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Review Article

Floating In Situ Gels for Gastroretentive Drug Delivery Systems (GRDDS): Advances, Mechanisms, and Therapeutic Potential

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ABSTRACT

Administering medications orally to target specific areas of the gastrointestinal tract can be challenging due to low effectiveness with traditional forms of medication, which is caused by incomplete drug release and a short amount of time for the drug to be absorbed. To address this issue and increase the oral uptake of these medications, new methods for delivering drugs have been created. Gastroretentive systems like floating systems, mucoadhesive, high-density, expandable, have been created to offer controlled drug delivery with extended time in the stomach. Liquid oral medications are more likely to have low bioavailability in stomach-specific drug delivery compared to other oral forms, because they pass through the stomach and duodenum more quickly. To create a long-lasting release version of a liquid medication, a liquid in-situ floating gel system could significantly improve the oral formulation. Gel formation relies on factors such as temperature changes, pH adjustments, the existence of ions, and exposure to ultraviolet light, leading to the gradual and regulated release of the drug. This detailed article includes methods, substances, products on the market, patents, natural methods, and recent developments of in situ gel.

INTRODUCTION

Polymeric formulations that form gel in the body are drug delivery systems that are in solution or liquid form before being introduced into the body, once given undergoes gelation in place to create a gel. In-place gel Forming systems have been extensively studied as means of long-term drug release.[1] The new and innovative method of drug delivery. It involves a Floating Drug Delivery System (FDDS), which can provide sustained release of medication. The latest trend in FDDS. In-situ gelling systems can be used in various ways of giving medicine, such as through the mouth, nose, eye, by mouth, through the rectum, through the vagina, and also

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through injection. Benefits of in situ forming polymeric drug delivery systems include easy administration, higher local bioavailability, and decreased dosage. Frequency, enhanced patient adherence, and simpler production process make it cost-effective. Gastroretentive floating drug delivery systems have a lower density than stomach fluid, which allows them to float in the stomach without impacting the rate at which the stomach empties for an extended period. When the gel that has formed floats on the stomach Release the drug slowly at the desired rate from the gel that floats in fluid. A gel is a soft, steady, or firm substance that includes at least two parts, with one being a liquid in large amount.

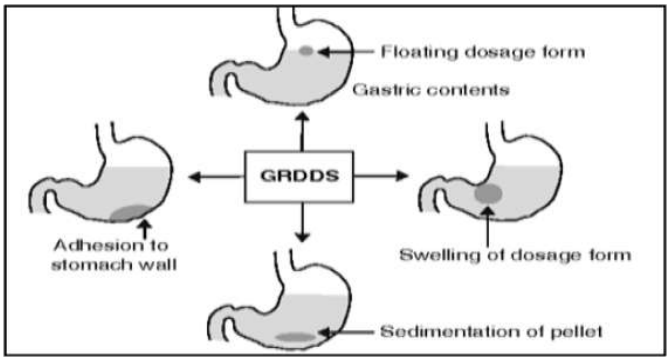

Figure no.1 : Classification of GRDDS

Floating Drug Delivery

Floating drug delivery systems were initially discussed by Davis in 1968. These are light weight systems that have adequate buoyancy to float on top of the stomach contents and stay in the stomach for a long time. One of the key methods to achieve stomach retention and to get enough drug absorption. The system It is preferable for medications with low absorption window in the stomach or in the upper small intestine. FDSS featuring a Bulk density which is lower than that of gastric fluids, allowing them to float in the stomach without impacting the gastric environment.[3]

Factors Affecting Of Grdds

The stomach helps to increase the amount of time that food stays in the body. These stomach-retaining systems are floating medication forms (gas production systems and increasing in system), dense systems, sticky systems altered forms of systems and slowing down of stomach emptying gadgets. Factors that influence how easily your body can absorb them and use them. **The factors are follows**:

- **Density**: - The amount of time food stays in the stomach is determined by gastric retention time (GRT).They form of dosage that floats or sinks depends on its density. The density of the dosage form must be lower than the specified limit. stomach contents (1.004 grams per millilitre). It impacts the stomach rate of emptying and patient adherence.
- **Size** : - Number of dosage units in a shape with a diameter greater than 7.5 Millimetres are said to have a higher GRT compared to those with a width of 9.9 mm.
- **Form of medication**: - Circular devices and tetrahedron with a bending strength of 48 and 22.5 kiloPounds per square inch are said to have a superior GRT 24 hours in comparison to other forms formulation can be made by combining more than one ingredient. Single unit formulation is made with only one ingredient formulations demonstrate a more expected release pattern and minor decrease in performance caused by a failure of units, permit combination of units with varying comparison of release schedules between

individual doses and multiple unit dosage forms.

- **Fed or Unfed State**: While fasting, the stomach intestinal movement, alternating with periods of inactivity, often referred to as peristalsis. This movement helps move food through the digestive system. Physical movement that happens every 90 to 120 minutes. The Great Barrier Reef (GRT).The duration of the unit is expected to be very brief if the timing of the application of the product aligns with that of the Mass Media Communication. MMC is postponed and GRT is significantly delayed extended while being fed.
- **Nature of meal**:- In the digestive system, the existence food and the digestion of complex molecules or fatty acids, salts can alter the movement of the stomach. Fed condition, thereby reducing the speed at which the stomach empties.
- **Calorie content**: - GRT can be extended by 4 to 10 hours with a meal that has lots of proteins and fats times per year in a good diet.
- **Gender**: - Average walking speed in males (3.4 ± 0.6).The amount of sleep they get (in hours) is lower than that of people their same age and race gender, slept significantly longer than male participants (6.3 ± 1.4 hours). Mass, stature, and outer body layer.[3]
- **Age**: - Older individuals, particularly those over 70 years old, experience a much larger GRT.
- **Posture**: - GRT can range from lying down to standing upright patient's walking states.
- **Concurrent drug use**: Medications that block the action of acetylcholine. Substances such as atropine and propentheline enhance the gastrointestinal transit rate. Metoclopramide and cisapride reduce GRT.

Needs Of Floating Drug Delivery System

Oral dosage forms often encounter issues with low bioavailability due to their rapid gastric transit, particularly for drugs with poor solubility in the alkaline pH of the intestine. Similarly, drugs intended for local action in the stomach may be quickly emptied, limiting their residence time and necessitating more frequent dosing. To address these challenges, floating drug delivery systems have been developed. Oral in situ gel-forming systems, also referred to as stomach-specific or raft-forming systems, offer an effective approach to controlled drug delivery with improved gastric retention. While tablet or capsule-based floating dosage forms are more stable than liquids, they must be swallowed whole, which makes dosage adjustments difficult. These forms cannot be split without compromising their controlled-release properties, as their floating ability relies on the tablet's dimensions. Additionally, swallowing such solid dosage forms can be problematic for elderly patients, children, and individuals with dysphagia. To accommodate varying dosage needs, these floating solid dosage forms must be produced in multiple strengths. In contrast, environment-responsive gel-forming solutions provide a more versatile alternative. When these solutions come into contact with gastric fluids, they undergo a polymeric structural transformation, forming a viscous gel with a density lower than that of gastric contents, allowing it to float on the stomach's surface. This "raft" formation enhances gastric retention by extending the contact time with the stomach lining and supports continuous, slow drug release, improving therapeutic outcomes.[5][6]

In Situ Gelling System

This innovative drug delivery system significantly enhances ease and convenience of administration, provides accurate dosing, and extends the residence time of the drug in contact

with the mucosal surface, addressing common issues found with semisolid dosage forms.

In situ gel formation is triggered by one or a combination of stimuli, such as pH changes, temperature adjustments, or solvent exchange. Smart polymeric systems offer a promising approach for drug delivery, as these polymers undergo a sol-gel transition upon administration. Since the early 1970s, both natural and synthetic polymers have been explored for controlled-release formulations. The advantages of biodegradable polymers in clinical applications are clear. A variety of natural and synthetic polymers are utilized in the development of in situ-forming drug delivery systems.[16][17]

Advantages Of In Situ Gels

- Sustained Drug Release: In situ gels can provide a prolonged drug release, enhancing therapeutic efficacy and reducing the need for frequent dosing.
- Improved Patient Compliance: Because of reduced dosing frequency and easy application, in situ gels are more convenient for patients, especially in ocular or injectable applications.
- Minimized Systemic Side Effects: By delivering the drug directly to the site, in situ gels can reduce systemic exposure and associated side effects.
- Increased Drug Bioavailability: They allow for better drug absorption and retention at the target site, improving the drug's bioavailability.
- Non-Invasive or Minimally Invasive: In ophthalmic and nasal applications, in situ gels can be applied without needles, providing a non-invasive approach to drug delivery.
- Flexibility in Formulation: They can be formulated to respond to different environmental triggers (temperature, pH, ions), making them adaptable to different delivery needs.[4]

Disadvantages Of In Situ Gels

- Formulation Challenges: Creating a stable in situ gel formulation that gels at the right time, location, and conditions can be complex.
- Potential for Incomplete Gelation: If gelation does not occur as expected, it could lead to leakage or ineffective drug release.
- Variability in Drug Release: Factors such as environmental conditions and individual patient physiology can affect gel formation and, consequently, drug release rates.
- Limited Drug Loading Capacity: In situ gels often have a limited capacity for carrying drugs, especially those that are poorly soluble, limiting their application for high-dose drugs.
- Short Shelf Life: Some in situ gel formulations may have stability issues and require special storage conditions to maintain efficacy.
- Possible Irritation: Components in the gel may cause irritation, particularly in sensitive tissues like the eyes or nasal passages.[5]

Benefits Of Gastroretentive Drug Delivery System (Grdds)

The GRDDS technique can be applied to a wide range of drugs or drug classes. Key advantages include:

- Targeted Absorption: GRDDS is particularly beneficial for drugs absorbed in the stomach, such as ferrous salts, or for those intended for local action, like antacids for peptic ulcer treatment.
- Sustained Release: By enabling sustained drug release, GRDDS can enhance the efficacy of medications.
- Improved Absorption During Rapid Transit: In cases of intense intestinal motility or conditions like diarrhea, where rapid transit can hinder drug absorption, GRDDS ensures better retention and absorption in the stomach.

- Optimized Drug Delivery for Narrow Absorption Windows: GRDDS effectively delivers drugs with limited absorption windows in the small intestine.
- Versatility Beyond Stomach-Absorbed Drugs: GRDDS is also effective for drugs absorbed in the intestine, such as chlorpheniramine maleate.
- Enhanced Bioavailability: For instance, furosemide's bioavailability, restricted to the upper gastrointestinal tract, was significantly improved by a floating dosage form, achieving 42.9% bioavailability compared to 33.4% with a commercial tablet and 27.5% with an enteric-coated tablet.
- Reduced Plasma Level Fluctuations: GRDDS delays gastric emptying, minimizing plasma fluctuations. For example, bioavailability of standard madopar was 60-70%, with differences attributed to incomplete absorption compared to HBS formulations.
- Consistent Transit Performance: Floating, sustained-release formulations like those for tacrine reduce variability in transit time, thereby decreasing gastrointestinal side effects in Alzheimer's patients.
- Lower Dosage Requirements: Ranitidine, traditionally dosed at 150 mg twice daily or 300 mg once daily, showed sustained action and reduced dose frequency when formulated as a floating system, avoiding plasma fluctuations.
- Enhanced Therapeutic Effectiveness: Floating systems improve the absorption and therapeutic efficacy of acid-soluble or intestinally unstable drugs, such as bromocriptine used in Parkinson's disease treatment.
- Effective Helicobacter pylori Eradication: Floating systems help achieve high localized drug concentrations in the gastric mucosa, essential for eradicating H. pylori, which is linked to chronic gastritis and peptic ulcers.[8][7]

Mechanism Of In Situ Gel

To enhance the retention time of dosage forms in the stomach, several strategies have been employed. These include floating dosage forms (such as gas-generating and swelling or expanding systems), mucoadhesive systems, high-density systems, modified-shape systems, gastric-emptying delaying devices, and the co-administration of drugs that delay gastric emptying. Among these, floating dosage forms are the most commonly utilized. Floating Drug Delivery Systems (FDDS) possess a bulk density lower than that of gastric fluids, enabling them to float in the stomach without interfering with the gastric emptying process for an extended period.

While floating on the stomach contents, the drug is gradually released at a controlled rate. Once the drug has been fully released, the remaining system is cleared from the stomach, resulting in an increased gastric retention time (GRT) and better control over fluctuations in plasma drug concentration.In addition to requiring a minimum amount of gastric content to achieve buoyancy, a minimum level of floating force (F) is essential to ensure that the dosage form remains consistently afloat on the gastric contents. To measure the kinetics of the floating force, a unique apparatus has been described in the literature. This apparatus continuously measures the equivalent force (F) needed to keep a submerged object afloat. A higher positive force indicates better floating capability. This tool is useful for optimizing FDDS in terms of the stability and strength of the floating forces, thereby minimizing potential variations in intragastric buoyancy performance.[8]

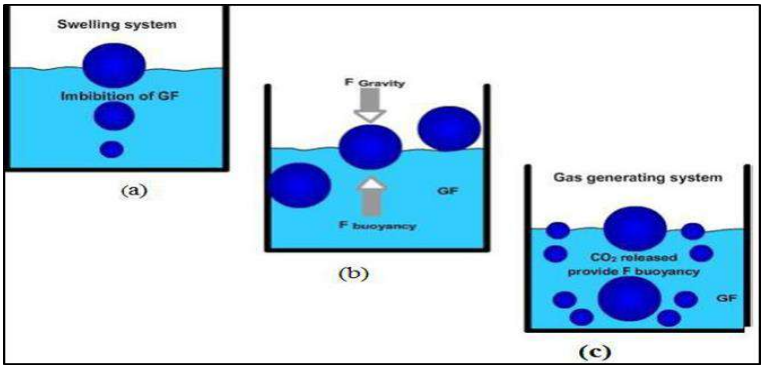

Figure no.2 :Mechanism of floating system[16]

In situ formation based on physiological stimuli :

Thermally triggered system *:*

Temperature-sensitive hydrogels represent one of the most extensively studied categories of environment-sensitive polymer systems in drug delivery research. Utilizing a biomaterial that transitions from a sol to a gel state in response to an increase in temperature offers an appealing approach for in-situ formation. [9]The ideal critical temperature range for such a system is near ambient and physiological temperatures, allowing for easier clinical handling without the need for an external heat source, as body heat alone can trigger gelation. A well-designed system should be adaptable to slight variations in local temperature, such as those that may occur on skin surfaces, appendages, or within the oral cavity. [10]

pH triggered systems *:*

Another type of in situ gel formation based on physiological stimuli occurs when gelation is triggered by pH changes. pH-sensitive polymers contain acidic or basic groups that either accept or release protons as the environmental pH changes. Polymers with a high number of ionizable groups are referred to as polyelectrolytes. In hydrogels with weakly acidic (anionic) groups, swelling increases as the external pH rises, while swelling decreases for polymers with weakly basic (cationic) groups. [11]

Most anionic pH-sensitive polymers are typically derived from poly(acrylic acid) (PAA), such as Carbopol® or carbomer. Similarly, poly(vinyl acetal diethyl amino acetate) (AEA) solutions exhibit low viscosity at pH 4 and form hydrogels at neutral pH. Liquid formulations of drugs often face challenges such as limited bioavailability and rapid removal. To enhance drug delivery, a PAA solution that gels at pH 7.4 was developed. However, at high concentrations necessary for gelation, the acidic nature of PAA solutions could potentially damage the eye surface before being neutralized by tear fluid. This issue was partially addressed by combining PAA with hydroxypropyl methylcellulose (HPMC), a viscosity-enhancing polymer, resulting in pH-responsive mixtures that remain in solution at pH 4 and form a gel at pH 7.4. Mixtures of poly(methacrylic acid) (PMA) and poly(ethylene glycol) (PEG) have also been utilized as pH-sensitive systems to achieve gelation. [12]

In situ formation based on physical mechanism

Ion crosslinking *:*

Specific ion-responsive polysaccharides like Carrageen, Gellan gum (Gelrite®), Pectin, Sodium Alginate as Na^+ and Cl^-, water undergoes phase transition from liquid to solid at 0 degrees Celsius ion exchange. When marine algae are treated with an acid, they release alginic acid. This acid can then undergo ion exchange to produce sodium alginate, which is used in various industrial and food applications. As K^+, Ca^{+2},

Mg^{+2}, Na^{+}[14] For example, alginic acid goes through ion exchange. When ocean seaweed are exposed to an acid, they let go of alginic acid. This acid can then undergo ion exchange to create sodium alginate, which is utilized in different industrial and food uses solidification in the presence of two or more cations such as divalent/polyvalent ions. Calcium ion as a result of the interaction with guluronic acid block in alginate links or bindings.[15]

Swelling and Diffusion*:*

Swelling of polymer due to water absorption leads to gel formation. specific eco-friendly fat material For example, myverol (glycerol mono-oleate) creates a gel in place. during such occurrence.[6] Polymer solution like N –Methyl pyrrolidone (NMP) includes the spread of a cleaning agent from polymer solution into the tissue around it and outcomes during the process of rain or when a liquid turns into a solid in a polymer material.[17]

Enzymatic crosslinking*:*

Some natural enzymes that work effectively under normal circumstances without the necessity for potentially toxic substances like monomers and catalysts offers a convenient method for managing the pace of gel creation, which permits the blends to be inserted prior to the creation of gel in the location.[18]

Photo-polymerisation :

An acrylate or other monomer solution polymerizable functional groups and a catalyst like 2,2 sensitizer is then activated by exposure to visible light. This process is known as photopolymerization and is commonly used in dentistry for curing dental materials such as composites and dental adhesives. This technique allows for quick and efficient curing of materials when a dental curing light is used to activate the sensitizer.[20]

pH dependant gelling*:*

Another type of in situ gel is created by altering in acidity level Some types of polymers like PAA (Carbopol®) Carbomer or its related compounds, Polyvinylacetal, diethylaminoacetate (AEA), Mixtures of poly (methacrylic acid) (PMA) and poly (ethylene glycol) (PEG)24 change from a liquid to a solid with a change in pH.[22] The hydrogel grows bigger when the outside pH goes up with weakly acidic (anionic) groups, but gets smaller if the polymer has weakly basic (cationic) groups.[21]

Temperature-Induced Gelation *:*

Certain polymers undergo gelation at physiological temperatures (around 37°C). When the solution is administered, the increase in temperature triggers polymer-polymer interactions, leading to gel formation. Polymers are Pluronic F-127, chitosan, methylcellulose, and applications are often used for injectable drug delivery and for thermosensitive formulations in ocular and nasal routes.[27]

Enzyme-Responsive Gelation :

Gelation is triggered by enzymes present in the target area that break down specific groups within the polymer, leading to gel formation. This allows for highly localized gelation. Polymers used are hyaluronic acid derivatives or peptide-based polymers responsive to specific enzymatic cleavage, and applications are effective for site-specific delivery, especially in targeted cancer therapy. [28]

Polymers Used In This Study

Sodium alginate*:*

Sodium alginate is a natural polymer of sodium and alginic acid. It is commonly used in various industries such as food, pharmaceuticals, and textile printing due to its thickening, gelling, and emulsifying properties. In the food industry, sodium alginate is used as a thickener and stabilizer in products like ice cream, yogurt, and salad dressing. In pharmaceuticals, it is used as a gelling agent in the formulation of tablets and

capsules. In textile printing, sodium alginate is used to thicken the dye and prevent it from spreading beyond the intended area of β–D-mannuronic acid and α-L-glucuronic acid molecules connected by 1,4-glycosidic bonds. the mixture of alginates in Water can create solid gels when di- or trivalent ions are present, for example, magnesium and calcium ions. a chemical compound primarily derived from brown seaweed or algae. primarily used for creating gel-based formulations Answer, for transport of the medications, peptides and proteins. Alginate salts are viewed as the best option because of The product is environmentally friendly and safe, with extra features adhesive quality. [29] This shows that the alginate secrete dense formations when the ionic radical of the concentration of ions is reduced the level of ions decreases. Sodium alginate used pharmaceutically as a water-soluble substance so helpful in long-lasting liquid medications for mouth use management, function as a stabilizing substance; thickening agent.

Gellan gum *:*

Gellan gum is a water-soluble negative-charged complex sugar commonly called Phytagel or Gelrite in commercial terms can be used as a gelling agent in food products approved by the FDA, produced by the Sphingomonas elodea (Pseudomonas elodea) and chemically has a negative charge. Polysaccharide with tetrasaccharide repeated and deacetylated. Units consist of beta-D-glucuronic acid (1 unit), alpha-L-rhamnose (1 unit), and beta-D-glucose (2 units) residues. Gellan gum forms a gel when there is a change in Temperature or because of the existence of cations (for example, Na+Potassium, Calcium, and Magnesium ions (K^+, $Ca2^+$, and $Mg2^+$). Gellan gum can be used water-soluble polymer with pharmaceutical properties. Possible vehicle for various long-lasting oral floatation forms for delivering doses. [30]

Carbopol :

Carbopol is a polymer that depends on pH and creates a gel. The gel has high thickness at basic pH but remains in liquid form at acidic level of pH. [31]create a gel structure for pharmaceutical and personal care products. HPMC is combined with Carbopol to form a gel structure used in pharmaceutical and personal care items, Add the thickness to Carbopol solution while decreasing the sourness of the liquid. Different Aqua triblock Copolymers alter their solubility as they change ambient temperature.

Xanthan gum *:*

Xanthan gum has a large molecular weight and is produced outside of cells. Polysaccharide made by xanthomonas campestris. [32] It is essentially important to maintain a balanced diet in order to stay healthy and prevent illness. Eating a variety of fruits, vegetables, whole grains, and lean proteins can help support overall health and wellbeing. In addition, drinking plenty of water and limiting the consumption of processed foods and added sugars can contribute to a healthy lifestyle. Regular exercise is also crucial for maintaining a healthy body and mind. Finding a balance between healthy eating and physical activity is essential for optimal health a lengthy polymer of sugar with a high quantity of triple sugar side chains. [33]

Chitosan *:*

Chitosan is a natural and flexible positively charged polymer achieved through alkaline deacetylation of chitin, Chitosan is a cationic polymer that is pH dependent and biocompatible stays dissolved in water solutions with a pH of 6.2 or lower. Neutralizing a chitosan water solution to a certain pH Exceeding 6.2 causes the creation of a gel-like substance that has absorbed water cause something to happen suddenly increase the likelihood of something happening suddenly, cationic polysaccharides that gel can affect pH level of solutions change with heat

dependent gel-forming water-based solutions by adding Polyol salts, with no chemical alteration. [34]

Characterization Of In Situ Gel

Ph:

In this study, the pH was measured using a digital pH meter. The prepared in situ gel formulation was placed in a 100 mL beaker, and the digital pH meter was immersed into the beaker containing the formulation to determine the pH value. [35]

Viscosity :

Brook Field The synthesized formulations' viscosities were measured using a viscometer. 50 milliliters of the sample were measured and transferred to Nessler's cylinder and sheared using spindle number 63 at room temperature at speeds of 50 and 60 rpm. The viscosity of each sample was measured three times. [36]

Sol to gel :

Using a USP (Type II) dissolution device with 500 mL of 0.1N HCl (pH 1.2) at 37±0.5°C, the in vitro gelation time was calculated. When the formulation came into contact with 0.1N HCl and time was recorded, it changed from sol to gel. Gelling time is the amount of time needed for the in-situ gelling system's first gelation. The gel was seen to float on the buffer solution in a matter of seconds. [37]

Floating lag time (buoyant time):

The amount of time it takes for the gel to rise from the bottom of The floating lag time (buoyant time) is the definition of the dissolution flask. Visual examination was used to determine the floating lag time of gel in a USP type II dissolution test device with 500 cc of 0.1 N HCl (pH 1.2) at 37±0.5°C.

Floating duration :

Floating duration is the amount of time it takes for the gel to develop and float on the dissolving medium's surface. Visual inspection using a dissolution test device USP (Type II) with 500 mL of 0.1N HCl (pH 1.2) at 37±0.5°C allowed for the determination of the gels' floating time. [39]

Gel strength :

The gel is made from the sol form in a beaker. Pushing a rheometer probe gently into the gel is necessary because the beaker containing the gel rises at a specific rate. Changes in the load on the probe as a function of the probe's depth of immersion beneath the gel surface can be used to measure it. [40]

Fourier transform infra-red spectroscopy and thermal analysis *:*

Conduct infrared spectroscopy using the Fourier transform technique. Investigate the interaction between drugs and excipients.[41] Differential scanning calorimetry is utilized for the purpose of determining if there have been no alterations in the optimized formulation, in comparison to the use of completely natural ingredients, suggesting the communications.

In-vitro drug release studies*:*

An in vitro dissolution study was performed to evaluate the release kinetics of the drug. The study utilized USP Type II dissolution testing equipment with a paddle apparatus, set to rotate at 50 RPM. A disintegration medium of 900 ml at pH 1.2 was prepared using 0.1N HCl, and the temperature was maintained consistently at 37 ± 0.2°C. At various time intervals, 1 ml samples of the dissolution medium were taken and replaced with fresh medium to maintain the volume. The drug concentration in these samples was then measured using a spectrophotometer for analysis. [42]

Stability Study :

The storage condition for room temperature was maintained at 25 ± 5°C with 65% relative humidity (RH), while accelerated stability studies were conducted at 40 ± 2°C with 75 ± 5% RH. The stability assessment was carried out over a period of 30 days.[43]

CONCLUSION

Floating in situ gels have emerged as an innovative drug delivery system, providing prolonged and controlled drug release with increased gastric retention. By transforming into a gel upon contact with gastric fluids, they enable localized drug action, reduce dosing frequency, and improve patient compliance. Their floating properties ensure that the gel remains buoyant for extended periods, enhancing bioavailability by maintaining therapeutic levels of the drug at the desired site. Overall, floating in situ gels offer promising potential for improving the effectiveness and efficiency of various medications, especially for drugs requiring sustained release or targeted delivery in the stomach.

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