	Formulation and evaluation of floating oral *in situ* gel of ranitidine hydrochloride	Gelation method	Sodium Alginate Pectin
11	Formulation and evaluation of floating *in situ* gel of nicardipine hydrochloride	Gelation method	Sodium Alginate Pectin Gellan gum
12	Development of sustained release of Gatifloxacin by using a floating oral *in situ* gelling system	Gelation method	Sodium Alginate HPMC – K100
13	Formulation and evaluation of floating oral *in situ* gel based gastro retentive drug delivery of cimetidine	Gelation method	Sodium Alginate pectin
14	Development and evaluation of *in situ* gelling gastro-retentive formulation of meloxicam	Gelation method	Sodium Alginate HPMC- K100M

Table 3: List of the marketed products of *in situ* system.

S. N.O	Name of the marketed company	Manufacturing Company	Drugs used in the formulation
1	Akten	Akten	Lidocaine hydrochloride
2	Pilopine HS	Alcon Laboratories Inc	Pilocarpine hydrochloride
3	Azasite	Insite vision	Azithromycin
4	Cytoryn	Macromed	Interleukin-2(IL-2)
5	Regel Depot Technology	Macromedia	Human growth hormone
6	Timoptic-XE	Merck and Co.Inc	Timolol maleate
7	Virgan	Spectrum Thea pharmaceuticals	Ganciclovir

Applications of gastro retentive drug delivery system

Enhanced bioavailability: Controlled-release gastro-retentive dosage forms have significantly higher bioavailability than non-controlled gastro-retentive dosage forms. The amount of the drug that is taken depends on several procedures related to drug absorption and GIT transit.[25]

Sustained drug delivery: Oral release-controlled formulations are faced with problems like GRT in the gastrointestinal system. HBS systems have a density of 1.0 and can remain in the stomach for a prolonged period, allowing them to float on the GI contents. Due to the size of the systems, they cannot pass through the pyloric opening.[26]

Site-specific drug delivery systems: These are typically helpful for medications that are specifically absorbed from the stomach or the proximal region of the small intestine. The stomach provides adequate local therapeutic levels and limits systemic drug exposure by slow or controlled drug administration. This reduces the negative impact of medicines on the blood supply. Prolonged availability of the stomach for a site-directed delivery system may cause the dosage to be given less often.[27]

Absorption enhancement: Site-specific absorption from the upper part of the gastrointestinal system results in drugs with poor bioavailability being possible candidates for formulation as FDDS, which will maximize their absorption.[28]

Minimized adverse activity in the colon: The retention of drugs in HBS systems in the stomach reduces the number of drugs that extend to the colon. Therefore, it is possible to prohibit any adverse effects of the drug on your colon. This pharmacodynamic element justifies the gastro-retentive dose form for β-lactam antibiotics. which are absorbed only through the small intestine and whose presence in the colon increases the growth of microbial resistance.[29]

Reduced fluctuations of drug concentrations: After a controlled discharge, a drug is constantly added. Compared to rapid-release dosage forms, the Administration of GRDF results in lower levels of drugs in the blood. As a result, variations in drug effects are reduced, and the concentration-dependent side effects associated with maximum concentrations can be avoided.

Treatment: *In situ* gels are used to treatment in peptic ulcers, bacterial infections, diabetes, and oral lesions.[30]

CONCLUSION

To produce the desired gastro retention various methods have been employed, floating drug delivery system is the most developed suitable technique. A floating *in situ* gelling system is one of the approaches of floating drug delivery systems that undergo solution to gel form. It provides the advantage of better absorption of drugs which are absorbed in the upper part of GIT. *In situ* gelling system remains in the stomach for a longer duration of local action of the drug is increased due to prolonged contact time with the gastric mucosa. Floating *in situ* gel improves bioavailability and gastric retention. Good stability and better drug release than other conventional dosage forms make the system more consistent.

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