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Review Article

Gastric Floating Drug Delivery Systems: A Promising Carriers for The Delivery of Controlled Release Drugs

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Abstract: Low density systems or adaptively coordinated systems that has enough buoyancy to float on over contents of the stomach for a significant length of time without noticeably decelerating the rate of gastric emptying are known as floating systems. To accomplish stomach retention, the principle process of flotation was specifically examined in this drug delivery system. It is advantageous to construct medications in an oral sustained release gastro-retentive dose form for those that are absorbed in the upper portions of the GIT. The development of dynamically controlled systems depends on the rate at which the stomach empties. The most recent FDDS advancements are strategies to reduce the variability that lengthens the drug delivery system's retention period to more than 12 hours. This paper also contains an overview of several contemporary in-vitro methods that demonstrate the correct. This review on floating drug delivery systems (FDDS) was written with the intention of gathering the most recent research with a particular focus on the main mechanism of flotation to induce stomach retention. The most recent changes in A detailed discussion of FDDS is provided, covering the physiological and formulation factors impacting stomach retention, design methods for single-unit and multiple-unit floating systems, and their classification and formulation characteristics. The techniques used in vitro, the in vivo tests used to gauge the effectiveness and use of floating systems, and the applications of these systems are all summarised in this paper. These systems are helpful for a number of issues that arise during the creation of a pharmaceutical dosage form.

Keywords: Gastro Retention Time, Carrier System, Floating Drug, Stomach Retention, Buoyancy Lag Time.

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1. INTRODUCTION

The oral route of intake of medicinal substances is the most conventional and effective method since it is less costly and simpler to administer.[1] Effective oral medication delivery may be influenced by the rate at which the stomach empties, the length of the GI tract, how the drug is released as dosage form, as well as the location of absorption.[2] Drugs that are gastro retentive may delay the timing of release by floating in stomach juice or fluid for a number of hours.[3]. Additionally, the usual period for stomach emptying in humans is between two and three hours[4]. Specifically, through the primary absorption zone, the upper intestine and stomach could result in the insufficient drug release from the carrier system that reduces the effectiveness of the given dose[5]. Low density systems or adaptively coordinated systems that have enough buoyancy to swim over the contents of the stomach for a significant period of time without a significant slowdown in the rate of emptying the stomach are known as floating systems. Floating systems are Low-density systems that are a part of controlled process and possess enough buoyancy to float above the stomach's contents float around in the stomach without changing the duration of the gastric transit over a lengthier time[6].Fig-No.1 represents the route of GI tract and process of digestion.

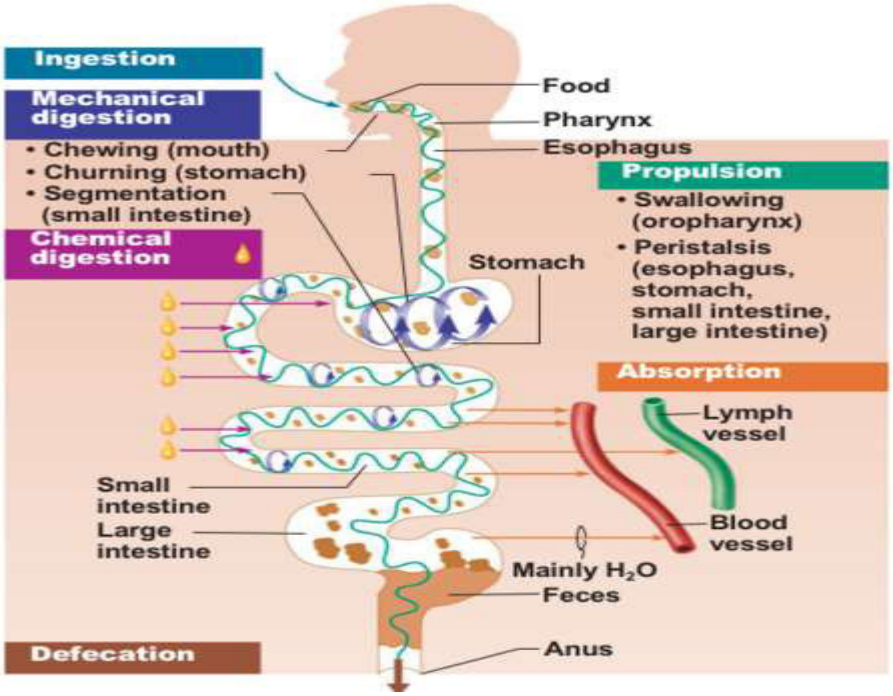

Fig No.1: Gastero intestinal system

Difficulties are encountered in formulating such improved sustained release systems to enhance bioavailability and absorption[7].Formulating such improved sustained release systems to enhance absorption and bioavailability is challenging[7].One of these challenges is being unable to place the dose form precisely where it needs to be in the gastrointestinal tract[8]. The major absorption zone, which includes the upper portion of the intestine and stomach, has a gastric emptying time (GET) of 2-3 hours in humans. The drug release from floating tablets may be impacted by this relatively brief GET, which might reduce the therapeutic dose's efficacy[9]. Several methods are now used to lengthen the gastric residence times (GRT), including magnetic devices.[10,11] FDDS, high density systems, ultra porous hydro gels, raft systems made of alginate gels, bio adhesive or mucoadhesive systems. This article quickly discusses why the FDDS is one of the most promising methods for developing gastro-retentive drug formulations[12]. There have been several buoyant systems developed[13,14] based on powders, hollow microspheres, grains, laminated films, tablets, and capsules. The system floats over the stomach's contents while the medication is administered slowly and correctly, lengthening the period of gastro-retention and reducing volatility.

1.1 Needs For Gastro Retention[15]

Drugs that enter the body through the proximal gastrointestinal tract (GIT). drugs that are less soluble or are destroyed by the alkaline pH that they come into contact with in the lower GIT. medications that are absorbed because stomach emptying times can vary. Particularly helpful for the treatment of peptic ulcers brought on by H. pylori infections is local or sustained medication administration to the stomach and proximal small intestine.

1.2 Ideal Drug Characteristics For GRDDS[15]

1. Drugs that operate locally in the stomach, such as antacids and misoprostol for H. pylori
2. Medicines whose absorption occurs largely in the stomach and upper GI tract, such as Amoxicillin, calcium supplements, chlordiazepoxide, and cinnarizine.
3. Medications that are poorly soluble at alkaline pH, such as furosemide, diazepam, verapamil hydrochloride, chlordiazepoxide, etc.
4. Drugs with a limited window of GIT absorption, such as levodopa, riboflavin, para aminobenzoic acid, and cyclosporine
5. Drugs that are quickly absorbed from the GI tract.
6. such as tetracycline and metronidazole.

7. Drugs that are unstable or break down in the colon.
8. for instance, captopril, metformin HCl, ranitidine HCL, and metronidazole.

1.3 Basic Gastrointestinal Tract Physiology

The Body, Fundus, and Antrum are the 3 main anatomical divisions of the stomach. While the antrum acts as the primary location for mixing and serves as a pump for gastric emptying, the fundus and body of the stomach serve as storage areas for undigested material. However, there are differences in the two states' variations of stomach content flow[16]. The inter-digestive myloelectric cycle, also known as the migratory myloelectric cycle (MMC), is a series of electrical events that take place although during fasting period and occurs every 2 to 3 hours. It is controlled by the stomach and intestine. It is further divided into the subsequent four stages, which are detailed below and shown in Fig. 2 and Fig. 3, respectively. Various Gastroretentive techniques for no flow from gastric sphincter are shown in Fig. 2. The mucus spreads throughout the GI tract, covering the mucosal surface of the stomach as well. The digestive system is always moving in two modes: the interdigestive motility pattern and the digestive motility pattern. The former predominates in the fasted condition and has as its main duty the removal of any remaining upper GIT content. The "migrating motor complex" (abbreviated "MMC"), which organises the interdigestive motility pattern into cycles of activity and quiescence, is a term used frequently.

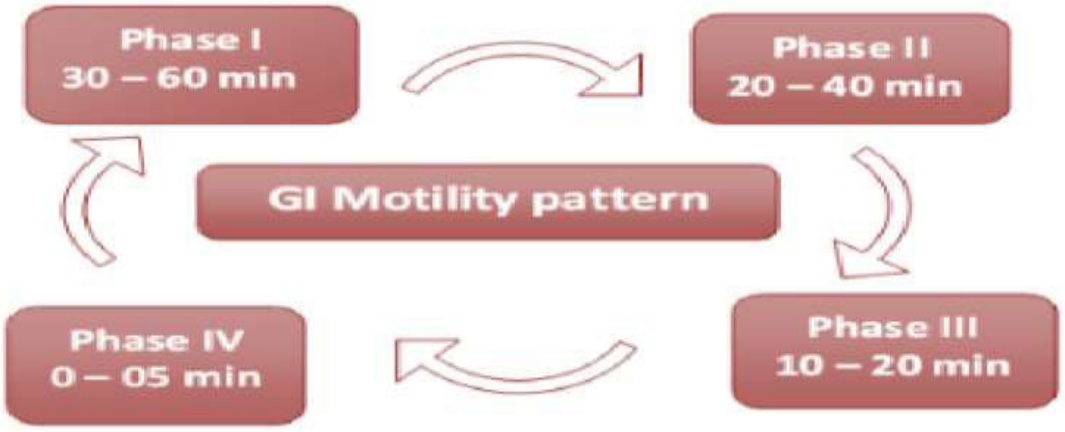

Fig No.2: Gastero intestinal motility pattern

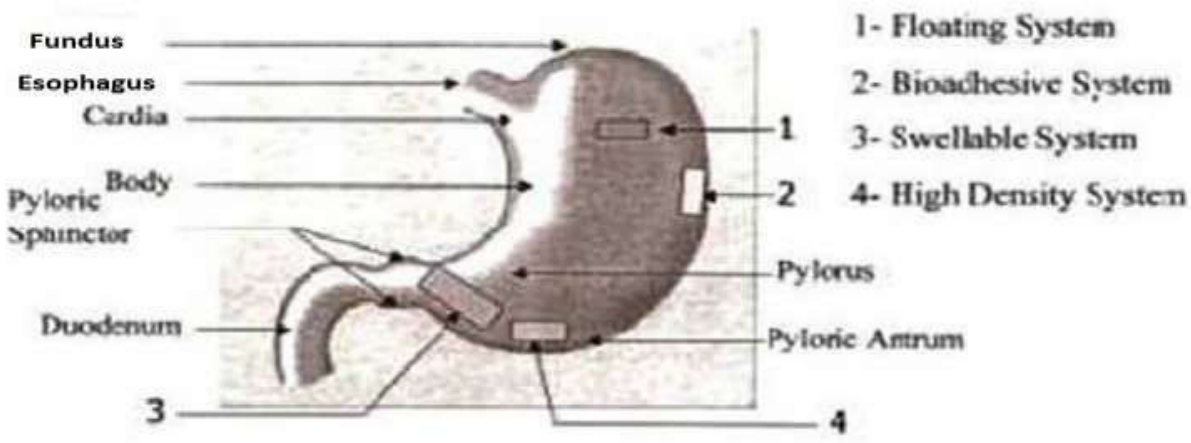

Fig No.3: There are several methods for gastroretentive systems (GRS) that facilitate there is no movement from the gastric sphincter.

1.4 Duration of Phase-I (Basal phase)

forty to sixty min (occurs in between meals).

1.5 Phase-II (Pre burst phase)

lasts for forty to sixty min and consists of contractions and sporadic action potentials. As the phase progresses, the frequency and intensity gradually increase.

1.6 Phase III (Burst phase)

Often known as the "burst phase," lasts 4 to 6 minutes. It contains brief, recurring contractions that are strong and frequent. All of the undigested material is pushed out of the

stomach and into the small intestine as a result of this wave. Another name for it is the housekeeper wave.

1.7 Phase-IV

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which lasts 0 to 5 minutes and comes after phase III but before phase I of two successive cycles[17]

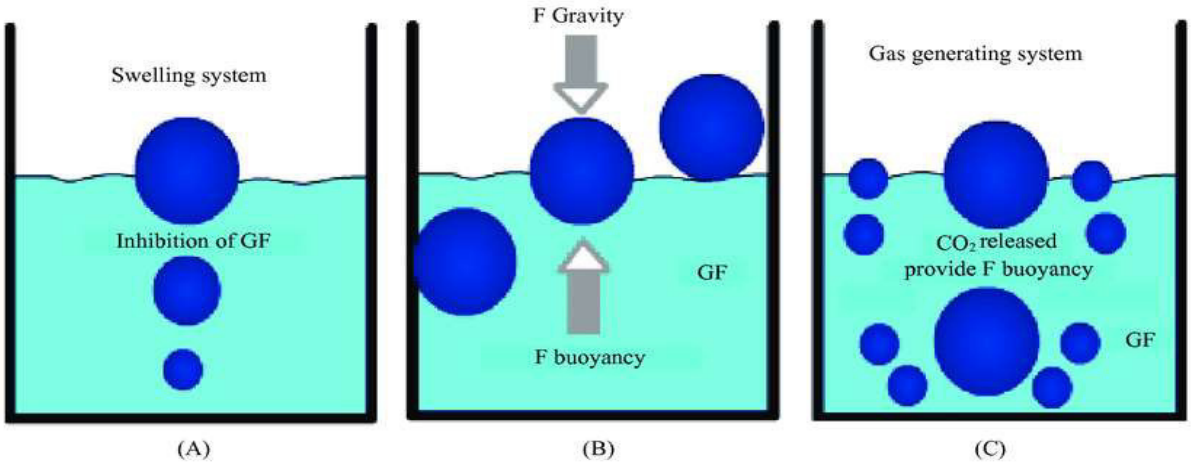

Fig- 4 The Floating Drug Delivery System Mechanism (FDDS) GF= Gastric fluid

However, in addition to the minimum stomach content required to properly achieve the buoyancy retention principle, a minor amount of floating force (F) is also required to keep the dosage form afloat on the surface of the meal. In order to estimate the mechanics of the floating force, special apparatus is required to hold the submerged item in place while the force equivalent to F is being measured (as a function of time). The dosage form floats more successfully if F resides on the positive side, as it is in fig.4 In order to prevent or lessen the unfavourable impacts of unanticipated intragastric buoyancy capacity fluctuations, this device helps with FDDS optimization with reference to stability and durability of floating time[18].

$$F = F\,buoyancy - F\,gravity = (DF - Ds)\,gv\_\_ \quad (1)$$

here, Ds = Object density, DF = Fluid density, F = Total vertical force, g = Acceleration due to gravity, v = Volume Important factors Affecting GRDDS Effectiveness

The effectiveness of gastroretentive dose forms is influenced by a number of factors. These elements primarily fall into three categories: pharmacological, physiological, and patient-related.

1.8 Pharmacutical Factors[54]

Understanding how excipients and polymers affect different types of GRDDS is crucial for the effective design of GRDDS . For instance, high mucoadhesion strength polymers like carbopol and hydroxypropyl methylcellulose (HPMC) may be necessary in the mucoadhesive system for the successful design of the mucoadhesive dosage form. In the same way, polymers with strong swelling capabilities are preferred for the expandable system. High swelling qualities of polymers are preferred. Additionally, the dosage form may be impacted by the molecular weight, viscosity, and physiochemical characteristics of polymers. different formulation For superporous hydrogels, it could be necessary to include ingredients such gas-generating agents in an effervescent floating tablet, sodium croscarmellose excipients with high swelling, and crospovidone.

1.9 Physiological Factors[55,56]

According to several studies, a number of extrinsic factors, such as the type of food, caloric content, frequency of consumption, posture, sleep, and physical activity, might influence the GRTs of medications in the stomach. In fasting settings, the MMC, which happens every 90–120 minutes, is a proxy for gastrointestinal motility. Motor action clears the stomach of any remaining undigested matter during this time. The unit's GRT is extremely brief if the timing of formulation administration and the MMC are the same. Though the MMC is interrupted and no housekeeper waves are produced when there is food in the stomach, this results in a prolonged GRT.

1.10 Patient-Related Factors[57,58]

GRDDS may be impacted by patient-related variables as gender, age, sickness, and emotional state. Gender was found to influence intraluminal pH and stomach emptying time in a recent study. The authors provided evidence that females empty their stomachs more slowly than males. The longer GRT in females than in males could be attributed to hormonal effects. According to a different study, men secrete more stomach acid than women do. The patient's age also has an impact on the GRT. Patients who are older have a longer GRT than patients who are younger.

1.11 Floating Drug Delivery Approaches (FDDS)[19]

By utilising a variety of concepts, many sorts of methods have been designed to lengthen the gastro-retentive period of dosage forms. According to the gastric retention concept, FDDS have been categorized.

1.12 Floating drug delivery systems (FDDS)

Low-density systems that float above the stomach's contents.

1.13 Bioadhesive systems

They adhere to stomach mucosa, allowing the system to be retained locally.

1.14 Expanding and swelling systems

These systems expand in size as a result of absorbing water.

1.15 High density systems

They remain in the stomach for a longer amount of time by resting on the folds of the stomach.

1.16 Classification of FDDS

Classification of floating drug delivery system is depicted in Figure No.5

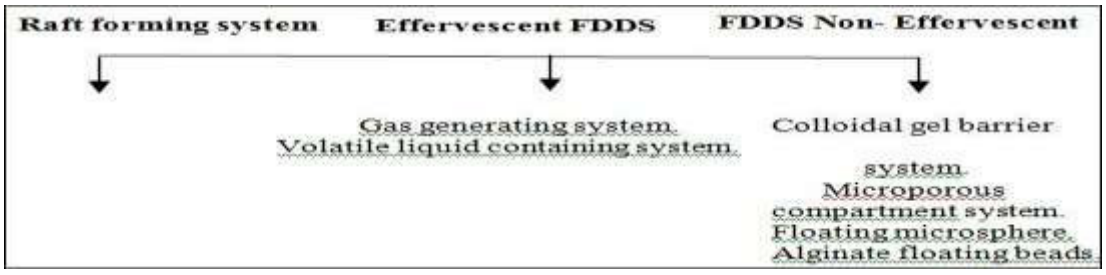

Fig No5: FDDS Classification

1.17 Advantage of FDDS

1. Floating dosage forms, such as tablets or capsules, will remain in the fluid for a considerable amount of time, regardless of the alkaline pH of the gut.
2. FDDS are useful for drugs like aluminium hydroxide gel that are intended for local action with in stomach.
3. To maintain the medication floating in stomach fluid during dierrhoea and other instances of extreme gastrointestinal movement and to produce a much better response, FDDS dosage forms are useful.
4. Since medicines like aspirin that are acidic cause irritation to the lining of the stomach whenever they come into contact with it, FDDS preparations would be beneficial for the prescription of these kind of drugs and similar ones[2021]

1.18 Disadvantage of FDDS

5. FDDS are not appropriate for medications that have issues with solubility or stability in stomach juices.
6. Medicines like nifedipine, which has a significant first pass metabolism and is well absorbed throughout the GIT, would not be appropriate for FDDS.
7. Fluid levels in the stomach are high enough for the medicine dosage form to float there and function effectively.
8. To prevent their stomach emptying, these systems also need food[22–24].

1.19 Effervescent Floating Dosage Forms

These systems, which are classified as matrix kinds, include a system for producing gas and another for holding volatile liquids. They are manufactured of materials that may swell, such as methylcellulose, HPMC, and chitosan-based polymers, as well as effervescent elements including tartaric acid, calcium carbonate, sodium carbonate, as well as citric acid[25]. In order to provide dosage forms like amlodipine and famotidine besylate buoyancy[26,27], they are made in such a manner that when they come into touch with the acidic stomach contents, CO_2 is released and retained in the swelling hydrocolloids.

1.20 Floating dosage forms that are not effervescent

These dosage forms make use of polymers that form matrices, including polycarbonates, polymethacrylates, and polystyrene, as well as cellulose hydrocolloids that may gel or swell. The formulation is made comprised of the medication plus a hydrocolloid that, when taken orally, gels and expands when it comes into contact with stomach fluid. Air is trapped within the swollen, gel-like structure, acting as a reservoir and allowing the gelatinous mass to continuously release the medicine, the dosage form's floating characteristics are obtained (For instance, Famotidine with Levodopa)[28,29]

1.21 Drugs suited for FDDS[30]

1. Drugs that work locally in the stomach, such as antacids and misoprostol.
2. Medicines with a limited window of absorption in the digestive tract (GIT), such as L-DOPA, para aminobenzoic acid, furosemide, riboflavin etc.
3. Medicines that are unstable in an acidic or basic environment, such as captopril and ranitidine HCl.
4. Medicines that affect the typical intestinal microorganisms, such as antibiotics for Helicobacter pylori.
5. Drugs have low solubility at high pH levels, such as verapamil HCl, chlordiazepoxide, and
6. diazepam.

1.22 Drugs unsuited for FDDS[31]

1. Medicines with an extremely low acid solubility,such as phenytoin.
2. Drugs that are unstable in the stomach, such as erythromycin, etc.
3. Pharmaceuticals designed for colonic release. such as corticosteroids and 5-aminosalicylic acid.

1.23 Ingredients used to manufacture floating drugs, include polymer[32]

1.23.1 Polymers

The following polymers are used to make floating drug preparations: HPMC K4M, Ethyl cellulose, Eudragit RL, Eudragit S100, Polycarbonate, Sodium alginate, Propylene foam, Cyclodextrin, Poly methyl methacrylate, Polyethylene oxide, HPMC, PEG, Calcium alginate, Methocel K4M, Eudragit RS, various grades of HPMC CMC, Metolose S.M. 100.

1.24 Inert fatty substances (5 - 75 percent)

Utilizing edible inert fatty substances with specific gravities under one can lengthen the floating time of a dosage form by reducing its solubility. For instance, fatty acids, long chain fatty alcohols, and beeswax.

1.25 Effervescent substances

Di-SGC (Di-Sodium Glycine Carbonate), and tartaric acid, sodium bicarbonate (Citroglycine), Acidic citrus Accelerators of release (5 - 60 percent) like mannitol and lactose. *Releasing rate retardants (5 - 60 percent)* Talc, magnesium stearate, dicalcium phosphate, etc. *Agents that increase buoyancy (upto 80 percent)* such as Ethyl cellulose.

1.26 Low density material

Powdered polypropylene foam is a low density material (Accurel M.P. 1000).

1.27 LIST OF MEDICINALS TESTED FOR MANY FLOATING DOSAGE FORMS[32]

Microspheres, Pills / Tablets

Amoxycillin trihydrate, Ampicillin, Tranilast, Terfenadine, Chlorpheniramine maleate, Atenolol, captopril, Aspirin, Acetylsalicylic acid, Griseofulvin, Isosorbide dinitrate, P-nitroaniline, and theophylline.

1.28 Films

Gluconate, Doxylamine succinate, Cinnarizine, Prednisolone, Quinidine, and P-Aminobenzoic Acid.

1.29 Granules

Fluorouracil, Isosorbide dinitrate, Indomethacin, Diltiazem, Isosorbide mononitrate, and Cinnarizine are some examples of drugs that fall under this category.

1.30 Powders

Sotalol, theophylline, and riboflavin phosphate.

1.31 Capsules

Furosemide, Propranolol HCl, Verapamil HCl, L-Dopa, and Benserazide, Ursodeoxycholic acid, Chlordiazepoxide HCl, Diazepam, Misoprostol, and Nicardipine29 are few examples of medicine under prescription.

1.32 A Floating drug delivery system's evaluation (FDDS)[33]

There are many factors that should be considered while developing gastro-retentive formulations, such as:

1.33 Evaluation parameters

1.33.1 Size and Shape Analysis

The solubility rate of the medications and, consequently, their potential bioavailability, are significantly influenced by the shape and size of the particle. The formulation's particle size is determined using a variety of methods, including microscopy, photoanalysis, sedimentation techniques, air elutriation analysis, laser diffraction methods, optical counting methods, sieve analysis, electro resistance counting methods (Coulter counter), ultrasonic attenuation spectroscopy, air pollution emissions measurements, etc.[34,35].

1.34 In-vitro buoyancy Analyses

0.1 N HCl maintained at 37° C or simulated gastric juice are typically used for the floating time test.The dissolve medium for this investigation is 900 cc of 0.1 N HCl in a USP dissolution equipment.The duration for which the dosage form floats is referred to as the floating or flotation time[36]. The time it takes for the dosage form to float is referred to as the floating lag time.

1.35 Surface topography

Atomic force microscopy (AFM), contact profiliometer34, scanning electron microscope (SEM) operation at a 10KV acceleration voltage, and contact angle metre are used to determine this[37].

1.36 Swelling Analyses

In order to estimate the molecular features of swollen polymers, swelling investigations are carried out. Which can be determined through the use of optical microscopy as well as other cutting-edge methods like H1 NMR imaging, Light scattering imaging (LSI), Confocal laser scanning microscopy (CLSM), etc. The following formula was used to determine the swelling studies using the Dissolution apparatus[38,39].

$$Swelling\ ratio\ = \frac{Weight\ of\ wet\ formulations}{Weight\ of\ formulation}.$$

1.37 Estimation of the drug content

The quantity of the drug in the preparation determines the percentage drug content, and it should not be more than what is allowed by the standard monographs. The presence of drugs can be detected by spectroscopy methods, near-infrared spectroscopy, microtitrimetric procedures, and HPLC methods[40].

1.38 Efficacy of Percentage Entrapment[41]

The produced formulations' phase distribution of the medication may be measured with accuracy using percentage entrappment efficiency. Utilizing the pressure ultra filtration, ultra centrifugation, as well as the microdialysis method, the effectiveness of entrapment was assessed.

1.39 Studies on In vitro release

The USP dissolving equipment is typically used to conduct in vitro drug release tests using simulated stomach and intestinal fluids kept at a constant 37 °C. After a certain period of time, the samples are removed, and a similar volume of fresh medium is added each time. UV spectroscopy is utilised to ascertain the drug content of the discarded samples after the proper dilution. Furthermore, it has been shown that traditional dissolve methods are poor indicators of floating dosage form effectiveness in vitro[42,43]. According to the USP or British Pharmacopoeia (BP), protocols.

1.40 X-Ray Power Diffraction

The most common method for examining polycrystalline materials is powder X-ray diffraction, which is ideal for routinely characterizing pharmaceutical solid samples. Samples are heated between 2-60oC after receiving radiation irradiation. The employed current and voltage are 30mA and 30KV, respectively[44].

1.41 Infrared Fourier Transform Analysis (FT-IR)

The primary usage of Fourier transform infrared spectroscopy (FT-IR) is to analyze the functional group level interactions of inorganic polymeric, and organic materials. On FT-IR, measuring pure medication quantities, polymers, formulations of polymers loaded with drugs, and other physical mixtures are produced. The KBrpress method was used to create the pellets, and 150 kg/cm2 of hydraulic pressure was used. The frequency bands were examined across the range of wave numbers of 3600 to 400 cm-1 at room temperature[45].

1.42 Differential Scanning Calorimetry (DSC)

Pharmaceutical hydration water is characterized using DSC.Using a DSC equipment with an intracooler, the thermograms of prepared substances were measured. The DSC temperature and enthalpy scales were calibrated using indun/zinc standards. The sample preparations were hermetically sealed in an aluminium pan and heated across a temperature range of 25 °C to 65 °C at a rate of 10 °C/min.[45-47]

1.43 FLOATING Drug Delivery System Application (FDDS) [48-51]

Enhanced Bioavailability

Riboflavin CR-GRDF has a considerably better bioavailability than sustained release polymeric compositions without GRDF. Numerous distinct mechanisms which are associated in the uptake as well as transport of the medication via the GIT have an impact on the quantity of drug absorption.

1.44 Sustained Drug Delivery

One problem that could occur with oral sustained drug release compositions of FDDS is gastric residence time in the GIT. HBS systems, which stay in the stomach for extended periods of time as well as may thus float on the stomach contents, may be able to overcome these issues. These systems are not allowed to pass via the pyloric orifice since they are relatively bigger in size.

1.45 Drug Delivery to Specific Sites

Drugs that are specifically absorbed from either the distal or stomach area benefit greatly from either of these systems. The medication is continuously and gradually released in the stomach, supplying adequate local therapeutic concentrations as well as limiting absorption of the drug, which decreases the negative impact the medication has on bloodflow. Additionally, a site-directed administration device may minimize the dose frequency because to the prolonged gastrointestinal availability. Example: Vitamin B2 and acetazolamide.

1.46 Absorption Enhancement

Low bioavailability medications may be produced using floating drug delivery methods owing to site-specific absorbing in the GIT's upper section, hence increasing their absorption.

1.47 Decreased drug concentration fluctuations

Contrary to typical dosage forms, continuous drug administration after CRGRDF results in blood drug concentrations that fall within a tighter range. Thus, variations in the therapeutic drug's effects are reduced, undesirable effects that are concentration dependent and linked to peak concentrations can be avoided, as well as the healing index is also improved.

Table 1: Examples of some Drugs for FDDS[52]

Name of the Drugs	Category	Half life	Peak time (hrs)	Bioavailability
Diltiazem	Calcium channel blocker	3-4.5	50 min.	40%
Propranolol	Antihypertensive	4-5	4	26%
Atenolol	Antihypertensive	4	3	40-50%
Verapamil	Antihypertensive	6	1.8	35%
Lidocaine	Local anaesthetic	1.5-2	4	35%
Nifedipine	Calcium channel blocker	2	0.5-0.2	45-65%
Verapamil	Calcium channel blocker	6	1-2	20-35%
Ramipril	ACE inhibitor	2-4	3-5	28%
Clarithromycin	Antibiotic	3-4	2-2.5	50%
Omeprazole	Proton pump inhibitor	1-2	1	35-60%

Table 2: Some Marketed preparations of Floating Drug Delivery System (FDDS)[53]

Product	Active Ingredient
Topalkan	Aluminium magnesium antacid
Madopar	Levodopa and Benserzide
Almagate	Antacid
Cifran OD	Ciprofloxacin
Valrelease	Diazepam
Liquid gavison	Sodium bicarbonate and Alginic acid
Glumetza	Metformin HCl

1.48 LIMITATIONS OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

GRDDS may be able to shift the "absorption window" of medicines' BA. They do, however, have some restrictions. The requirement of high amounts of fluids in the stomach for the delivery system to float and function well is one of the main drawbacks of the floating system.[59]

1. Demand a greater volume of fluids in the stomach.
2. Unsuitable for use with medications that could lead to stomach lesions, such as non-steroidal anti-inflammatory medicines. These systems do not significantly outperform traditional dosage forms for medications that are absorbed throughout the GIT or compounds that are unstable in a strong acidic environment.
3. Medications designed for colon selective release such as corticosteroids and 5-a minosalicylic acid, etc.

1.49 FUTUREPOTENTIAL

According to numerous recent articles, floating dosage forms provide a variety of future prospects for controlled release medications.

2. CONCLUSION

Absorption of drug in the GIT is a dynamic process that is influenced by gastric emptying in addition to other physiological considerations. One method which has the potential to cause gastric retention is FDDS. To create a workable GRDDS, the physicochemical characteristics of the drug as well as its physiological actions in the GIT should always be carefully investigated. It is difficult to formulate FDDS effectively, and research will continue until an optimum strategy with industrial applicability and viability is found.

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4. AUTHOR CONTRIBUTION STATEMENT

Mohammad Rashid Iqbal.: conceptualization, Resources, Material, Data collection or processing, Writing manuscript, Critical review, Design, Analysis, Literature search

5. CONFLICT OF INTEREST

Conflict of interest declared none.

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