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Oral Floating Drug Delivery Systems: Recent Advances, Controlled Release Strategies, and Future Perspectives

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ABSTRACT

Background: The oral route is the most prevalent pathway for drug administration, yet its efficiency is frequently hindered by the highly variable nature of gastric emptying, which compromises the bioavailability of drugs with a narrow absorption window. Objectives: This review aims to examine the evolution of floating drug delivery systems (FDDS) as a primary gastroretentive strategy to prolong gastric residence time (GRT) and ensure a controlled release of therapeutic agents. Methodology of Literature Selection: A systematic search was conducted using high-impact databases including PubMed, Scopus, and Web of Science, focusing on peer-reviewed research and technological breakthroughs reported over the last 10–15 years. Key Technological Advances: Groundbreaking innovations such as 3D extrusion printing (printlets), hot-melt extrusion (HME), and the integration of nanoparticulate carriers (e.g., solid lipid nanoparticles) are highlighted for their ability to create high-precision, low-density matrices. Major Findings: FDDS effectively maintain a bulk density lower than gastric fluid (~1.004 g/cm³), allowing the dosage form to remain buoyant and resist the Migrating Myoelectric Complex (MMC). This review uniquely explores the role of stimuli-responsive smart polymers in providing environmental control and the application of AI-based formulation strategies via Design of Experiments (DoE) to predict buoyancy kinetics and dissolution profiles. Limitations: The primary constraints identified include the requirement for adequate gastric fluid levels (~250 ml) for buoyancy and the unsuitability of these systems for medications that cause mucosal irritation, such as NSAIDs. Future Perspectives: The field is transitioning towards personalised medicine and biomimetic platforms, such as yeast-derived microcapsules, for targeted delivery to distal lesions beyond the gastrointestinal tract.

Keywords : Oral floating drug delivery systems, gastroretentive drug delivery, controlled release, smart polymers, buoyancy mechanisms, recent advances.

INTRODUCTION

The **oral route** remains the most prevalent and preferred pathway for drug administration due to its non-invasiveness, cost-effectiveness, and high levels of **patient compliance**[1]. However, the development of efficient oral delivery systems is frequently hindered by the **harsh and complex microenvironment** of the gastrointestinal tract (GIT). Conventional oral dosage forms face significant physiological constraints, primarily the **highly variable and unpredictable nature of gastric emptying**, which can range from mere minutes to over 12 hours depending on the subject's state and meal intake[2]. This variability often leads to non-uniform absorption profiles and makes the **bioavailability** of many drugs unpredictable[3].

Unmet Clinical Need and Conventional Limitations

A major limitation of traditional controlled-release systems is their inability to remain localized within the desired absorption regions of the GIT[4]. Many therapeutic agents possess a **"narrow absorption window" (NAW)**, meaning they are preferentially absorbed in the stomach or the proximal part of the small intestine[5]. Once a conventional dosage form passes this specific site, any remaining drug remains unabsorbed, leading to **incomplete drug release** and diminished therapeutic efficacy[6]. Furthermore, single-unit conventional forms often suffer from an **"all-or-nothing" emptying process**, which increases the risk of **dose dumping** and inter-subject variability[7].

There is also a critical need to address drugs that are **poorly soluble in the high-pH environment** of the lower intestine or those that are unstable and prone to **degradation in colonic fluids**[8]. To achieve required therapeutic effects, drugs with **short half-lives** currently require frequent recurrent dosing, which often results in fluctuations in plasma drug concentration and reduced patient adherence[9].

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Rationale for Oral Floating Drug Delivery Systems (FDDS)

To overcome these adversities, **gastroretentive drug delivery systems (GRDDS)** have been engineered to turn the stomach into a **"depot"** for sustained release[10]. Among various strategies—such as mucoadhesion, expansion, and high-density systems—**floating drug delivery systems (FDDS)** continue to attract intense research interest because they do not interfere with the natural motility of the GIT[11].

FDDS are designed with a **bulk density lower than gastric fluids (~1.004 g/cm³)**, allowing them to remain buoyant on the surface of the gastric contents for a prolonged period[12]. This buoyancy enables the system to resist the **Migrating Myoelectric Complex (MMC)**, specifically the Phase III **"housekeeper wave"** contractions that typically clear undigested material from the stomach[13]. By extending the **gastric residence time (GRT)**, FDDS ensure a continuous and controlled drug supply to the absorption window, significantly enhancing bioavailability and reducing the fluctuations in plasma drug levels[14].

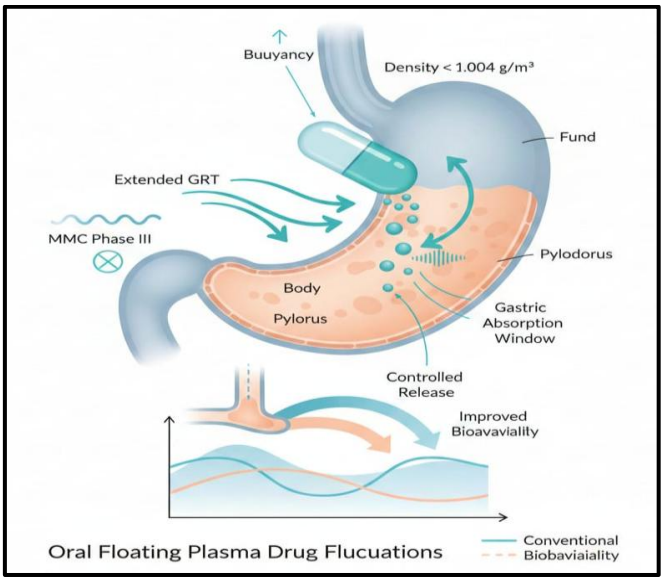

Fig.no.1: Rationale for Oral Floating Drug Delivery Systems (FDDS).

Objectives and Novelty of the Review

While earlier reviews have established the basic physical principles of buoyancy and traditional polymer use, this present review aims to provide a comprehensive update on the **recent technological leaps** in the field[15]. The primary objective is to examine the evolution of FDDS from simple hydrodynamically balanced systems to sophisticated **controlled-release strategies** that utilize **smart polymers** and advanced manufacturing techniques[16].

The novelty of this review lies in its critical discussion of:

- **Innovative Manufacturing:** Specifically focusing on the integration of **3D extrusion printing (printlets)** and **Hot-Melt Extrusion (HME)** to create precise, foamed internal matrices that ensure immediate buoyancy without a lag time[17].
- **Smart Material Integration:** The use of **stimuli-responsive polymers** and nanoparticle-loaded systems to protect sensitive drugs and target specific gastric sites[18].
- **AI and Design Strategies:** Highlighting the shift toward **AI-based formulation strategies** and **Design of Experiments (DoE)** to predict floating kinetics and optimize drug release profiles[19].
- **Advanced Evaluation:** Discussing modern in vivo tracking tools like **gamma scintigraphy** and **MRI** as the current gold standards for assessing gastroretention[20].

By synthesizing findings from the most recent decade of research, this review distinguishes itself from previous literature by moving beyond formulation basics toward the future of **personalized pharmacotherapy** and biomimetic delivery platforms[21].

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Physiological Basis of Gastroretention and Controlled Drug Release

The success of **Oral Floating Drug Delivery Systems (FDDS)** is intrinsically linked to an intimate understanding of the human stomach's anatomy, its motility patterns, and the biochemical environment it presents[22]. These physiological factors dictate whether a buoyant dosage form will remain at its site of action or be prematurely emptied into the small intestine[23].

Anatomical Considerations

The stomach is a J-shaped organ situated between the oesophagus and the small intestine, functioning primarily as a reservoir and a digestion chamber[24].

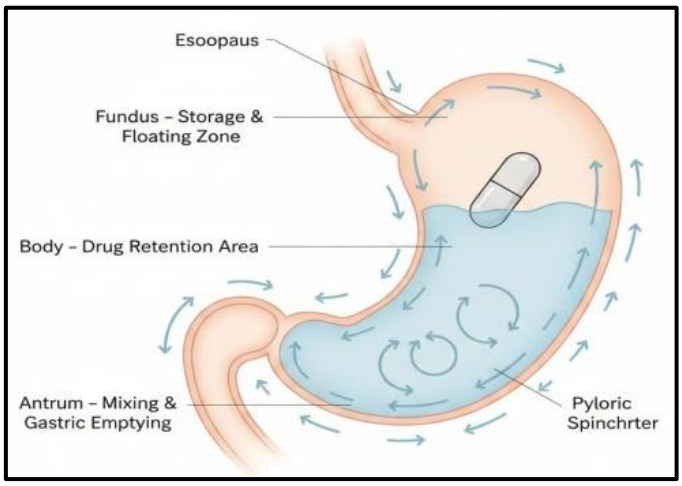

Fig.no.2: Anatomical Structure Of Stomach.

Anatomically, it is divided into three main regions: the **fundus**, the **body**, and the **antrum (or pylorus)**. The **proximal stomach** (fundus and body) serves as a storage site for ingested material, while the **distal region** (antrum) is the primary site for mixing motions and acts as a pump to facilitate **gastric emptying**[25]. Floating systems are designed to remain in the upper regions (fundus and body), effectively isolating them from the pyloric sphincter located in the antrum[26].

Motility Patterns and the Migrating Myoelectric Complex (MMC)

In the fasted state, gastric motility is governed by a cyclic electrical event known as the **Migrating Myoelectric Complex (MMC)**, which repeats every 90 to 120 minutes[27]. The complex consists of four distinct phases:

- **Phase I (Basal Phase):** Characterised by 40–60 minutes of relative inactivity with rare contractions.
- **Phase II (Pre-burst Phase):** Lasts 40–60 minutes with intermittent contractions that increase in frequency and intensity, eventually leading to the discharge of fluids and small particles.
- **Phase III (Burst Phase):** Known as the **"housekeeper wave,"** this 4–10 minute period consists of intense, regular contractions that sweep all undigested material out of the stomach and into the small intestine.
- **Phase IV:** A brief transition of 0–5 minutes occurring between Phase III and the start of the next cycle[28].

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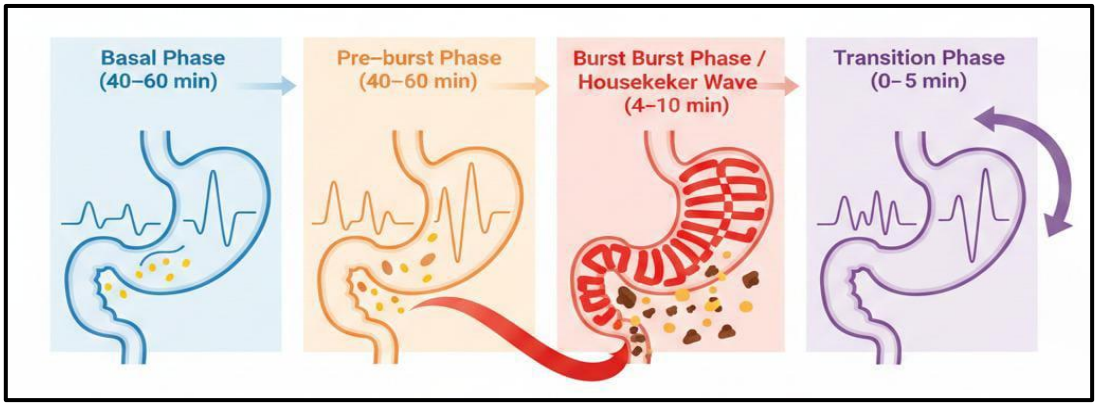

Fig.no.3: Phases Of Migrating Myoelectric Complex (MMC).

A critical correlation for FDDS is that these systems must either be large enough to resist the housekeeper waves or maintain sufficient **buoyancy** to stay floating above the contents being swept out[29].Non-floating units typically sink to the lower part of the stomach and are subjected to the propelling waves of the digestive phase, leading to faster emptying[30].

Fed versus Fasted Conditions

The ingestion of food fundamentally alters gastric dynamics from a fasted pattern to a **digestive motility pattern**[2]. In the **fed state**, the onset of the MMC is significantly delayed, resulting in a marked slowdown of the gastric emptying rate. The **caloric content** of a meal is a primary determinant of this delay; high-fat and high-protein meals can increase the **gastric residence time (GRT)** by four to 10 hours[4]. Furthermore, successive meals (frequency of feed) can prolong the GRT by over 400 minutes compared to a single meal due to the continuous suppression of the MMC. FDDS are most effective when administered in the fed state, as the presence of food provides the necessary medium for flotation and delays the housekeeper waves that would otherwise clear the device[6].

Gastric pH Variability

The pH of the stomach is highly variable, ranging from **1.0 to 3.5** in fasting conditions. Following a meal, the pH may rise transiently to ranges of **3.0 to 6.0**. This variability has a profound impact on the performance of **effervescent FDDS**, which rely on the reaction between gas-generating agents (like sodium bicarbonate) and the acidic gastric environment to produce CO_2[8]. If the pH rises too high or if there is insufficient gastric acid, the liberation of gas may be delayed, increasing the **floating lag time** and potentially allowing the dosage form to sink and be emptied. Conversely, controlled drug release from **smart polymers** can be tailored to respond to these pH shifts, ensuring the therapeutic agent is dissolved or released only when the system is securely buoyant in the acidic environment[10].

Correlation with Controlled Release Performance

The ultimate goal of correlating these physiological factors is to turn the stomach into a **"depot"** for sustained drug delivery. By extending the GRT through buoyancy, FDDS ensure that drugs with a **narrow absorption window** are released continuously at their optimal absorption site in the upper GIT[12]. This reduces the **"peak and valley" fluctuations** in plasma drug concentration often seen with conventional formulations, leading to improved bioavailability and reduced dosing frequency[14].

Fundamental Mechanisms Governing Buoyancy and Drug Release

The performance of **Floating Drug Delivery Systems (FDDS)** is governed by the intricate interplay between physical buoyancy and chemical kinetics. The primary requirement for flotation is the achievement of a **bulk density lower than that of gastric fluids (~1.004 g/cm³)**[16].

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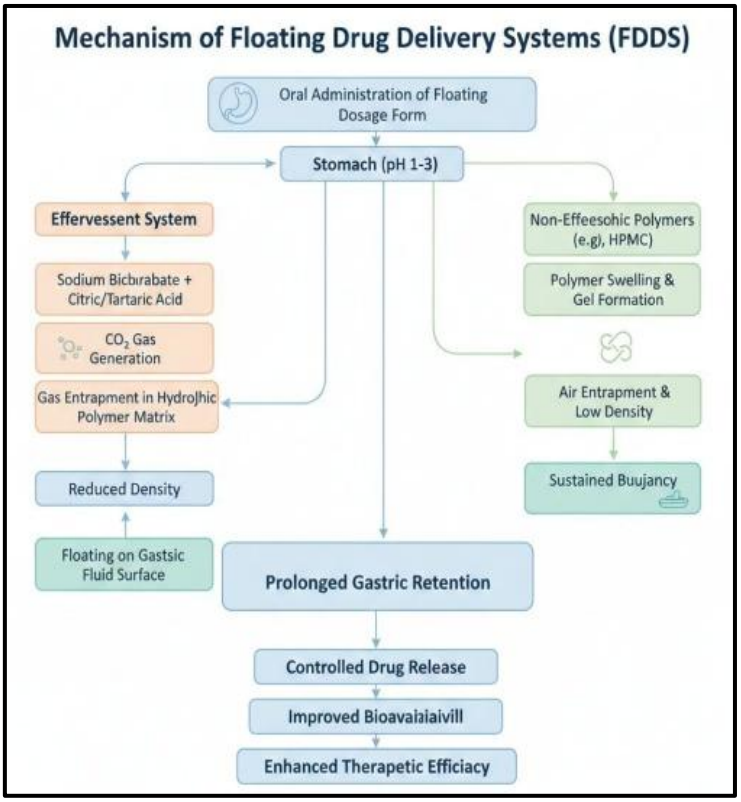

Fig.no.4: Mechanism Of Floating Drug Delivery Systems.

Density Reduction and Gas Generation

Density reduction is typically achieved through two main mechanisms. In **effervescent systems**, gas-generating agents such as **sodium bicarbonate and citric or tartaric acid** react with the acidic environment of the stomach to liberate **CO_2 gas**[18]. This gas becomes entrapped within the system's hydrocolloid matrix, creating an upward motion that maintains buoyancy. Alternatively, novel manufacturing techniques like **Hot-Melt Extrusion (HME)** use volatile liquids like ethanol to create **uniform vacuous regions** or air pockets within a polymer matrix through a liquid-vapor phase transition, ensuring immediate buoyancy without a lag time[20].

Swelling Behaviour and Matrix Formation

In **non-effervescent systems**, buoyancy is driven by the **hydration and swelling** of hydrophilic polymers. Upon contact with gastric fluid, the polymer chains (e.g., **HPMC**) imbibe water and expand to form a **thick gelatinous barrier** or colloidal gel[22]. This gel layer traps air within its structure, conferring buoyancy while simultaneously maintaining the **structural integrity** of the dosage form to prevent premature disintegration[24].

Controlled Drug Release Kinetics

The release of therapeutic agents from these matrices follows several mathematical models:

- **Diffusion-controlled:** Gastric fluid penetrates the gel barrier, dissolves the drug, and the solute moves out through the hydrated boundary.

- **Erosion-controlled:** In systems using erodible polymers, the outer gelatinous layer progressively wears away, releasing the drug at a rate determined by the polymer's dissolution[26].

- **Non-Fickian Transport:** Many modern FDDS exhibit **non-Fickian diffusion**, where drug release is a combined result of both diffusion and polymer rearrangement or relaxation. Factors such as **HPMC content** and **drug loading** significantly influence these kinetics, with drug loading primarily affecting initial release and polymer content controlling long-term sustained release[28].

Advanced Classification of Oral Floating Drug Delivery Systems

Modern research has expanded the classification of FDDS beyond classical tablets to include multi-unit and hybrid platforms that offer more predictable performance.

Effervescent and Volatile Systems

- **Gas-Generating Systems:** Matrix systems using carbonates that produce CO_2 bubbles trapped in a swollen hydrocolloid.

- **Volatile Liquid Containing Systems:** Features an **inflatable chamber** containing liquids like ether or cyclopentane that gasify at body temperature, causing the system to inflate and float[30].

Non-Effervescent High-Precision Systems

- **Hydrodynamically Balanced Systems (HBS):** These consist of drugs mixed with gel-forming hydrocolloids, often encapsulated in gelatin, which swell into a floating mass upon administration.

- **Hollow Microspheres (Microballoons):** Prepared using an **emulsion-solvent diffusion method**, these possess a central hollow cavity that allows them to remain buoyant for over 12 hours[1].

- **Floating Alginate Beads:** Freeze-dried calcium alginate beads create a porous, low-density system capable of sustained flotation[3].

Innovative Hybrid and Multi-Mechanistic Platforms

- **Raft-Forming Systems:** These form a **viscous cohesive gel (raft)** on the surface of gastric contents, acting as a physical barrier to prevent gastroesophageal reflux.

- **Expandable-Floating Hybrids:** Systems that utilize folding designs or shape-memory polymers to expand larger than the pyloric sphincter while maintaining buoyancy[5].

- **Multi-unit Floating-Bioadhesive Systems:** These combine the benefits of flotation with **mucoadhesion**, allowing the device to float above gastric contents while also adhering to the stomach wall to resist the **housekeeper wave** of the MMC[7].

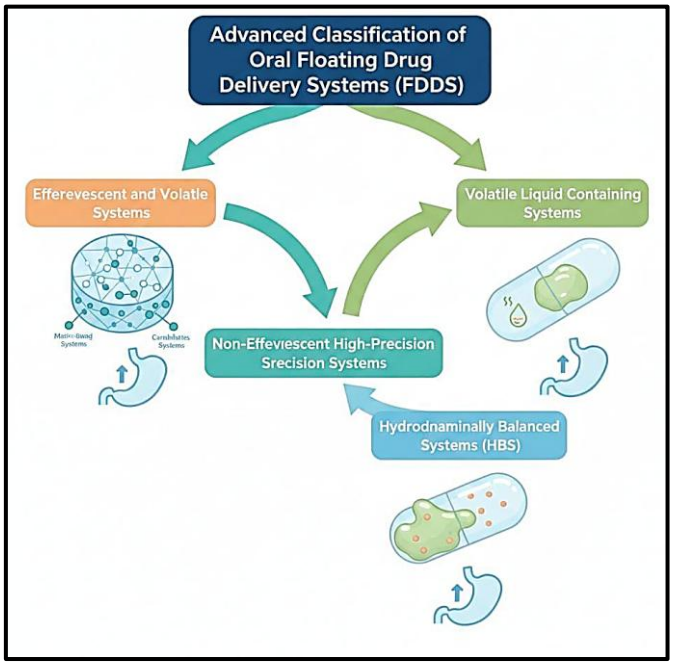

Fig.no.5: Advanced Classification of Oral Floating Drug Delivery Systems.

Role of Novel Polymers and Functional Excipients

The selection of polymers is the most critical factor in modulating the **buoyancy duration, mechanical strength, and release profile** of an FDDS[9].

Stimuli-Responsive "Smart" Polymers

Innovative "smart" polymers respond dynamically to physiological triggers. **Thermo-responsive polymers**, such as **poloxamers**, undergo a **sol-gel transition** at body temperature, enabling the formation of a floating gel depot *in situ*. **pH-sensitive polymers** (e.g., **Eudragit®**) can protect drugs from the acidic stomach environment or trigger release only at specific pH thresholds[11].

Bioadhesive and Natural Polymers

Bioadhesive polymers like **chitosan and Carbopol** are used to enhance the residence time by creating hydrogen or electrostatic bonds with the mucosal lining[13]. Natural gums, including **xanthan gum, guar gum, locust bean gum, and psyllium husk**, are increasingly favoured for their biocompatibility, safety, and excellent swelling properties[15]. For example, **tara gum** has been shown to improve gastroretentive effects and extend floating time when combined with other hydrophilic excipients[15].

Hydrophilic Matrix Formers and Functional Excipients

HPMC (in various grades like K4M, K15M, and K100M) remains the gold standard for creating hydrophilic matrices due to its reproducible swelling behaviour[17].Functional excipients like **stearic acid** are used in HME as processing aids to maintain crystalline stability, while **citric acid** acts as a porogen and gas-forming activator in effervescent formulations[19].

Recent Technological Advances in Floating Drug Delivery Systems

State-of-the-art developments in **Floating Drug Delivery Systems (FDDS)** have moved beyond simple matrix tablets toward high-precision engineered platforms. A major breakthrough involves the application of **Hot-Melt Extrusion (HME)** to create **uniformly foamed strands**[21]. In this process, a liquid foaming agent like ethanol is injected into the polymer melt, undergoing a **liquid-vapor phase transition** upon exiting the die due to a sudden decrease in external pressure[23]. This creates a matrix with uniform **vacuous regions/air pockets**, resulting in pellets with **zero floating lag time** and sustained buoyancy for over 24 hours[25].

Another revolutionary advance is **3D extrusion-printing technology**, used to fabricate personalised gastroretentive "printlets". By adjusting the **internal infilling density** (e.g., 30% or 50%), researchers can precisely control the tablet's porosity to ensure immediate buoyancy while tailoring the drug release profile to the patient's needs[27]. Furthermore, the development of **hollow microspheres (microballoons)** using the **emulsion-solvent diffusion method** continues to be refined[29]. In this technique, the evaporation of dichloromethane from dispersed polymer droplets generates an internal cavity, allowing the units to float on acidic media for more than 12 hours[1]. Recent research has also explored **nanostructured floating carriers**, such as incorporating **solid lipid nanoparticles (SLNs)** or polymeric nanoparticles into floating matrices to enhance the solubility of poorly water-soluble drugs and protect sensitive molecules from enzymatic degradation. Finally, **osmotically controlled floating systems** have been developed, featuring inflatable supports and collapsible bags that use osmotic pressure to pump the drug through a delivery orifice at a programmed rate[5].

Integration of Floating Systems with Controlled Release Approaches

Modern FDDS are increasingly integrated with sophisticated **release modulation strategies** to achieve complex pharmacokinetic profiles[7]. **Bilayer and multilayer tablets** are frequently employed, where one layer provides an **immediate-release loading dose** while the other acts as a **buoyant sustained-release reservoir**. For drugs requiring **chronotherapeutic delivery**, such as treating nocturnal acid breakthrough, floating systems are combined with **pulsatile release mechanisms**. These formulations use a swellable or erodible outer polymeric coating that creates a **programmable lag time** before the drug is released in a rapid pulse[3].

Innovations also include **compression-coated floating tablets**, such as zein-based systems, where the coating layer provides both buoyancy and tunable release characteristics[22]. Some researchers have developed **hybrid matrices** using a combination of swellable hydrocolloids (like HPMC) and erodible polymers; as the barrier layer erodes, it progressively exposes more drug, effectively achieving **zero-order release kinetics**[11]. Additionally, **site-specific delivery** is enhanced through the integration of **bioadhesive agents** into floating units, creating dual-action platforms that float above the gastric contents while also adhering to the mucosal wall to resist the **"housekeeper wave"** of the MMC[9].

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Advanced In Vitro and In Vivo Evaluation Techniques

The evaluation of FDDS has evolved from basic tests to highly **physiologically relevant models**[2]. While the **USP Dissolution Apparatus II** is standard, researchers have introduced **modified paddle methods** where the blades are positioned at the surface of the medium to more accurately simulate the conditions of a floating dosage form[15]. A critical parameter is the **floating force kinetics**, measured using a **resultant-weight apparatus** that continuously monitors the total vertical force (F) required to keep a submerged object buoyant over time[20].

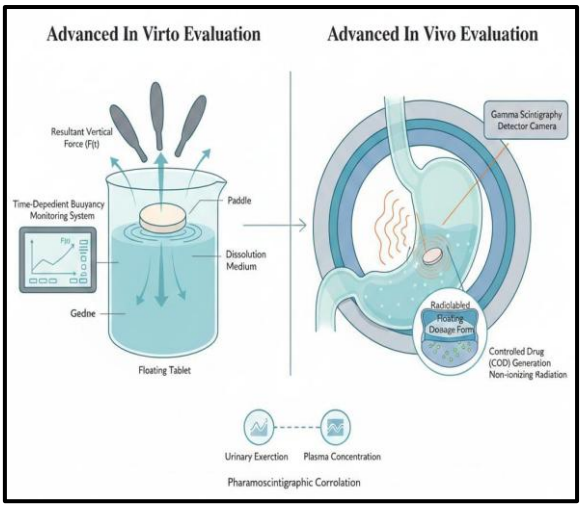

Fig.no.6: Advanced In Vitro and In Vivo Evaluation Techniques For Floating Drug Delivery Systems (FDDS).

For **in vivo assessment**, **Gamma Scintigraphy** remains the "gold standard". This non-invasive technique involves labelling the dosage form with a radionuclide (e.g., **Technetium-99m**) to track its precise position and transit through the GIT in real-time[22]. **Magnetic Resonance Imaging (MRI)** is also emerging as a powerful tool to observe the internal **hydration, swelling behaviour, and CO_2 generation** within the stomach without exposing subjects to ionising radiation[27]. Furthermore, **pharmacoscientigraphic studies** are now used to correlate the physical location of the buoyant unit with direct **urinary excretion or plasma concentration data**, providing a comprehensive view of how buoyancy improves bioavailability[11].

Computational Modelling, Simulation, and AI-Assisted Design

The application of **mathematical modelling** and **Artificial Intelligence (AI)** is significantly accelerating the development of FDDS[1]. Researchers utilize **Design of Experiments (DoE)** models, such as the **Plackett-Burman or Factorial designs**, to systematically evaluate how independent variables—like **screw speed, feed rate, and polymer ratios**—affect floating strength and drug dissolution[30]. **Response Surface Methodology (RSM)** is then used to map these interactions, allowing for the **tailoring of release profiles** by predicting the exact concentration of HPMC or gas-generating agents needed to meet a target profile[26].

AI tools and **regression analysis** are being deployed to forecast **buoyancy kinetics**, particularly for HME-processed pellets where the degree of foaming is dependent on die temperature and injection rates[21]. By inputting formulation parameters into these models, scientists can predict the **swelling index and floating duration** with high accuracy (R^2 values > 0.9), reducing the need for extensive trial-and-error laboratory work[25]. This shift toward **in silico optimisation** not only enhances the reproducibility of FDDS but also supports the transition toward **personalised medicine**, where dosage forms are digitally designed to match an individual's specific gastric motility patterns[6].

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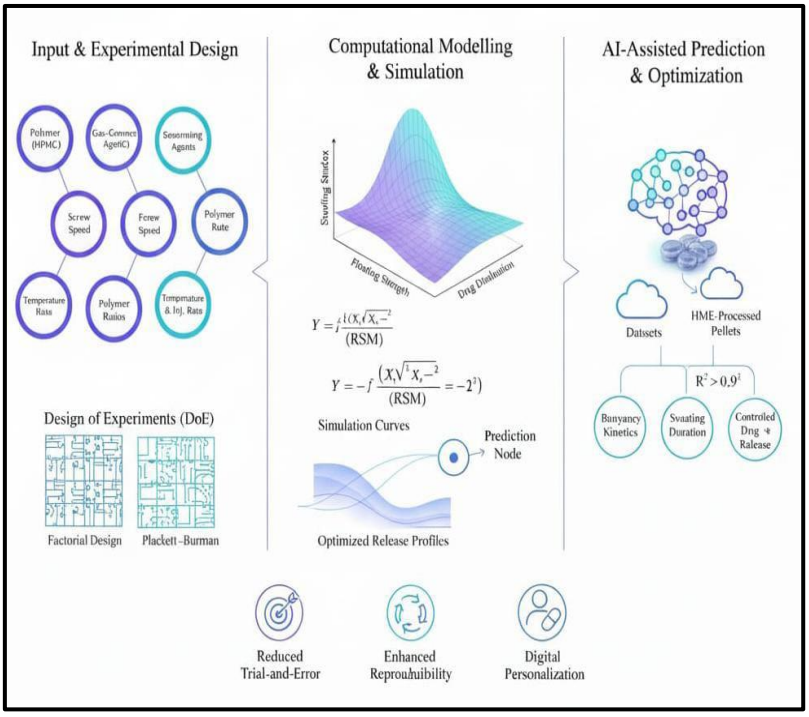

Fig.no.7: Computational Modelling, Simulation, and AI-Assisted Design.

Therapeutic Applications and Clinical Relevance

Floating Drug Delivery Systems (FDDS) provide a robust platform for improving the pharmacotherapy of various disease states by turning the stomach into a controlled-release reservoir[8]. These systems are particularly clinically relevant for therapeutic agents that act **locally in the stomach** or those possessing a **narrow absorption window (NAW)** in the upper gastrointestinal tract (GIT)[9].

- **Antibiotics and Gastric Infections:** FDDS are widely utilized to treat **Helicobacter pylori** infections associated with peptic ulcers[21]. By extending the contact time with the gastric mucosa, antibiotics like **clarithromycin, amoxicillin, and metronidazole** can penetrate the sub-mucosal tissues more effectively to eradicate deeply buried bacteria[15]. Recent evidence suggests that floating in-situ gelling systems can reduce the required dose of clarithromycin by ten times while maintaining therapeutic efficacy[4].

- **Anti-ulcer Agents:** Drugs such as **ranitidine HCl, famotidine, and lansoprazole** benefit from prolonged gastric residence because they work directly on the parietal cells or provide a protective coating to the stomach lining[8]. Marketed products like **Liquid Gaviscon** utilize a raft-forming mechanism to create a physical barrier against gastroesophageal reflux[17].

- **Antihypertensives:** Medications with site-specific absorption, such as **furosemide and diltiazem**, show significantly improved bioavailability when formulated as buoyant units[27]. For instance, the **Area Under the Curve (AUC)** for floating furosemide tablets has been reported to be 1.8 times higher than conventional formulations[2].

- **Antidiabetic Drugs:Metformin HCl** is a primary candidate for FDDS due to its restricted absorption in the upper segments of the small intestine[1]. Gastroretentive systems ensure that metformin is delivered steadily to its optimal absorption site, preventing drug loss in the lower GIT[8].

- **Parkinson's Disease:** The clinical management of Parkinson's using **Levodopa and Benserazide** is vastly improved via floating capsules like **Madopar HBS**, which reduce the "on-off" fluctuations in plasma levels by providing a continuous supply to the NAW in the duodenum[11].

Regulatory Considerations and Industrial Scale-Up Challenges

The transition of FDDS from laboratory prototypes to **commercial pharmaceutical products** involves complex regulatory and manufacturing hurdles. Despite their potential, the clinical translation of these systems remains slower than that of conventional forms[13].

- **Manufacturing and Scale-Up:** Industrial production often faces challenges in maintaining **consistent buoyancy** across large batches[24]. Advanced technologies like **Hot-Melt Extrusion (HME)** are increasingly preferred for scale-up because they offer a continuous manufacturing process with highly stable torque and die pressure, which serve as excellent indicators for scalability[22].

- **Quality Control and Stability:** Regulatory bodies require stringent proof of **in vitro-in vivo correlation (IVIVC)** regarding floating lag time and duration[3]. Polymer selection is critical for high-dose formulations, as the material must provide sufficient compressibility while maintaining a bulk density below **1.004 g/cm³**. Stability concerns also arise for drugs that are sensitive to the **highly acidic environment (pH 1.2)** of the stomach during prolonged retention[5].

- **Regulatory Frameworks:** Currently, there are gaps in standardized regulatory guidelines specifically tailored for **gastroretentive systems**[11]. In India, the **Central Drugs Standard Control Organization (CDSCO)** governs the introduction of these novel forms, requiring extensive safety and efficacy data to justify their use over conventional alternatives[12].

- **Cost and R&D Investment:** The requirement for specialized excipients, such as **buoyant hydrophilic polymers** and gas-generating agents, increases the overall development cost and time compared to traditional immediate-release tablets[13].

Limitations, Safety Concerns, and Clinical Translation Barriers

While FDDS offer significant advantages, they possess inherent **physiological and technical limitations** that can impede their reliability[14].

- **Fluid Requirement:** A critical limitation is that floating systems require a **sufficient high level of fluid** (approximately 200–250 ml of water) in the stomach to function effectively. Buoyancy cannot be guaranteed if the stomach is empty, as there is no medium on which the dosage form can float[15].

- **Biological Variability:** Gastric motility is highly unpredictable and varies based on **age, diet, posture, and disease state** (e.g., gastroparesis). The **Migrating Myoelectric Complex (MMC)**, particularly the Phase III **"housekeeper wave,"** can sweep single-unit floating systems out of the stomach prematurely if they are not large enough or administered in a fed state[16].

- **Risk of Dose Dumping:** If a single-unit floating system loses its buoyancy or its matrix integrity is compromised, there is a risk of releasing the entire dose at once, leading to **potential toxicity**. This risk is significantly reduced in **multi-unit systems** like microspheres or beads[17].

- **Mucosal Irritation:** Some drugs, specifically **NSAIDs and Aspirin**, are inappropriate for FDDS because prolonged contact with the gastric mucosa can cause **gastric lesions or irritation**[18].

- **Posture Dependency:** The effectiveness of floating systems can vary between the **supine and upright ambulatory states**. In a supine position, floating units may be emptied faster as they move away from the pylorus[19].

Future Perspectives and Emerging Research Directions

The future of oral controlled release is moving toward **precision medicine** and the integration of sophisticated engineering technologies.

- **3D Printing and Personalisation:** The use of **3D extrusion printing** allows for the creation of "printlets" with customized internal geometries and porosity (e.g., 30–50% infilling). This technology enables healthcare providers to tailor the dose and release kinetics to match the **individual gastric motility patterns** of a specific patient[20].

- **AI-Guided Formulation:** Researchers are increasingly adopting **Artificial Intelligence (AI)** and **Design of Experiments (DoE)** to predict buoyancy kinetics and optimize polymer ratios. AI can forecast the **swelling index and floating lag time**, reducing the need for extensive trial-and-error in formulation development[21].

- **Biomimetic and "Trojan Horse" Strategies:** Innovative platforms like **yeast-derived microcapsules** are being explored for their ability to protect sensitive peptides (e.g., insulin) and facilitate absorption via **lymphatic transport**[23]. These systems can even target non-gastrointestinal diseases, such as **cardiovascular plaques and brain tumors**, after oral administration[22].

- **Smart and Biodegradable Platforms:** The development of **stimuli-responsive polymers** that react to specific biomarkers or enzymatic triggers will provide more precise control over drug release[28]. Future GRDDS may also incorporate **biodegradable shape-memory devices** that expand in the stomach and safely disintegrate after the drug has been released, eliminating the risk of gastric obstruction[29].

- **Digital Health Integration:** There is a growing interest in combining FDDS with **smart drug delivery technologies**, such as ingestible sensors that monitor the dosage form's position and release profile in real-time, providing feedback to clinicians and patients[30].

Conclusion

- **Floating drug delivery systems (FDDS)** represent a transformative advancement in oral therapeutics, successfully overcoming physiological barriers such as short gastric residence time and unpredictable emptying. By maintaining a **bulk density lower than 1.004 g/cm³**, these systems stay buoyant on gastric contents, effectively bypassing the **Migrating Myoelectric Complex's "housekeeper wave"**.

- Technological breakthroughs like **Hot-Melt Extrusion (HME)** and **3D printing** have further refined these platforms, ensuring immediate flotation and highly tailorable drug release profiles. This results in significantly **enhanced bioavailability** for drugs with narrow absorption windows and provides sustained therapeutic levels that improve patient compliance. While challenges such zas biological variability and the necessity of adequate gastric fluid remain, the continued integration of **AI-assisted design** and personalised medicine approaches offers a promising roadmap for future clinical applications.

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