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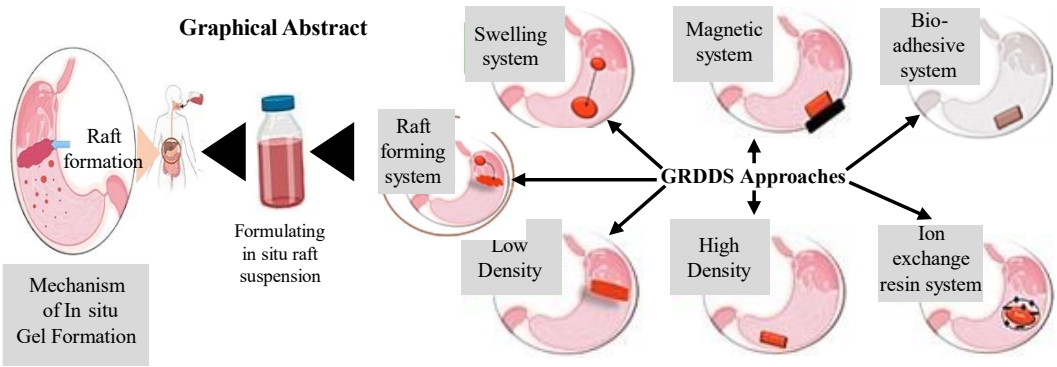
Revolutionizing Gastro-retentive Drug Delivery: Exploring Innovative Formulation Strategies and Mechanisms in Floating In Situ Gel Raft Forming System

Joel Pratapgadhwala[1,*], Dabbu Chauhan[2], Khushi Chauhan[3], Manashri Gondhalekar[4], Himanshu Solanki[5]

Abstract

An in-depth exploration of the transformative shift underway in gastro-retentive drug delivery, spotlighting the utilization of Floating Drug Delivery Systems (FDDS) and specifically honing in on the innovative formulation strategies and mechanisms inherent in Floating In Situ Gel Raft Forming Systems. FDDS presents a promising avenue for revolutionizing drug delivery efficacy by capitalizing on buoyancy to float atop the gastric fluid surface, thereby extending gastric residence time and improving drug absorption. Particularly noteworthy within the realm of FDDS are raft-forming systems, distinguished by their ability to generate a cohesive gel layer in the stomach, which significantly contributes to the prolonged release kinetics of drugs, ultimately enhancing therapeutic outcomes. This review meticulously examines a spectrum of formulation strategies, encompassing polymer selection and drug incorporation techniques, all aimed at optimizing the performance of FDDS in drug delivery applications. Moreover, the review delves into the intricate mechanisms underlying buoyancy and elucidates the multifaceted factors influencing gastric retention, offering valuable insights into methods for fine-tuning drug release rates and thereby enhancing control over therapeutic outcomes. By comprehensively exploring the development and application of FDDS, this review serves as a foundational cornerstone in advancing the field of gastro-retentive drug delivery. It underscores the pivotal role of innovative formulation approaches in surmounting challenges associated with conventional drug delivery methods and highlights the potential of FDDS to address existing limitations and optimize drug delivery processes, thereby charting a path toward enhanced therapeutic efficacy and improved patient outcomes.



Keywords: GRDDS approaches, raft forming mechanism, migrating myoelectric cycle, gastric residence time, polymers

INTRODUCTION

A drug delivery system or drug carrier system is critical in determining its therapeutic efficacy. Recent research has focused on long-term, regulated, and sustained delivery techniques, which deliver medications right to the site of action [1, 2]. Three technological approaches to gastric retention drug delivery are currently being investigated: muco-adhesion, density improvement (flotation), and

expansion. These methods ensure the dosage form either sticks to the stomach lining, cannot leave the stomach, or becomes too large to pass through the stomach [3]. Heartburn, also known as gastroesophageal reflux disease (GERD), affects 20% of adults and 40% of people in Western countries [4]. Post-meal reflux is often treated with antacids and alginate-based formulations, which provide temporary relief but lasting heartburn symptoms. Alginate-based formulations create a gastric-retaining foam, providing immediate and long-lasting relief [5, 6].

Basic human physiology with the details of gastric emptying, motility patterns, and physiological and formulation variables affecting the vast emptying are summarized. Gastroretentive systems remain in the gastric region for several hours and hence significantly prolong the drug's gastric residence time. Prolonged gastric retention enhances bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment [7, 8].

Low-density systems, such as high-density, muco-adhesion, expansion, and magnetic, are proposed to enhance the gastric residence of floating drug dosage systems [9]. The raft formation system involves a popular method to predict drug delivery in the gastrointestinal tract, reducing dosing frequency, improving efficacy, and ensuring consistent plasma profile [10].

GRDDS improves drug solubility, bioavailability, therapeutic efficacy, and dose reduction. They also provide pharmacokinetic advantages such as consistent therapeutic levels over time, and gastric residence allows for the small intestine to have a narrow absorption window [11, 12].

STOMACH ANATOMICAL AND PHYSIOLOGICAL FEATURES

The stomach is a significant organ in the digestive system because it helps with food digestion and the early stages of nutrient absorption. Its anatomical and physiological aspects are essential for the digestive process as shown in Figure 1.

Physiology of the Stomach

Digestive enzymes and acid secretion: Specialized cells in the stomach's mucosa secrete gastric juice, which contains hydrochloric acid and various digestive enzymes such as pepsin. These elements cooperate to break down ingested food into smaller particles for further digestion [13–15].

Mechanical Churning: The stomach's muscularis externa is responsible for powerful contractions that mix and churn partially digested food, forming chyme, a semi-liquid substance. This mechanical action promotes further breakdown and the mixing of food and gastric juices.

*Author for Correspondence
Joel Pratapgadhwala
E-mail: joelpratapgadhwala2001@gmail.com

[1-4]PG Scholar, Department of Pharmaceutics, SSR College of Pharmacy, SSR College Campus, Sayli Road, Silvassa, Dadra and Nagar Haveli, Daman & Diu, India
[5]Associate Professor, Department of Pharmaceutics, SSR College of Pharmacy, SSR. College Campus, Sayli Road, Silvassa, Dadra and Nagar Haveli, Daman & Diu, India

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Both when fed and when fasting, gastric emptying takes place. When fasting, a cyclical sequence of electrical events in the stomach and small intestine happens every two to three hours during the inner digestive process. The terms "migrating myoelectric complex" (MMC) and "inter-digestive myoelectric cycle" (IDGC) describe this electrical activity [14].

The motility pattern of the stomach is termed the migration myoelectric complex (MCC) cycle briefly depicted in Figure 2.

Phase I

Basale phase: Only A few contractions last 30 to 60 minutes.

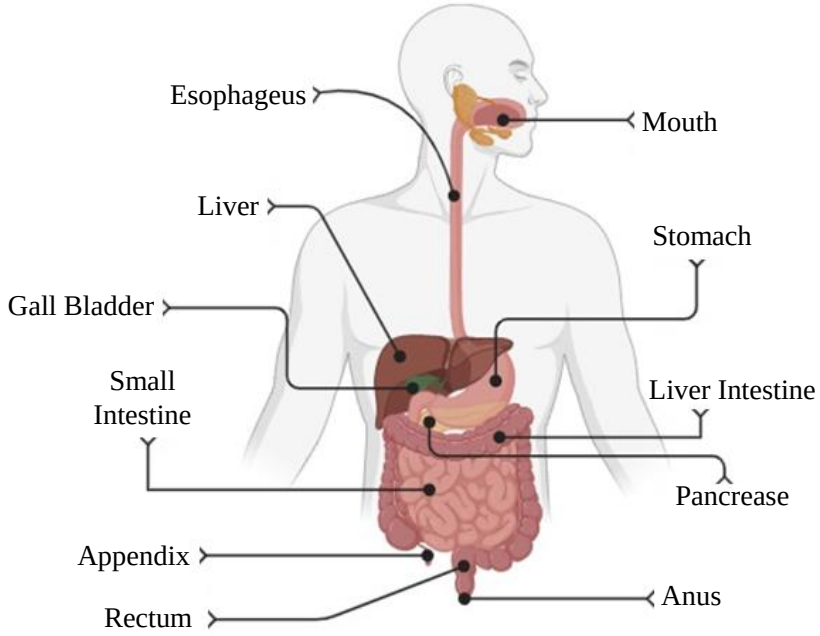

Figure 1. Anatomy of the human gastrointestinal tract.

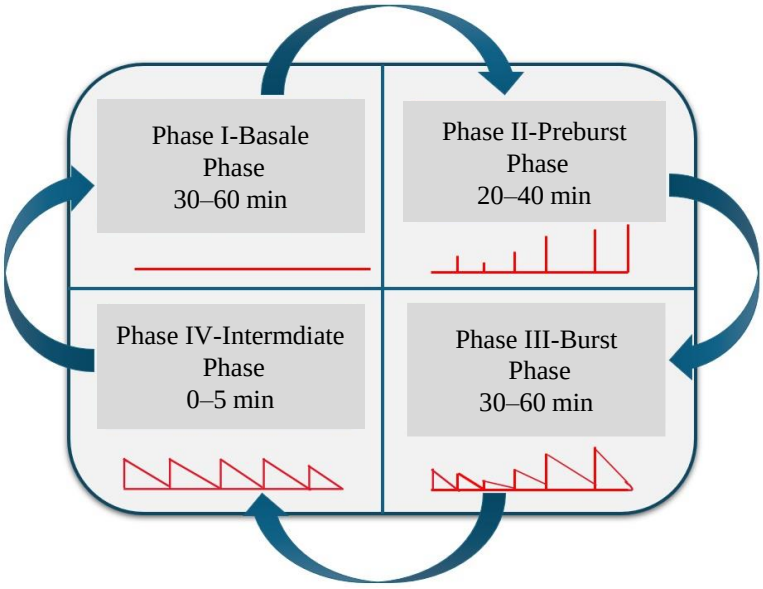

Figure 2. Migration myoelectric complex (MCC) cycle.

Phase II

Pre-burst phase: It is distinguished by irregular action potentials also contractions. The intensity and frequency gradually increase as the phase advances and lasts from 20 to 40 minutes.

Phase III

Burst phase: The process involves a brief 10 to 20-minute contraction that removes the stomach's undigested material, followed by a 'housekeeper' wave, which sweeps all remaining materials [15].

Phase IV

Immediate phase: A brief transitional Phase IV occurs between Phase III and I of two consecutive cycles brief transition time lasting between 0 and 5 minutes [16].

The fed state experiences slow gastric emptying, with motor Activity beginning 5–10 minutes after a meal and continuing as long as the food is still in the stomach. The duration of fed activity, typically 2–6 hours, increases food consumption. GRDDS administration during fasting affects MMC phases, affecting the total time taken for stomach retention and gastrointestinal transit.

GRDDS CONTROLLED FACTORS

Dosage form-related Factor

Dosage form-related factors refer to characteristics inherent to the specific form in which a medication is administered, such as tablets, capsules, or syrups. These factors can significantly influence the drug's efficacy and patient adherence. For instance, factors like bioavailability, dissolution rate, and ease of administration can vary between dosage forms, impacting how effectively the drug is absorbed and utilized by the body, as well as the patient's ability to take the medication as prescribed. Therefore, understanding and optimizing dosage form-related factors are crucial in ensuring the desired therapeutic outcomes.

Dosage Form Density

Dosage form density refers to the mass per unit volume of a medication form like tablets or capsules. Factors influencing it include formulation composition, manufacturing processes, and dosage form characteristics. Density affects size, dosing accuracy, and packaging considerations [16, 17].

Dosage Form Dimensions and Shape

Dosage form dimensions and shape refer to the physical size and geometric characteristics of a medication form, such as tablets, capsules, or suppositories. These factors can impact various aspects of the medication, including ease of administration, patient acceptance, and manufacturing processes. For example, a smaller tablet size may be preferred for ease of swallowing, while a specific shape may be chosen to facilitate handling or packaging. Therefore, controlling and optimizing dosage form dimensions and shape are important considerations in pharmaceutical formulation and manufacturing to ensure patient compliance and medication effectiveness.

Effects of Dosage Density

Low-density dosage floats to the stomach surface, high high-density systems sink to the bottom, isolating the system from the pylorus, with a density is 1.0 g/cm^3.

However, the dosage form is absorbed in the fluid, its floating propensity typically diminishes over time as a result formation of Hydrodynamic equilibrium [18, 19].

Swelling and Mucoadhesive Properties:

When dosage forms come into contact with gastric fluids, swelling polymers cause them to expand. This expansion aids entrapment of the dosage in the stomach.

Mucoadhesive polymers enhance retention by promoting adhesion to the gastric mucosa. Hydrogen bonding or other adhesive interactions can be used to achieve this adhesion.

Food Intake and Its Nature

Controlled Release: In situ gel compositions can be designed to control the release of their contents, allowing for the controlled release of nutrients or bioactive compounds. This controlled release can be beneficial for long-term energy release or achieving a desired physiological effect [19].

In situ, gels can enhance the bioavailability of nutrients or the efficacy of bioactive compounds by delivering specific ingredients to specific locations within the digestive system. The nature of the in-situ gel can affect the texture and palatability of the food product, allowing for the customization of viscosity and elasticity to achieve desired sensory characteristics [20].

Patient-related Factor

Patient-related factors in the effectiveness of gastroretentive drug delivery systems, which are designed to prolong the gastric residence time of drugs. These factors include gastrointestinal motility, pH of the stomach, presence of food, and individual patient variability.

Gastrointestinal motility can affect the retention time of dosage forms in the stomach. Patients with conditions that affect motility, such as gastroparesis, may have altered drug absorption from gastroretentive systems.

Therefore, it is important to consider these patient-related factors when designing and administering gastroretentive drug delivery systems to ensure optimal drug delivery and therapeutic outcomes. The gel formation process of raft-forming in situ gels, which are designed to respond to acidic stomachs, can be affected by gastric pH and dietary habits. Meal dosage and timing are critical for optimal results [21–23].

DIFFERENT GASTRO RETENTIVE APPROACH

Technological advancements aim to develop a stomach-retained dosage form, with proposed methods outlined in Figure 3 to enhance oral dosage retention in the upper gastrointestinal tract.

Floating and Non-floating Systems

Biological Adhesive Systems

Biological adhesive systems of gastro retentive drug delivery system adhere to the gastric mucosa, prolonging drug release and enhancing absorption. These systems utilize bio-adhesive polymers that interact with the mucus layer of the gastrointestinal tract, promoting intimate contact and sustained drug release.

By adhering to the gastric mucosa, biological adhesive systems can extend the time of drugs in the stomach, improving their bioavailability and therapeutic efficacy. Additionally, these systems offer the advantage of reducing fluctuations in plasma drug levels, potentially minimizing side effects and improving patient compliance. Overall, biological adhesive systems represent an approach to achieving controlled drug delivery in the gastrointestinal tract [24].

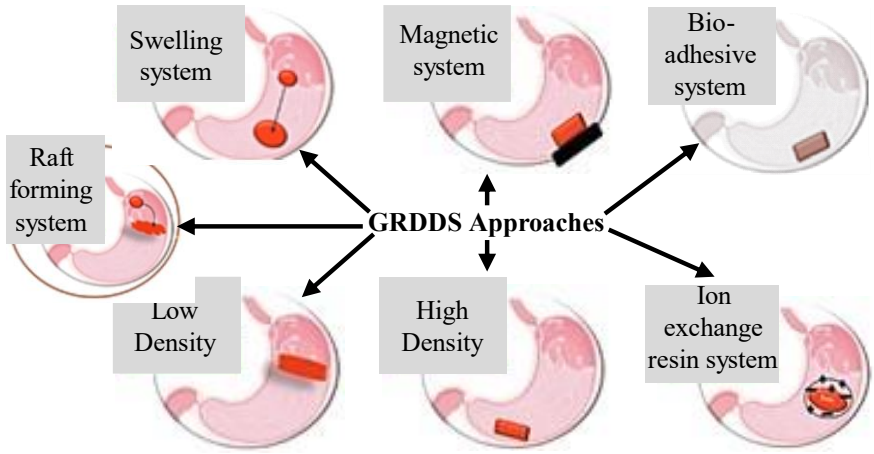

Figure 3. Depicts various approaches of GRDDS.

High-Density Systems

In drug delivery greater mass per unit volume, sinking in gastric fluids to prolong drug release and improve bioavailability. They are advantageous for drugs requiring prolonged gastric residence time and acidic environments for optimal absorption. These systems offer flexibility in design and can be tailored to specific release profiles and patient needs [25].

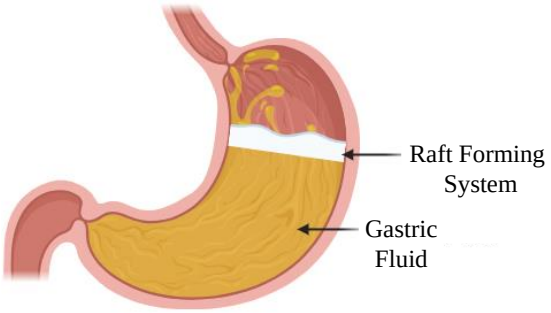

Figure 4. Schematic illustration of the barrier formed by a raft-forming system.

Low-density System

Low-density systems in drug delivery are formulations with a lower mass per unit volume, allowing them to float on gastric fluids. They prolong drug release by remaining buoyant in the stomach, enhancing absorption and bioavailability. These systems offer controlled drug release, reduced variability in plasma drug levels, and potential improvements in therapeutic outcomes and patient compliance [26].

Swelling Mechanisms

There are typically two main swelling mechanisms: osmotic and hydrophilic swelling. Osmotic swelling relies on the osmotic pressure gradient across a semipermeable membrane, leading to water influx and subsequent swelling of the delivery system. Hydrophilic swelling, on the other hand, occurs when material directly absorbs water from the surrounding environment, causing swelling. These mechanisms are fundamental in designing controlled-release systems that can modulate drug release rates based on environmental conditions, such as pH or the presence of enzymes.

Floating Bioadhesive Systems

Floating bioadhesive systems combine buoyancy with adhesion to the gastric mucosa. They adhere to the stomach lining while floating on gastric fluid, prolonging drug release and enhancing absorption. These systems are useful for drugs needing extended gastric residence for optimal effects [27].

RAFT FORMING MECHANISM

The raft forming system is one of the approaches that involve the formulation of effervescent floating liquid with in situ gelling properties, which has been assessed for sustaining drug delivery and targeting. Moreover, the gels formed in situ remained intact for more than 48 hours to facilitate the sustained release of drugs. The mechanism of the raft-forming system involves the formation of a continuous layer on the surface of gastric fluid (Figure 4) called a raft. The system involves the formation of a viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft [28–30].

Because CO_2 production results in low density, the gel layer floats on top of the gastric fluid because its bulk density is lower than that of the gastric fluid. As a result, the system floats in the stomach for a long time without slowing down the rate at which food leaves the stomach. Because the gel created by in situ gelling is lighter than gastric fluid, it either floats over the contents of the stomach or sticks to the gastric mucosa because the polymer is bioadhesive. This acts as a barrier between the stomach and the esophagus to stop gastric content from refluxing into the esophagus. As a result, it prolongs drug administration in the gastrointestinal tract by producing dosage form retention and lengthening the stomach residence duration. The medicine is removed from the system gradually and at the desired pace when it is floating on the contents of the stomach. The stomach is cleared of the drug's leftover system once it has been released. As a result, the changes in plasma drug concentration are better controlled and the gastric retention duration is increased [31–32].

Raft Forming System of Design

The raft-forming system's formulation is influenced by drug properties, diseased conditions, patient populations, and marketing preferences, requiring a slow-release, stomach-resistant, low-specific gravity dosage form for gastric retention [33].

To achieve gastric retention of the dosage form, the dosage form must be able to satisfy the following criteria [34–36].

1. The drug should be released slowly from the system.
2. The dosage form must be able to withstand the force exerted by peristaltic waves in the stomach and the constant contractions, grinding, and churning moments.
3. Should maintain specific gravity lower than gastric contents (1.004–1.01 g/cm^3).
4. The dosage form must remain in the stomach for a prolonged period.
5. Better patient compliance.
6. Easy for administration for the patient.
7. After the release of the drug, the device should be easily evacuated from the stomach.

Drugs Used in the Raft-formation System

The raft-forming systems can distribute antacids and medications to treat gastrointestinal infections and illnesses. The raft-forming technology may be used to treat esophagitis and heartburn. This method performs well with acid-soluble compounds. Poorly soluble or unstable intestinal medicines. There are several drugs available for use in the raft formation system as shown in Table 1 [37–58].

Polymers Used for Formulations

Pectin

After alginates, pectin is the most extensively researched biopolymer in terms of Its Effectiveness raft-formation agent. Commercially, it is produced using citrus peels and apple pomace. Pectin, a polymer Made up of galacturonic acid and methyl ester units, may reach molecular weights of up to 150,000 and polymerization degrees of up to 800.

Pectin is classified based on its degree of esterification. High-methoxy (HM) is the most common. Pectin containing at least 50% DE and low-methoxy (LM) pectin containing less than 50% DE. Both types have different properties, such as gelling requirements and raft-forming agents. Gamma scintigraphy was used to study Aflurax's antireflux activity [38–41].

Table 1. Drugs that can be used for the raft-forming system.

Therapeutic Class	Drugs	Reference
Proton pump inhibitor	Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole, Esomeprazole	[59]
Antacid	Aluminum Hydroxide, Aluminum Phosphate, Magnesium Silicate, Magnesium Hydroxide, Calcium Carbonate	[60]
Anti-cholinergic	Oxyphenonium, Propantheline, Telezepine, Pirenzepine	[61]
Anti-helicobacter	Amoxicillin, Clarithromycin, Tetracycline	[62]
Histamine H2 receptor antagonist	Cimetidine, Ranitidine, Loxatidine, Famotidine, Nizatidine	[63]

Pectin has been used as a raft-forming agent in antacid compositions treating upper gastrointestinal dyspeptic disorder, alleviating symptoms like regurgitation, epigastric pain, and nausea. It also forms resilient rafts in low pH conditions without calcium or sugar [42].

Gellan Gum

Gellan gum, an exocellular polysaccharide discovered in Sphingomonas elodea, is composed of one L-rhamnose, one D-glucuronic acid, and two D-glucuronic acid residues.

The tetrasaccharide repeat unit of the polysaccharide Gellan gum, an exocellular polysaccharide from Sphingomonas elodea, is It consists of one Lrhamnose, one D-glucuronic acid, and two D-glucuronic acid residues.

Gellan gum, often referred to as GelriteTM or KelcogelTM, demonstrates cation-or temperature-dependent gelation, which is typified by aggregation and double helical junctions. Through complexation and hydrogen bonding, this gum forms a three-dimensional network. Because of temperature fluctuations or the presence of cations, the gellan gum formulation, which contains calcium chloride and sodium citrate complex, creates a gel in the stomach [43, 44].

Xanthan Gum

In the past, an anti-reflux suspension containing alginate and xanthan gum served as the raft-forming agent and stabilizer, respectively. Researchers are developing a composition that protects and heals the esophageal mucosa by combining xanthan gum's bioadhesive properties with other polysaccharides, specifically focusing on raft formation.

Xanthomonas campestris bacteria are used in pure culture aerobic carbohydrate fermentation to create xanthan gum, a polysaccharide. Xanthan gum forms a weak structure in water, leading to low concentrations of high-viscosity solutions. The viscosity is consistent between 0 and 100°C. It has a stringy texture but is pseudoplastic throughout a broad range of shear rates and concentrations. In addition to being resistant to common enzymes, Xanthan gum is extremely soluble and stable in acidic, alkaline, and salt-containing conditions. Guar and xanthan gum have a viscosity and when mixed with locust bean gum, xanthan gum may generate thermos-reversible gels at certain doses.

The invention incorporated xanthan gum as a raft-forming agent and hexanol-stabilized aluminum hydroxide, an antacid, in the formulation [45].

Alginic Acid

Polymer is found in brown seaweed and marine algae and is utilized in pharmaceuticals due to its biodegradability, nontoxicity, and mucoadhesive properties. It is commonly used in floating drug delivery systems and can produce gels.

In 95% ethanol, ether, and chloroform, sodium alginate is essentially insoluble; however, it slowly dissolves in water to create a thick colloidal solution. When the cation's ionic radii are lower, alginates form a compact structure. Alginates form firm gels in diluted aqueous solutions with the addition of metal ions, glucuronic residues, and sodium citrate. This process creates [46, 47].

Chitosan

Complexation with unbound Ca^{2+} ions releasing them only in stomach acid. With its antibacterial and antifungal qualities, chitosan has been thoroughly studied as a possible natural antimicrobial agent for use in food, cosmetic, pharmaceutical, and agricultural sectors. Chitosan's pH, acetylation level, and molecular weight all affect its antibacterial qualities. Chitosan concentrations in foods are generally higher than those in laboratory media due to interactions with complex food ingredients that can change chitosan activity. Even though it is anticipated that chitosan will be utilized in more commercial items, research is still being done to pinpoint the precise mechanism underlying the material's biological activities and structure-function link [48].

Chitosan, a pH-dependent, dissolves in aqueous solutions up to 6.2. Forming a hydrated gel and providing controlled drug release in acidic and neutral media [49, 50].

Locust Bean

The molecular weight of this Branched beta-1, 4-D-galactomannan is abundant. The nonionic polymer must be heated to fully hydrate; it is partly soluble in cold water and expands in cold water

The idea deals with pharmaceutical formulations that shield and repair the mucosal surface thanks to enhanced bio-adhesive qualities. Different amounts of xanthan gum, carrageenan, and locust bean gum are used in the formulation to obtain its bio-adhesive properties [51, 54].

Gaur Gum

Cyamopsis tetragonolobus, a plant in the Leguminosae family, creates a long-chain, linear beta-1,4-D-galactomannans molecule with alpha-1,6 links beta-1,4-D-galactomannans.

The molecular weight of D-galactose is around 1,000,000. Guar gum is a polymer that dissolves in cold water and readily hydrates to Create high viscosity liquids at low concentrations. These show interfacial binding. Indicating that they are true emulsifiers. Guar gum and xanthan gum work synergetically to increase viscosity. By mixing known antacids with guar gum's raft-forming properties, an antacid preparation was created that created a protective layer.

To treat gastric diseases formulation in which the gum's gelation was inhibited or delayed until after it had passed into the stomach. This formulation contained guar gum, as well as other polysaccharide gums [52, 53].

EVALUATION PARAMETER OF RAFT FORMING SYSTEM

Raft Forming Time

The duration it takes for a formulation to transform into a cohesive gel raft upon exposure to gastric fluid. It indicates how quickly the formulation can initiate gastro retention and drug release within the stomach environment. A shorter raft forming time suggests a faster onset of drug action and improved patient compliance.

To determine raft forming time, prepare the formulation and simulate stomach conditions with a gastric fluid solution. Introduce the formulation and monitor for visible gel formation, recording the time it takes to fully transform. Repeat for consistency and calculate the average time [55].

Raft Strength

It involves subjecting the raft to simulated gastric conditions, such as agitation or exposure to different pH levels, and measuring its ability to maintain its structure without disintegration. Testing methods include assessing raft resilience to physical stress, such as compression or stirring, and evaluating its resistance to chemical degradation over time. The strength of the raft is crucial for ensuring prolonged retention within the stomach and sustained drug release.

To evaluate raft strength, subject the gel raft to simulated gastric conditions and apply stress, such as mechanical agitation or compression. Observe changes in structure and measure parameters like thickness or weight loss. Repeat experiments for reliability and analyze results to assess raft stability [56].

Buoyancy

The ability of the gel raft-formed formulation to float on the surface of gastric fluid. This is typically achieved by immersing the raft in a simulated gastric fluid and observing its behavior. A buoyant raft remains on the surface, while a non-buoyant one sinks. Parameters like raft density and surface tension are important for buoyancy. Testing methods involve visual observation, measuring the time taken for raft flotation, or quantifying the percentage of time the raft remains buoyant. Buoyancy is critical for prolonged gastric retention and sustained drug release [57].

In Vivo Study

A range of in vivo imaging methods, such as direct endoscopic vision, scintigraphy, and radiography, have demonstrated the existence and development of floating rafts.

Several formulas exist. One kind of imaging that is noninvasive is gamma scintigraphy. This method incorporates a radioisotope that emits gamma rays into the formulation. The method allows for noninvasive visualization of raft formation and dynamics. Demonstrated alginate raft floating behavior, combined this technique with radio telemetry capsule to visualize stomach distribution, demonstrating safety.

pH telemetry, which employs a pH-sensitive radio telemetry capsule, allows for the evaluation of the preparation's neutralizing capacity in comparison to traditional antacids. Alginate preparations exhibit raft formation and neutralizing capacity, retaining neutralizing capacity despite conventional antacids increasing gastric pH.

These results demonstrated notable distinctions between the mechanisms of action of conventional antacids and raft-forming anti-reflux preparations, emphasizing the protective role of the antacids included in the former and the pH maintenance function of the latter [54].

In Vitro Drug Release

The releases medications in 0.1 N HCl for 0–8 hours using a USP type V at 50 rpm. Drug concentration is measured using simulated gastric juice USP class II equipment is used for in vitro drug release.

The drug release rate from a prolonged suspension by adjusting the USP dissolving testing apparatus, spinning the basket at 50 rpm, and adding 900 ml of 0.1 N HCl at 37°C [58].

CONCLUSION

To improve oral absorption of medications with a limited absorption window implies partial release and brief residence time, an NDDS is created. Gastroretentive drug delivery devices enhance absorption, bioavailability, and therapeutic efficacy by extending drug residence in the stomach. Raft formation, a novel technique, uses polymers or gelling agents. Ion exchange, High density, mucoadhesive, expandable, swelling, and floating are some of the gastro-retentive drug delivery methods being used. The raft-forming system has proven an effective method for increasing bioavailability and controlling drug delivery. It prolongs release that is localized to the stomach, enhancing local activity and lowering the frequency of dosage. This system is appropriate for pediatric and geriatric patients, and it provides a liquid dosage form with the benefits of an oral solid dosage.

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