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FLOATING DRUG DELIVERY SYSTEMS: AN EXTENSIVE REVIEW OF DESIGN PRINCIPLES, RECENT ADVANCEMENTS, AND CLINICAL SIGNIFICANCE

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ABSTRACT

The development of Gastro-Retentive Drug Delivery Systems (GRDDS), especially Floating Drug Delivery Systems (FDDS), which extend gastric residence time and improve the bioavailability of medications with limited absorption windows, acid-soluble medications, and those requiring localized gastric action, has greatly advanced oral controlled-release drug delivery. In order to obtain dependable stomach retention, floating, swellable, expandable, mucoadhesive, and raft-forming platforms must be designed because conventional oral systems fail due to quick gastric emptying, variable motility, and partial drug release. In order to provide buoyancy and sustained release for ten to twenty-four hours, FDDS reduce dosage-form density through gas production or polymer swelling. Recent developments include super porous hydrogels that react to gastric pH and ionic conditions, nanosized citrus pectin-based in-situ rafts, and hybrid systems that combine flotation with mucoadhesion or expansion. By providing exact control over geometry, porosity, density, and multi-compartment structures, additive manufacturing (3D printing) has further revolutionized GRDDS, permitting complicated release patterns and individualized therapy. Despite their promise, GRDDS face challenges like physiological variability, inconsistent buoyancy in fasted conditions, manufacturing complexities, and regulatory requirements for proving in-vivo retention and safety. Looking ahead, there is an emphasis on multimodal systems that integrate various retention mechanisms. AI-driven formulation design can help optimize polymer behavior and buoyancy. Additionally, biomimetic devices are being developed to mimic gastric physiology.All of these developments put next-generation GRDDS in a position to be extremely flexible platforms that can support personalized medicine for a variety of gastric and upper-intestinal disorders, increase therapeutic efficacy, and decrease dosing frequency.

KEYWORDS: Gastro-retentive drug delivery system, Floating drug delivery system, Buoyancy, Controlled release, 3D printing, AI-driven formulation design, Biomimetic.

1. INTRODUCTION

The most practical and favored method of getting medications into the systemic circulation is oral administration. Oral controlled-release drug delivery systems have drawn a lot of interest in pharmaceutical research in recent years because of the therapeutic benefits they provide, including easier administration, better patient compliance, and more formulation flexibility.[1] The idea behind floating drug delivery (FDDS) is to make the dosage form less dense than the gastric fluids so that it floats on them. FDDS was developed to keep drugs in the stomach and is applicable for drugs with poor solubility and low stability in intestinal fluids. FDDS are low density, hydrodynamically controlled systems that have enough buoyancy to float over the contents of the stomach and stay buoyant there for an extended amount of time without interfering with the rate of gastric emptying.[2] Conventional drug delivery techniques may not be able to address issues brought on by the gastrointestinal tract

(GIT), such as partial drug release, reduced dose activity, and frequent dose demand. The incapacity of conventional drug delivery techniques to retain drugs in the stomach may also contribute to GRDDS. These techniques have several benefits, such as improved drug absorption that boosts therapeutic efficacy, extended gastric residence time (GRT) of dosage forms in the stomach for several hours, and adaptability for targeted distribution in the stomach.[3] Numerous FDDS have emerged in recent times, each with unique advantages and disadvantages. These include gas-generating systems, raft-inducing systems, single or multiple unit hydro dynamically balanced systems (HBS), and hollow microspheres.[4,5] The residence time of medications in the gastric environment can be significantly extended by these systems, which can remain in the stomach area for several hours. For drugs that are poorly soluble in a high pH environment, prolonged gastric retention improves bioavailability, reduces drug loss, and increases solubility. Additionally, it is used to deliver drugs locally to the upper small intestine and stomach.[6]

1.1. Rationale and Objectives of GRDDS

Because traditional oral dose forms don't stay in the stomach long enough to prevent inadequate drug release, decreased effectiveness, and frequent dosing, GRDDS were created. They must get past a number of obstacles, including poor absorption in the lower GIT, fast stomach emptying, and low bioavailability.[6]

1. To Overcome Short Gastric Residence Time

Motility changes (MMC) cause conventional systems to rapidly exit the stomach, resulting in incomplete drug release and decreased dose effectiveness.[7]

2. To Prevent Incomplete Drug Release

Drugs may be partially released before leaving the stomach due to the short gastric emptying time (2–3 h), which reduces the dose's effectiveness.[7]

3. To Improve Bioavailability of Drugs with Narrow Absorption Windows

Numerous medications are primarily absorbed in the upper part of the small intestine (the duodenum and jejunum). GRDDS holds them at their ideal absorption location, enhancing both bioavailability and therapeutic effectiveness.[8]

Particularly for

Drugs with low absorption in lower GIT
Drugs unstable at alkaline pH
Narrow absorption window drugs such as metformin, riboflavin, levodopa, and cilostazol.[8]

4. To Enhance Solubility of Drugs Best Absorbed at Low pH

Drugs that are

Highly soluble in acidic pH
Unstable at alkaline pH

5. To Support Local Drug Delivery to the Stomach

For local action in the stomach and proximal small intestine, such as treating H. pylori and peptic ulcers, GRDDS are very helpful.[9]

6. To Overcome Physiological Challenges

GRDDS are specifically made to avoid physiological problems such as
MMC (Migrating Myoelectric Complex)
Variations between fed-state and fasted
Quick emptying of the stomach.[9]

7. To Reduce Dosing Frequency

Patient compliance and therapeutic efficacy are enhanced by sustained drug release during extended gastric retention.[8] To ensure long-lasting drug action, reduce the frequency of doses, and greatly increase patient compliance.[9]

8. To Improve Plasma Concentration Stability

Because FDDS maintains continuous release while floating, it improves control over variations in plasma drug concentration.[9] To achieve stable plasma drug concentrations and avoid the fluctuations of peak-and-trough typically seen with immediate-release formulations, thus providing a more reliable therapeutic effect.[9]

By increasing drug absorption and extending gastric residence time, GRDDS overcome the drawbacks of traditional oral forms. They improve the bioavailability of medications that require local gastric action, have limited absorption windows, or are acid-soluble. Sustained release, stable plasma levels, fewer doses, and efficient treatment of gastric disorders are among their main goals.[9]

2. PHYSIOLOGICAL CONSTRAINTS AND IDEAL DRUG CANDIDATES

2.1. Gastric Physiology and Motility

1. Quick and Unpredictable Gastric Emptying

Conventionalsystems have a short gastric residence time and are rapidly removed from the stomach as a result of fast gastric emptying, which restricts controlled release and drug absorption.[9]

2. Dependence on Stomach Motility Conditions (Fasted vs Fed State)

Changes in gastric motility affect the duration that formulations remain in the stomach. Fluctuations in gastric motility complicate the task of achieving gastro-retention.[11]

3. Variations in Gastric pH

Drug solubility and polymer swelling behavior, which affects buoyancy and release, are impacted by gastric pH fluctuations, which range from 1–3.5 in the fasted state to 3–7 in the fed state.[14]

4. The Need for Sufficient Gastric Fluid Levels
For floating formulations to swell polymers like PEO and produce CO2 for buoyancy, there must be enough gastric fluid. The efficiency of floatation is decreased by low fluid levels.[14]

5. Migrating Myoelectric Complex (MMC) Cycles' Impact
Strong contractions in MMC Phase III during fasting remove undigested material from the stomach every two to three hours, reducing the amount of time floating dosage forms are retained unless they are given in the fed state.[17]

6. Strong Gastric Motions / Peristaltic Forces
Particularly in single-unit systems, the antrum's powerful contractions (mixing and propulsive forces) may cause floating dosage forms to be expelled too soon.[16]

8. Need for Proper Dosage Form Density and Size
For the system to float, its density must remain less than 1 g/mL; inadequate swelling or gas production could result in sinking.[18]

7. Unsuitability for Certain Drugs
GRDDS are not suitable for:
Drugs that irritate gastric mucosa,
Drugs unstable in acidic pH.[18]

2.2. Physio-chemical Characteristics of Drug Candidates
1. High Solubility in Acidic pH
The best medications for GRDDS are those that are poorly soluble in intestinal alkaline pH and more soluble in acidic gastric pH.[17]

2. Poor Solubility / Instability in Alkaline pH
Medications that break down or show decreased solubility in the alkaline conditions of the intestines are advantageous for remaining in the stomach.[17]

3. Narrow Absorption Window in Upper GIT
Ideal candidates are medications that are primarily absorbed from the stomach, duodenum, or jejunum.
Propranolol, atenolol, ciprofloxacin, and amoxicillin are a few examples.[18]

4. Drugs Requiring Local Action in Stomach
Ideal for drugs used to treat:H. pylori infection, Peptic ulcer, GERD.
These require localized gastric delivery.[19]

5. Dose Should Be Small to Moderate
Drugs with low-to-moderate dosages work best with floating and swellable systems because high doses increase tablet weight and decrease buoyancy.[20]

6. Ideally High Gastric Fluid Solubility
In an acidic medium, high solubility promotes improved absorption, quicker wetting, and a steady release rate.[20]

3. Classification and Design Strategies (Figre 1)
1. Single-unit Floating Dosage Systems
Low-density materials (such as ethyl cellulose matrices or HPMC) are used in single-unit floating systems to enable the tablet to float on stomach fluids while releasing the medication gradually. GI fluid enters a gas-filled chamber and microporous reservoir in fluid-filled floating chamber designs to dissolve the medication. Hydrodynamically Balanced Systems (HBS) are appropriate for medications with acidic solubility and upper-GIT absorption because they extend gastric retention by preserving density <1 and creating a stable gel barrier. Single-unit systems, however, have the potential to cause irritation if they adhere to one another or become stuck in the GI tract.[17,18]

2. Multiple-unit Floating Dosage Systems
Higher bioavailability, predictable gastric residence, decreased dose dumping, and decreased irritation risk are some benefits of multiple-unit floating systems (pellets, beads, microspheres).[17] Their small size ensures smoother transit through the GI tract and reduces variability. However, their drug-loading capacity is reduced because they need more excipients. These systems frequently employ polymer-coated reservoir units, where drug release happens when the coating ruptures due to swelling, gas production, or osmotic pressure.[18]

A. Effervescent Systems
Mechanism: To reduce system density and facilitate floatation, use gas-generating agents (such as sodium bicarbonate + citric/tartaric acid) to produce carbon dioxide. In order to provide buoyancy, released carbon dioxide becomes trapped in swollen hydrocolloids. Stoichiometric ratio of $NaHCO_3$: citric acid ~ 0.76:1 for optimum gas generation. Gas-generating matrices and volatile-liquid systems are examples of effervescent systems.[18]

Types under Effervescent systems
Gas-generating systems ($NaHCO_3$ + organic acid)
Volatile liquid–containing systems (ether, cyclopentane liquefy → vaporize → expand chamber)[18]

B. Non-Effervescent Systems
Mechanism: Produce buoyancy without gas by relying on polymer swelling or gel formation.
produced with alginates, polyacrylates, sodium CMC, carbopol, HPMC, etc.
Gel-forming hydrocolloids retain a density of less than onewhile trapping air.[18]

Types under non-effervescent systems
Colloidal Gel Barrier System (Hydrodynamically Balanced System)
Maintain buoyancy by forming a gel barrier upon hydration.[18]

Microporous Compartment Systems
Air is trapped to allow the drug to float in a microporous reservoir wiAir is trapped to allow the drug to float in a microporous reservoir with sealed outer walls.[19]

Floating Microspheres / Micro balloons
Superior floatation due to a hollow interior cavity.[19]

Alginate Floating Beads
Sodium alginate is dropped into $CaCl_2$ and then freeze-dried to produce porous beads.[20]

Single-layer Floating Tablets
Drug + polymer matrix that swells and entraps air.[20]

Bilayer Floating Tablets
A gel barrier is formed by one IR layer and one SR floating layer.

3.1. Design Strategies for Floating Tablets
1. Raft-Forming Design
A formulation containing alginate and bicarbonate salts creates a viscous, low-density gel "raft" when it comes into contact with gastric fluid in raft-forming systems, an important gastroretentive design. A buoyant foamy structure that floats on the stomach contents is created when the bicarbonate and gastric acid combine to produce carbon dioxide, which gets trapped in the hydrated alginate matrix. In order to prevent acidic contents from flowing backward and to maintain localized drug delivery in the upper stomach area, this floating raft serves as a protective barrier and is mainly used in antacid and gastroesophageal reflux treatments. The device offers superior buoyancy, prolonged gastric retention, and quick reflux relief.[17]

2. Gas-Generating Design Strategy
Used in effervescent systems.
Includes
Sodium bicarbonate + citric/tartaric acid
CO_2 entrapment in swollen polymer
Rapid hydration to form buoyant matrix.[18]

3. Bilayer Floating Tablet Strategy
Layer 1: Immediate release (IR) for rapid onset of action.
Layer 2: Sustained-release floating layer with gel barrier and gas generators.
Offers both extended retention and dual release.[18]

4. Density-Controlled Design Strategy
Low-Density System Design
Because of their design, floating tablets can float for extended periods of time because their bulk density is lower than that of gastric fluid (1.004 g/mL).
accomplished by employing polymers such as ethyl cellulose, carbopol, PEO, xanthan gum, and HPMC.
These polymers hydrate and form a gel barrier that traps air and reduces density.[19]

High-Density System Design
High-density GRDDS as a design strategy, despite it being the opposite of floating:
Materials such as titanium dioxide, zinc oxide, and barium sulfate must have a density greater than 3 g/mL.
They resist peristaltic motions and sink.[19]

5. Dry, Wet, or Direct Compression Strategies
Wet granulation enhances flow and uniformity when combined with HPMC, NaHCO3, and citric acid.
For simpler polymer formulations, direct compression is used.
Slugging, or dry granulation, is used for medications that are sensitive to moisture.[20,21]

6. Floating Strength / Buoyancy Optimization Strategy
Key parameters:
Floating Lag Time (FLT) must be short
Total Floating Time (TFT) ideally > 12 hours
Evaluated in 0.1 N HCl (pH 1.2). (20,21)

4. EVALUATION

4.1. In vivo study
a. In-vivo buoyancy studies: Radiographic (x-ray) or γ scintigraphy studies can be used to observe buoyancy in vivo. BaSO4 can be used as a radio opaque material in radiographic studies, while radio-labeled Technetium (99mTc) can be used in γ-scintigraphy. Images obtained using X-ray or γ-scintigraphy studies at different time intervals can be used to determine the buoyancy character of the formulation or placebo after it has been administered.[22]

b. In-vivo drug release studies: Two-way cross-over design is one statistical model that can be used for in-vivo drug release studies. Blood samples must be taken at prearranged intervals in accordance with the protocol, and after necessary processing, the drug must be analyzed using an appropriate analytical method, such as HPLC. As a result, the drug absorption profile can be reported and the data can be fitted to different kinetic models. It is also possible to determine a number of pharmacokinetic parameters, such as Cmax, tmax, KE, t1/2, AUC.[22]

4.2. In vitro study
Pre-Compression Study
1) Angle of Repose: Angle of repose is the maximum angle possible between the surface of the powder pile and the horizontal plane [height].[22]

$$\text{Tan } \theta = h / r$$
$$\theta = \text{Tan-1 } h / r$$

Where θ= Angle of repose, r = radius of pile, h= height of pile

2) Density: The bulk density (BD) and tapped density (TD) were determined using the following formulas,

Bulk density = weight of powder / Bulk volume
Tapped Density = Weight of powder / Tapped volume[22]

3) Compressibility Index: The compressibility index of was determined by following formula,

Carr's Index % = TD-BD/ TD x 100 18

4) Hausnser's Ratio: It is calculated using the formula,

Hausner's ratio = TD / BD[23]

5) Drug-excipient interactions: FTIR is used for this. The DE interaction is indicated by the appearance of a new peak and/or the disappearance of the initial drug or excipient peak. In addition to the evaluation criteria listed above, the impact of aging using a Differential Scanning Calorimeter or Hot Stage Polarizing Microscopy.[23]

Post-Compression Study

General Appearance: A tablet's size, shape, color, taste, odor, surface texture, and physical imperfections all contribute to its overall appearance.

1) Tablet Thickness: Three tablets were taken randomly, and their thickness and diameter were measured by vernier caliper or calibrated screw gauze.[22]
2) Weight Variation Test: 20 tablets are selected and weighed individually. Then the deviation of individual weight from the average weight is calculated.

Weight Variation = (Iw -Aw)/Aw x 100% 12

Where, Iw = Individual weight of tablet; Aw = Average weight of tablet.[24]

3) Hardness: The hardness of the tablet determines how resistant it is to capping, abrasion, or breakage during handling, storage, and transit. Three tablets are chosen at random to measure it using a Monsanto hardness tester. The unit of measurement is kg/cm2.[24]
4) Friability: The durability of tablets during packing and transportation is tested using friability testing. After ten tablets are chosen, weighed, and put in a Roche friabilator, it rotates for four minutes at a speed of 25 rpm. The tablets are weighed again after four minutes. A formula is used to determine friability.

%F= [1-(Wt./ W)] *100

W – Initial weight of tablet, wt. - Weight of tablet after revolution

If % Friability of tablets is less than 1%, it is considered as acceptable.[25]

5) Floating lag time and floating time: - Time required for the tablets to rise on the surface of the medium is floating lag time. The total duration of tablet floating on the medium was considered as floating time.[26]
6) Stability study: -Stability testing is required for new drug substances and products, per ICH Q1A (R2). Rules stability testing seeks to determine recommended storage conditions, a shelf life for the drug product, and a retest period for the substance under test. It also shows how different environmental factors, such as temperature, humidity, and light, affect a medicinal product's or drug substance's quality over time. To determine the variation in the in vitro dissolution profile and on storage, a short-term stability analysis of the optimal batch was carried out at 40°C in a humidity container with 75% relative humidity (RH). After a month, samples were taken out to see if the pattern of drug release in vitro had changed.[26]
7) FTIR Study- The physical and chemical interactions between the drug and excipients were investigated using Fourier transform infrared (FT-IR) technology. The FTIR-1700 Shimadzu FT-IR analyzer in the institute's central instrument laboratory was used to record the FT-IR spectra of both the pure drug and the floating tablet using the KBr mixing method.[27]

5. RECENT ADVANCEMENTS AND EMERGING TECHNOLOGIES

5.1. Hybrid and Combination Systems

In order to overcome the drawbacks of traditional floating tablets, recent developments in gastroretentive systems have focused on hybrid formulations that combine multiple retention mechanisms. One notable example is the raft-forming system based on nanosized citrus pectin (NCP), which functions as a mucoadhesive matrix and a floating device. The ibandronate study that was uploaded shows that NCP produces a highly porous floating raft that adheres to the gastric mucosa and traps carbon dioxide. This leads to superior gastric retention and significantly increased bioavailability (Cmax = 653 ng/mL compared to 493 ng/mL for the marketed product). The polymer's nanoscale structure and potent gel-forming ability in acidic media enable the dual functionality of floating and adhesion.[32]

The use of gas-generating systems embedded within swellable polymer matrices, such as formulations utilizing HPMC K4M, K15M, and K100M, is another hybrid advancement. These effervescent–swellable hybrids create a strong, low-density gel that sustains buoyancy for up to 12 hours while preserving controlled, diffusion-based drug release by combining quick CO2 generation with polymer hydration. Reliable floatation and a long-lasting therapeutic effect are guaranteed by this dual mechanism.[29]

Furthermore, hybrid floating–mucoadhesive systems and density-modulated shapes that combine mechanical retention with floatation are highlighted in uploaded GRDDS reviews. This allows for extended gastric residence even in the presence of strong gastric motility. These combination systems mark a significant change toward gastroretentive platforms that are more dependable, stable, and versatile.[30]

5.2. 3D Printing and Personalized Medicine

One of the most important developments in recent GRDDS progress is the use of 3D printing, also known as Additive Manufacturing. The 2025 GRDDS review shows that 3D printing technologies like Fused

Deposition Modeling (FDM) and Semisolid Extrusion (SSE) let researchers create floating drug delivery systems with great control over internal structure, porosity, shape, and density. This allows for the design of hollow structures, low-density devices, capsule-in-device configurations, and complicated shapes made to improve floatation and achieve specific drug release profiles. The flexibility of 3D printing enables the creation of tablets with different infill percentages and shapes, such as ellipsoid, ring, and multi-compartment designs. This results in customizable buoyancy and controlled release rates.[30]

3D printing directly supports personalized medicine. It enables the creation of patient-specific tablets that match individual disease severity, absorption characteristics, and gastric physiology. Studies in your uploaded article show successful production of floating tablets for pregabalin, amoxicillin, theophylline, budesonide, and puerarin using 3D printing. This method achieves controlled, zero-order, or pulsatile release solely based on structural changes.[31]

Additionally, the technology makes it possible to print multi-layered or capsule-in-device GRDDS, which enables distinct compartments for immediate, delayed, and sustained release—something that is not achievable with traditional compression techniques. These developments show how 3D printing's accuracy, adaptability, and structural engineering are revolutionizing floating medication delivery.[30,31]

5.3. Smart and In-Situ Systems

Smart GRDDS are the next generation of floating drug delivery technologies. These systems react to gastric signals like pH, ionic strength, and temperature. They form and hold their structure only after they reach the stomach. A key example is the nanosized citrus pectin (NCP) raft system from the uploaded ibandronate study. NCP gels in place when it contacts gastric fluid, creating a lightweight, porous floating raft. This raft can neutralize gastric acid for a long time. This smart system not only floats because of CO_2 entrapment, but it also acts as a local antacid reservoir. It provides strong protection for the stomach and significantly improves ibandronate absorption by keeping the drug concentrated in its absorption area.[29] Sol-gel transitioning polymers like alginate and pectin, which transform into a floating gel matrix inside the stomach, are another example of smart in-situ systems. These systems rely on chemical reactions with gastric acid to form the floating device, doing away with the need for prefabricated low-density structures. Superporous hydrogels and environment-responsive polymers that can expand dramatically, swell quickly (within seconds), and retain mechanical stability even during intense gastric peristalsis are further introduced in uploaded GRDDS reviews. By responding quickly to gastric conditions, these hydrogels guarantee consistent drug release and extended gastric retention.[30] In-situ gelling systems are also perfect for treating ulcers, reflux disease, and medications with limited upper-GIT absorption because they minimize mucosal irritation and enable precise therapy localization.[29,30]

6. CHALLENGES AND REGULATORY CONSIDERATIONS

6.1. Physiological Variability

Floating tablets rely heavily on stomach function, leading to different levels of gastric retention in different people. This inconsistency is one of the main challenges in creating an effective gastro-retentive drug delivery system (GRDDS).

a. Gastric emptying time (GET) and gastric residence time (GRT)

The performance of floating drug delivery systems is highly unpredictable due to the wide physiological variability. The average GRT in most people is between 8 and 10 hours, but it can vary from a few minutes to over 12 hours based on gastric motility patterns. One of the most powerful factors is meal composition; meals high in calories, fat, and protein considerably increase gastric retention. Meal's high in fat increase bile secretion and slow gastric transit, while foods high in protein can lengthen GRT by about 4–10 hours. Furthermore, eating frequency has a significant effect on retention; several consecutive meals can suppress the migrating myoelectric complex (MMC), extending GRT by more than 400 minutes in comparison to a single meal. Gastric motility is also influenced by significant inter-individual differences, including age, stress, posture, concurrent medications (such as prokinetics and anticholinergics), and medical conditions like hypothyroidism, diabetes, or GERD. Because of this variability, people with abnormally fast stomach emptying cannot be adequately compensated for by floating systems, which results in early dosage form transit and decreased therapeutic efficacy.[24,25]

b. Variability in Gastric Motility and Migrating Myoelectric Complex (MMC) Patterns

Depending on a person's physiological state, gastric motility varies from person to person and even within the same individual.

Every two to three hours, the stomach experiences interdigestive MMC cycles. There are four stages to these cycles:

Phase I: 30 to 60 minutes with hardly any contractions

Phase II: sporadic, erratic contractions lasting 20 to 40 minutes

Phase III (Housekeeper Wave): For ten to twenty minutes, strong contractions force contents—including floating tablets—into the intestine.

Phase IV: Transition time (0–5 minutes)[28]

Problem for floating systems

A Phase III strong wave may force the tablet into the small intestine too soon, ending gastric retention even if it is floating well.

Gender, stress, sleep, hormonal status, and medical conditions (such as diabetes with gastroparesis) all influence these erratic cycles.[29]

6.2. Manufacturing Scale-Up Challenges

a) Reproducibility of Buoyancy and CO_2 Generation

It's crucial to incorporate sodium bicarbonate and citric acid correctly. Lag time and total floating time are affected by small changes.[28]

b) Polymer Behavior Variability During Compression

Hydrophilic polymers (HPMC, carbopol) exhibit swelling-dependent release; batch, compression force, and granulation conditions affect their hydration and viscosity.[28]

c) Complex Wet Granulation Control

Wet granulation with PVP-IPA is necessary for many formulations; incorrect granule size affects swelling, floating, and release.[28]

d) Stability Issues of Polymers at Larger Batch Size

Release kinetics may be impacted by swellable polymers' changed viscosity as a result of mechanical or thermal stress.[29]

6.3. Regulatory Pathway Challenges

a. Demonstrating Gastric Retention In-Vivo

Regulators need evidence of consistent gastric retention, but individual differences in GRT make standardization challenging.

Retention must confirmed by imaging (X-ray, gamma scintigraphy), which adds expense and complexity.[25]

b. Risk–Benefit Assessment for Special Populations

Patients with diabetes, GERD, ulcers, or gastroparesis may have changed stomach motility, necessitating further safety justification.[26,27]

c. Requirement of Predictable Release Kinetics

IVIVC is complicated by the non-Fickian (anomalous) release seen in many formulations as a result of swelling-diffusion mechanisms.[28]

6.4. Potential for Obstruction and Safety Concerns

Systems that are too big to fit through the small intestine's entrance can accomplish the objective of extending the dosage form's residence time in the stomach. Slower transit times, the impact of different pH levels, high meal intake, and the difficulties with smaller tablet sizes are some significant drawbacks that may limit wider use. Effective oral drug delivery is significantly hampered by gastrointestinal incompetence and the breakdown of pharmaceutical agents in the stomach. Reduced oral medication effectiveness is caused by a number of serious issues, including poor patient compliance, drug degradation and elimination, and variations in bioavailability. It is essential to consider both the preformulation aspects and the different properties of polymers. These include mechanical and rheological properties, polymorphism, density, water penetration time, mass variation, friability, disintegration time, and the tendency of tablets to warp.[30] The uniformity of the printed tablet layer height determines the overall tablet uniformity. This is crucial for floating tablets because irregular layer heights may cause large voids in the shell that could prevent floating.[31]

7. CLINICAL SIGNIFICANCE AND FUTURE DIRECTIONS

FDDS improve the bioavailability of medications with a limited absorption window and those requiring localized gastric action, like pantoprazole, glipizide, nizatidine, and ofloxacin, as shown in the uploaded formulation studies, floating drug delivery systems (FDDS) have substantial clinical value. However, significant drawbacks found in all of the reviewed paperssuch as unpredictable gastric physiology, inconsistent floating performance, and reliance on fed-state conditionsmust be addressed if gastro retentive systems are to succeed. As a result, new trends center on creating hybrid systems that combine mucoadhesion or expansion mechanisms with floating, using smart polymers that respond to pressure or pH, and utilizing 3D printing to create customized tablets with optimal density, porosity, and release profiles.[30] These systems decrease dosing frequency, minimize plasma level fluctuations, and enhance therapeutic efficacy in acid-related disorders by extending gastric residence time, especially for medications with short half-lives. Their capacity to sustain release for ten to twenty-four hours enhances therapeutic dependability and patient compliance.[31,32]

7.1. Therapeutic Applications(Table:1)

Table 1: Therapeutic Applications.

	Treatment	Mechanism	References
1	**Gastric and Duodenal Ulcers**	Pantoprazole and nizatidine floating tablets stay in the stomach for extended periods of time, preserving higher drug concentrations at the site of action. This promotes the healing of gastric erosions, duodenal ulcers, peptic ulcers, and mucosal damage caused by hyperacidity.	[12,26,27]
2	**Glycemic Control in Type-2 Diabetes**	Glipizide when administered via floating tablets, , which has a limited absorption window in the upper small intestine, exhibits noticeably increased bioavailability.	[25]
3	**GERD (Gastroesophageal Reflux Disease)**	Because prolonged retention improves acid reflux suppression and maintains a longer therapeutic window, floating systems are very beneficial for medications like pantoprazole and nizatidine.	[26]
4	**Hypertension & Cardiovascular Disorders**	Floating Metoprolol Succinate Tablets Floating Metoprolol tablets increase bioavailability and decrease dosage frequency by extending drug release for up to 12 hours. Perfect for managing heart failure, arrhythmia, angina pectoris, and hypertension.	[34]
5	**Gastrointestinal Infections**	Tablets of Ciprofloxacin HCl Floating Ciprofloxacin floating tablets increase the efficacy of treating upper gastrointestinal tract infections by allowing for a longer stay in the stomach.	[35]
6	**Glycemic Control in Type-2 Diabetes**	Depending on the polymer and tablet composition, pioglitazone release from all of the prepared floating tablets was gradual and dispersed over a 24-hour period. Diffusion control and zero order kinetics governed the release of pioglitazone from all floating tablets.	[36]
7	**Coronary artery diseases**	To achieve in vitro buoyancy, lovastatin floating tablet forming agent and gas generating agent were crucial. The optimized formulation maintained the drug release (99.45) for up to 12 hours and remained buoyant for more than 12 hours, according to the findings of the in vitro drug release and in vitro buoyancy study.	[37]
8	**Antihypertensive**	In animal models, amlodipine floating tablets significantly increased plasma concentration and had an antihypertensive effect. In animal models, amlodipine floating tablets significantly increased plasma concentration and had an antihypertensive effect.	[38]
9	**Gastric & Duodenal Infections**	Metronidazole floating raft tablets are made to stay in the stomach for a long time, creating a gel-like raft that floats on the contents of the stomach.	[39]
10	**Antiviral Therapy – HIV Management**	For the treatment of HIV, lamivudine floating tablets improve bioavailability and offer prolonged drug release.	[40]
11	**Angina pectoris**	Natural polymers like sodium alginate, guar gum, and xanthan gum are used in Nicorandil (NDL) floating/raft-forming tablets to provide a 24-hour controlled release.	[41]

7.2. Future Perspectives

1. Multi-Modal Systems

These various methods (floating, magnetic, expandable, high-density, raft-forming, hydrogels) are specifically listed in the GRDDS review, demonstrating the field's shift toward combination systems that use multiple retention strategies at once to guarantee stable gastric residence under both fed and fasted conditions.[23]

By describing hybrid 3Dprinted gastroretentive designs with multidrug release, pulsatile delivery, structural adaptability, and density-controlled buoyancy, the technology confirms the trend toward multi-modal dosage form engineering.[30]

2. AI-Driven Design

Formulation aided by AI and computation will be very beneficial for future GRDDS development. In order to optimize excipient behavior, floating dynamics, swelling, density distribution, and release mechanisms in complex 3D-printed systemsareas where predictive AI algorithms will significantly improve design precision and reduce trialanderror during formulation scale-upthe 3D-printing-focused approach emphasizes the growing need for advanced modeling.[30]

3. Biomimetic Devices

Advanced techniques that enable physiologically relevant testing that replicates in-vivo gastric motility, such as magnetic marker monitoring and flowthrough realtime tracking of dosage forms within the GI tract, are crucial for the development of biomimetic GRDDS in the future.[27]

The creation of biomimetic gastric models and bio-inspired devices is a significant future direction that the

articles support. A trend toward bio-replicating dosage forms that behave similarly to natural stomach contents is evident in the discussion of 3D-printed intragastric devices and structurally engineered tablets with design features that mimic stomach behavior, such as adaptive swelling, dynamic buoyancy, and mechanical robustness under gastric motility.[30]

8. CONCLUSION

By increasing drug absorption, extending gastric residence time, and improving therapeutic outcomes for medications with limited absorption windows or requiring localized gastric action, gastro-retentive drug delivery systemsparticularly floating formulationsoffer substantial benefits. While physiological variability, buoyancy consistency, and regulatory validation remain obstacles for GRDDS, new developments such as hybrid systems, intelligent in-situ gelling platforms, and precisely designed 3D-printed devices are gradually overcoming these constraints. In order to create more dependable, customized, and clinically successful gastro-retentive treatments, future development will depend on combining multi-modal retention techniques, AI-assisted formulation design, and biomimetic technologies.

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