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Floating Drug Delivery Systems: An Emerging Drug Delivery System

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ABSTRACT

By prolonging stomach residence duration and regulating drug release, floating drug delivery systems improve drug bioavailability and patient compliance. There have been various attempts in recent decades to overcome limitations such as short stomach residency periods and unexpected gastric emptying timings. The chronological and research developments in floating systems are highlighted in this overview. Among the several techniques to gastro retentive medication delivery systems, floating drug administration is thought to be the most effective. The two most essential characteristics that play a vital role in enhancing the bioavailability of medications with an absorption window at the stomach are short gastric residence times (GRT) and variable gastric emptying times (GET). The floating medication delivery technique is a low-density system that can be effervescent or non-effervescent and has enough buoyancy to flow over gastric contents and stay buoyant in the stomach for an extended period of time without influencing the stomachic emptying rate. Tablets, granules, capsules, microspheres, microparticles, and other floating dosage forms are among the commercially available formulations. This paper provides a complete overview of various floating medication delivery systems and their current condition.

1.1 INTRODUCTION [1-11]

Some of the distinctive aspects of oral route drug delivery have contributed to its popularity, including the reasonable cost of therapy, convenience of administration, improved patient compliance and acceptance, and a wide range of dosage forms accessible. Despite its versatility, the oral route of drug delivery has a number of difficulties when it comes to delivering the medicine to the upper intestine. It is said that the medicine taken orally takes 1 to 2 hours to go from the stomach to the intestine, and that it stays in the intestine for 14 to 24 hours. As a result of the short residence duration, medicines, particularly those with absorption windows in the stomach, suffer substantial bioavailability concerns.

According to the published literature, there has been an increasing interest in the development of oral controlled release dosage forms that can administer the medicine at a predetermined rate for a long time. Floating drug delivery systems (FDDS) are one of numerous methods that are expected to be employed to extend gastric residence periods (GRT). There are a variety of medication compounds that may benefit from longer GI transit times or stomach residency times, and as a result, bioavailability and therapeutic efficacy may improve, leading to a decrease in dosage frequency and improved patient compliance.

1.2 BASIC PHYSIOLOGY AND PROBLEMS [12,13]

The process of stomach emptying happens in both fasted and fed stages; however, the patterns of motility in the two states differ significantly. An interdigestive series of electrical events occurs during the fasting state, cycling through the stomach and intestine every 2 to 3 hours. The interdigestive myoelectric cycle, also known as the migrating myoelectric cycle (MMC), is divided into four parts, as depicted in Figure 1. Since the beginning of MMC is delayed, the stomach emptying rate is slowed in the fed condition. Most medications have a relatively short stomach transit time. Changes in stomach emptying caused by characteristics such as age, race, sex, and disease states can worsen these issues, as they can have a significant impact on the release of a drug from the delivery mechanism. As a result, a controlled release product with an extended gastric residence and a medication release profile that is independent of patient-related variables is desirable.

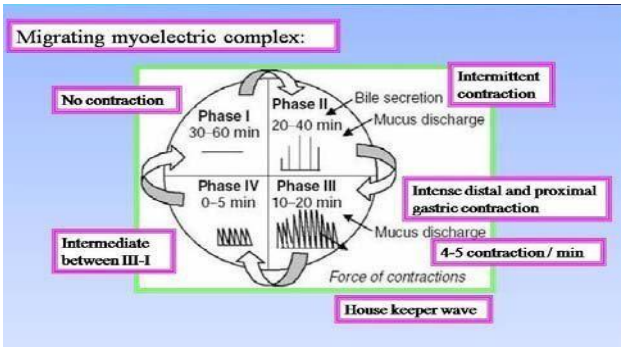

Figure 1:Schematic Presentation Of MMC [1]

1.3 APPROACHES TO GASTRIC RETENTION [12]

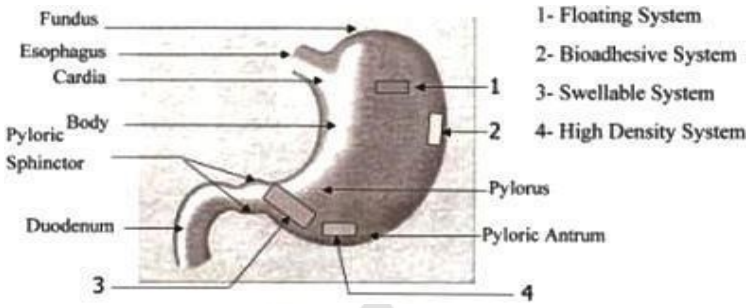

Figure 2: Various Approaches to Gastroretentive system to ensure no passage from gastric sphincter [1]

Various techniques have been created to improve the GRT of dosage forms using a variety of principles, as shown in Fig. 2. The notion of gastric retention was used to classify these systems.

- Floating drug delivery systems (FDDS): These devices float over the gastric contents due to their low density.
- Bio adhesive systems: They bond to the stomach mucosa, allowing for the system's localised retention.
- Swelling and expanding systems: These systems absorb water and grow in size as a result.
- High-density systems: They settle to the folds of the stomach, allowing them to stay in the stomach for longer periods of time.

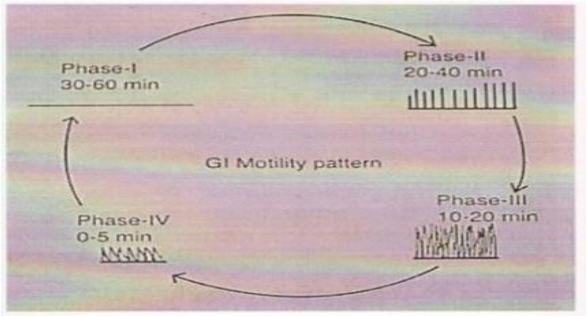

Figure 3: Gastrointestinal motility pattern [27]

1.4 TYPES OF FDDS [14,15]

FDDS can be classified into two types based on their buoyancy mechanisms:

- System of effervescence
- System with no effervescence

Drug delivery method for effervescent floating:

A floating chamber, which can be filled with vacuum, air, or inert gas, can be used to make a medication delivery system float in the stomach. Volatilization of an organic solvent or an effervescent reaction between organic acids and bicarbonate salts can both be used to bring gas into the floating chamber.

- The volatile liquid containing system: This system can contain volatile liquids such as ether, cyclopentane, and others.

- The gas generating system: This system mostly uses agents that release carbon dioxide after a chemical reaction. Sodium bicarbonate, citric acid, tartaric acid, chitosan, and other agents are commonly used for this.

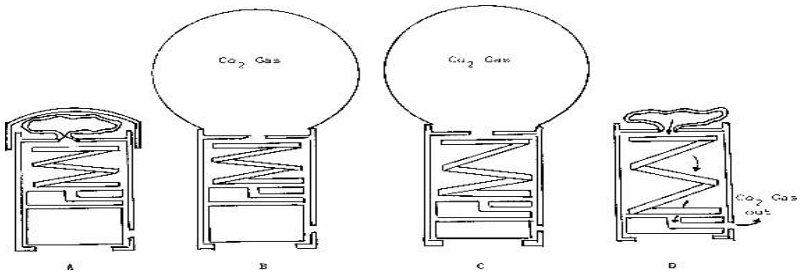

Figure 4: Mechanism of Effervescent systems [27]

Drug delivery method for Non-Effervescent System:

This system is mostly made up of low-density polymers that increase the dosage form's effective surface area and allow it to float for longer periods of time. This technique can use gel-forming or very swellable polysaccharides, kind hydrocolloids, matrix-forming materials like polycarbonate, polyacrylate, and polystyrene, and bio-adhesive materials like chitosan and Carbopol.

1.5 Mechanism of floating systems: [16,17]

Floating drug delivery systems (FDDS) have a lower bulk density than gastric fluids, therefore they float in the stomach for longer periods of time without altering the gastric emptying rate. The medicine is released slowly and at the correct rate from the system while it is floating on the gastric contents (Figure 1). The residual system in the stomach is emptied once the medicine is released. As a result, GRT is raised, and variations in plasma drug concentrations are better controlled. A minimum level of floating force (F) is also required to keep the dosage form stably buoyant on the surface of the meal, in addition to a minimum stomach content required to allow proper realization of the buoyancy retention principle. A unique apparatus for determining resultant weight has been disclosed in the literature to assess the floating force dynamics. The equipment works by continually measuring the force necessary to keep the submerged object submerged (as a function of time). If F is on the positive side, the object floats better. This device aids in the optimization of FDDS in terms of the stability and endurance of the floating forces produced, avoiding the disadvantages of unforeseen intra-gastric buoyancy capability fluctuations.

$$F = F_{buoyancy} - F_{gravity} = (Df - Ds)\, gV$$

Where F denotes total vertical force, Df denotes fluid density, Ds denotes object density, V denotes volume, and g denotes gravity acceleration.

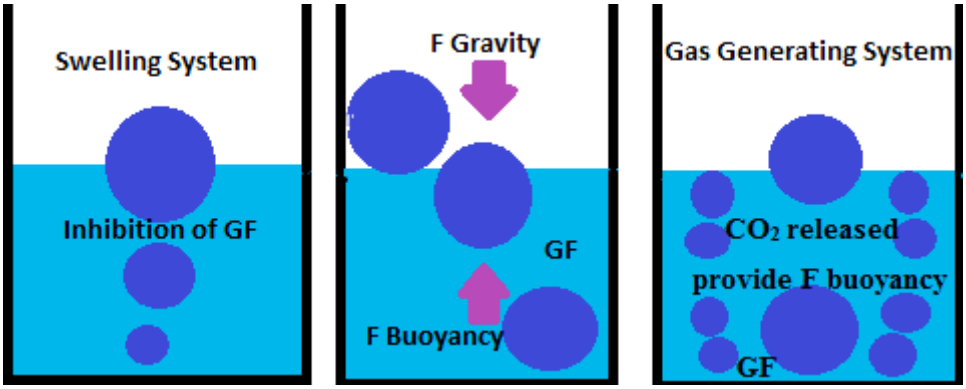

Figure 5: Mechanism of floating drug delivery system [16]

1.6 LIST OF DRUGS EXPLORED FOR VARIOUS FLOATING DOSAGE FORMS [18]

- Microspheres Tablets/Pills: Chlorpheniramine maleate, Aspirin, griseofulvin, Acetaminophen, p-nitroaniline, Acetylsalicylic acid, Ibuprofen, Amoxicillin trihydrate, Terfenadine, Ampicillin, Tranilast, Atenolol, Theophylline, Captopril, Isosorbide di nitrate.
- P-Aminobenzoic acid, Cinnarizine, Piretanide, Prednisolone, Quinidine gluconate are examples of films.
- Cinnarizine, Diclofenac sodium, Diltiazem, Indomethacin, Fluorouracil, Prednisolone, Isosorbide mononitrate, and Isosorbide dinitrate are examples of granules.
- Riboflavin, phosphate, Sotalol, and Theophylline are powders.
- Capsules: Verapamil HCl, Chlordiazepoxide HCl, Diazepam, Furosemide, Ldopa, and Benserazide Misoprostol, Propranolol HCl, Ursodeoxycholic acid, Nicardipine

1.7 Drug Candidates Suitable for FDDS [19-21]

- Drugs have a small absorption window in the GI tract (e.g., L-DOPA, paminobenzoic acid, furosemide, riboflavin).
- Drugs that have a local effect on the stomach (e.g., misoprostol, antacids).
- Drugs that are unstable in a colonic or intestinal environment (e.g., captopril, ranitidine HCl, metronidazole).
- Drugs that disrupt the natural microorganisms in the colon (e.g., antibiotics used for the eradication of Helicobacter pylori, such as tetracycline, clarithromycin, amoxicillin).

- Drugs with a limited solubility at high pH levels (e.g., diazepam, chlordiazepoxide, verapamil).

ADVANTAGES OF FDDS [22]

- Even at the alkaline pH of the intestine, floating dosage forms such as tablets or capsules will stay in the fluid for a long time.
- FDDS are beneficial for medications that have a local action in the stomach, such as antacids.
- FDDS dosage forms are beneficial in cases of diarrhea and vigorous intestinal movement because they preserve the medicine in a floating state in the stomach, allowing for a greater response.
- Because acidic substances, such as aspirin, irritate the stomach wall when they come into touch with it, HBS/FDDS formulations may be beneficial for the administration of aspirin and other similar medications.
- The FDDS is beneficial for medications that are absorbed through the stomach, such as ferrous salts and antacids.

Limitations/Disadvantages: [23-25]

- For drug delivery to float and act well, these systems require a high amount of fluid in the stomach-coat.
- ii. Incompatible with medications that have a problem with solubility or stability in the GI tract.
- Drugs like Nifedipine, which is well absorbed throughout the GIT and undergoes first-pass metabolism, may not be the best choice.
- Drugs that irritate the stomach mucosa are also undesirable or inappropriate.
- Drugs that are unstable in the stomach's acidic environment are not ideal candidates for incorporation into the systems.
- A full glass of water should be used to provide the dose form (200-250 ml).
- These systems do not provide considerable benefits over traditional drug dose forms that are absorbed throughout the gastrointestinal tract.

COMPONENTS OF FDDS: [26-30]

- Hydrocolloids- Hydrocolloids are synthetic, anionic or non-ionic slightly modified cellulose derivatives such as acacia, pectin, agar, gelatin, bentonite, and others that are utilized in the formulation of FDDS.

- Polymers employed in the development of floating drug delivery include HPMC K4M, HPMC K15M, HPMC K100M, polyethylene glycol, polycarbonate, sodium alginate, PVA, PVP, eudragit, Carbopol, methyl methacrylate, and acrylic polymers.

- In the manufacture of effervescent based floating formulations, effervescent agents such as sodium bicarbonate, citric acid, tartaric acid, nitroglycerin, and Di-sodium glycine carbonate are employed.

- Fatty materials with a specific gravity less than one have a lower hydrophilic characteristic and, as a result, have a higher buoyancy. Beeswax, fatty acids, long-chain alcohol, and mineral oil, for example.

- Excipients such as lactose and mannitol can be used to change the formulation's release rate.

- Release rate retardants reduce the solubility of medications, which slows their release rate. For example, dicalcium phosphate, talc, and magnesium stearate.

- Buoyancy-increasing agent—Materials such as ethyl cellulose, which has a bulk density of less than one, can be employed to make the formulation more buoyant. It could be present in up to 80% of the weight.

- Low-density materials are utilized to reduce the weight of the formulation in order for it to float, such as polypropylene foam powder.

- Miscellaneous — Preservatives, stabilizers, lubricants, binders, and other adjuvants can be employed in the formulation as needed.

Factors affecting Floating Drug Delivery System [31,32]

- Density: The dosage form's density should be smaller than the contents of the stomach (1.004gm/ml).

- Size and Shape: Dosage form units with a diameter of more than 7.5 mm had a higher GRT than those with a diameter of 9.9 mm, according to studies. When compared to other shapes, the dosage form with a shape tetrahedron and ring shape devises with a flexural

modulus of 48 and 22.5 kilo-pond per square inch (KSI) have greater GIT retention for 90 to 100 percent retention at 24 hours.

- Fed or Unfed: GI motility is characterized by periods of high motor activity, or migrating myoelectric complexes (MMC), which occur every 1.5 to 2 hours when fasting. The MMC removes undigested material from the stomach, so if the formulation is given at the same time as the MMC, the unit's GRT should be quite brief. MMC is delayed in the fed condition, and GRT is significantly longer.

- Meal Nature: Feeding indigestible polymers of fatty acid salts to the stomach can cause the motility pattern to transition to a fed state, slowing gastric emptying and prolonging medication release.

- Caloric Content: A high-protein meal can enhance GRT by 4 to 10 hours.

Evaluation Parameters: [33-40]

Particle size and shape: play a significant role in regulating medication solubility and consequently bioavailability. Sieve analysis (Jayant, Mumbai), Air elutriation (Bahco TM) analysis, Photo analysis, Optical microscope (Olympus, India, Pvt. Ltd), Electro resistance counting methods (Coulter counter), Sedimentation techniques, Laser diffraction methods, ultrasound attenuation spectroscopy, Air Pollution Emissions Measurements, and other methods were used to determine the particle size of the formulation.

Floating Properties: Using a continuous floating monitoring system and a statistical experimental methodology, the effect of formulation variables on the floating properties of a gastric floating medication delivery system was studied.

Surface Topography: The surface topography and structures were measured using a scanning electron microscope (SEM, JEOL JSM – 6701 F, Japan), a contact angle meter, Atomic Force Microscopy (AFM), and a contact profilometer.

Moisture Control Determination: The water content is rarely of relevance in and of itself. Rather, it determines if a product designed for commerce and manufacturing possesses common characteristics such as

- Storability
- In the case of powders, agglomeration
- Stability of microbes

- Viscosity and flow characteristics
- Concentration or purity of the dry substance
- Commercial quality (meets quality agreements)

Thus, Karl Fisher titration, vacuum drying, Thermo gravimetric methods, Air oven method, Moisture Meters, freeze drying, and physical methods were used to determine the moisture content of the manufactured formulations.

Swelling Studies: Swelling experiments were carried out to determine the molecular characteristics of swollen polymers. Dissolution equipment, optical microscopy, and more sophisticated techniques such as H1NMRimaging, Confocal laser scanning microscopy (CLSM), Cryogenic scanning electron microscopy (Cryo-SEM), Light scattering imaging (LSI), and others were used to determine swelling. The swelling studies were calculated using the following formula utilizing the Dissolution apparatus (USP dissolution apparatus (usp24) lab India disso 2000).

Weight of wet formulation / Weight of formulations = Swelling ratio

Determination of moisture content: The percentage drug content indicates how much of the drug was included in the formulation. It should not go beyond the bounds established by conventional monographs. HPLC, HPTLC procedures, near infrared spectroscopy (NIRS), Micro titrimetric methods, Inductively Coupled Plasma Atomic Emission Spectrometer (ICPAES), and spectroscopic techniques were used to evaluate drug content (Elico Limited, Hyderabad).

Percentage entrapment efficiency: For assessing the phase distribution of medication in pre-pared formulations, percentage entrapment efficiency was shown to be reliable. Three methods were used to determine entrapment efficiency: micro dialysis, ultracentrifugation, and pressure. Filtration at the highest level.

In-vitro Release Studies: In vitro release tests (USP dissolving apparatus (usp-24) lab India disso 2000) were carried out to determine the amount of medication released during a specific time period. The Franz diffusion cell system and synthetic mem- brane, as well as several types of dissolving apparatus, were used in the release studies.

Powder X-ray Diffraction: The most common method for studying polycrystalline materials is X-ray powder diffraction (Philips analytical, model pw1710), which is well suited for

routine characterization of pharmaceutical solids. Radiation was used to irradiate the samples, which were then evaluated at temperatures ranging from 2 to 60 degrees Celsius. 30KV and 30mA were employed as the voltage and current, respectively.

Fourier Transforms Infrared Analysis: Fourier transform infrared spectroscopy (FT-IR, Shimadzu, Model-RT-IR-8300) is a technique for identifying organic, polymeric, and certain inorganic materials, as well as determining their functional groups. Measurements of pure drug, polymer, and drug-loaded polymer formulations were obtained using Fourier Transform Infrared Analysis (FT-IR). The pellets were made on a KBr-press at a hydraulic pressure of 150kg/cm2, and the spectra were scanned at room temperature over the wavenumber range of 3600 to 400 cm-1.

Differential Scanning Calorimeter (DSC): Water of hydration of pharmaceuticals is characterized by DSC (Shimadzu, Model-DSC-60/DSC-50/Mettler Toledo). Using a DSC equipment with an intercooler, thermo grammes of prepared preparations were acquired. The DSC temperature and enthalpy scales were calibrated using indium/zinc standards. Over a temperature range of 25° C to 65°C, the sample preparations were hermetically sealed in an aluminum pan and heated at a constant rate of 10°C/min. Purging nitrogen gas at a rate of 50ml/min was used to maintain the inert environment.

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS: [22]

Enhanced Bioavailability: In comparison to the administration of non-GRDF CR polymeric formulations, riboflavin CR-GRDF has a much higher bioavailability. There are various processes involved in medication absorption and transit in the gastrointestinal tract that function in concert to determine the degree of drug absorption.

Sustained Drug Delivery: Problems with gastric residence duration in the GIT have been reported with oral CR formulations. These issues can be solved by HBS systems, which can stay in the stomach for long periods of time and have a bulk density of 1, allowing them to float on top of the gastric contents. These systems are greater in size, and passage through the pyloric aperture is not permitted.

Site-specific Drug Delivery Systems: These methods are especially useful for medications that are absorbed primarily through the stomach or the proximal small intestine. The controlled, gradual distribution of the medicine to the stomach ensures enough local therapeutic levels while limiting the drug's systemic exposure. The drug's adverse effects in

the blood circulation are reduced as a result. Furthermore, a site guided delivery system's longer stomach availability may lower dose frequency. For instance, furosemide and riboflavin.

Absorption Enhancement: Drugs with low bioavailability due to site-specific absorption from the upper part of the GIT could be designed as floating drug delivery devices to increase absorption.

Minimized Adverse Activity at the Colon: The amount of medicine that enters the colon is reduced because the drug is retained in the HBS systems at the stomach. As a result, the drug's unwanted effects in the colon may be avoided. The reason for GRDF formulation for betalactamase antibiotics that are absorbed only from the small intestine and whose presence in the colon contributes to the development of microorganism resistance is based on this Pharmacodynamic feature.

Reduced Fluctuations of Drug Concentrations:

When opposed to immediate release dosage forms, continuous input of the drug after CRGRDF administration produces blood drug concentrations within a tighter range. As a result, pharmacological impact variations are reduced, and concentration-dependent adverse effects associated with peak concentrations can be avoided. This is particularly important for medications with a limited therapeutic index.

FUTURE PERSPECTIVE OF FDDS:[42]

Floating drug delivery is a promising method that has become an important part of future study. Drugs with low bioavailability due to limited absorption in the upper gastrointestinal system can be administered successfully using the floating delivery method. Several concerns related to the rational evolution of FDDS in the fasted and fed phases, however, are currently being considered. The FDDS decreases medication plasma level changes caused by delayed stomach emptying. The floating principle can also be applied to the development of anti-reflux formulations, which could be useful in the treatment of Parkinson's disease.

MARKETED FORMULATIONS OF FDDS

Table 1: Commercially available floating drug delivery system

Brand name	Delivery system	Drug	Company
Valrelease®	Floating capsule	Diazepam	Hoffmann-LaRoche
Madopar® HBS(Prolopa® HBS)	Floating, CR capsule	Benserazide andL-Dopa	Roche Products, USA
Liquid Gaviscon®	Effervescent Floating liquid alginate preparations	Al hydroxide, Mg Carbonate	GlaxoSmithKline, India
CifranOD ®	Gas-generating floatingform	Ciprofloxacin	Ranbaxy, India
Conviron®	The colloidal gel-formingFDDS	Ferrous sulfate	Ranbaxy, India
Topalkan®	Floating liquid alginate preparation	Al – Mg antacid	Pierre Fabre Drug, France
Cytotech®	Bilayer floating capsule	Misoprostol	Pharmacia, USA

Table 2: List of Patents on Floating Drug Delivery System [43-47]

Title	Patent Number	Date	Inventors
Gastric floating system	WO02/102415A1	27 Dec2002	Avachat MK., Dhamne AG.
Floating drug delivery composition	WO01/58424A1	16 Aug 2001	Watts PJ, Smith A, Bond JR and Lafferty WCI
Gastro retentive drug delivery system comprising an extruded hydratablepolymer	WO03/105812A1	24 Dec2003	Hassan M
Gastro-retentive drug delivery system	WO2014/014348 A1	23 Jan2014	Meijerink HJC, Changoer L, Blom W, Visser MR, Frijlink HW,Eissens AC
Gastroretentive drug formulation & delivery systems and their method of preparation using functionalized calcium carbonate	WO2014/057026 A1	17 Apr2014	Gerard DE., Schoelkopf J, Gane PA.C, Eberle VA, Alles R, Puchkov M and Huwyler J

CONCLUSION

Medication absorption in the gastrointestinal tract is a highly variable process, and lengthening the dosage form's gastric retention lengthens the time it takes for the drug to be absorbed. FDDS appears to be a promising method for gastric retention. Despite the numerous challenges that must be overcome in order to achieve prolonged gastric retention, a big number of companies are working to commercialise this technology.

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