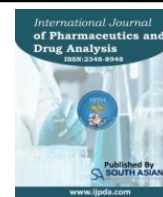




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ADVANCEMENT IN GASTRO RETENTIVE FLOATING TABLET: AN UPDATED REVIEW

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Abstract

The widespread use of oral dose forms in disease treatment may lead to inadequate pharmacokinetic properties due to rapid transit through the gastrointestinal tract. This makes it challenging to achieve therapeutic levels in situations where the medicine is barely soluble. Studies have been conducted to identify formulations that enhance these characteristics while extending stomach residence time, with gastro retentive controlled drug delivery systems being beneficial. This study evaluates recent developments in FDDS, focusing on how these systems function to make dosage forms float in stomach fluid for gradual release, better gastric retention, and improved bioavailability of oral medicine. It discusses the pharmaceutical importance of GRDDS, stomach physiology, and factors controlling gastric retention. The review also discusses the preparation of GRDDS, polymeric materials, dosage form evaluation, and comparisons between conventional and GRDDS. In this abstract, we will keep an eye on updated review on recent advancement in gastro retentive floating tablet.

Keywords: Gastroretentive, GRDDS, Gastric Retention, Gastro-Retentive Drug Delivery System.

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Introduction

The dosage types known as GRDDs are ones that the stomach can sustain. By continually releasing the drug for an extended period of time prior to it reaching its absorption site, GRDDs can enhance the controlled delivery of medications having an absorption window [1]. Prolonging the stomach retention of the drugs may occasionally be helpful to provide therapeutic benefits for medications that are absorbed from the proximal section of the GIT (gastro intestinal tract), are less soluble in alkaline pH, are destroyed by alkaline pH, or come into contact at the lower part of the GIT [2]. Many oral delivery systems have been created in the last 20 years to function as drug reservoirs from which the active ingredient may be administered at a regulated rate over a predetermined period of time. But there are a number of physiological problems with this method [3].

A drug delivery system that can sustain a therapeutically effective plasma drug concentration for an extended duration is being developed in an attempt to minimize fluctuations in plasma drug concentration at steady state and minimize the need for frequent dosing [4]. Reducing the problems with the existing oral sustained release dosage form and creating patient-beneficial medicine administration are the primary objectives of developing GRDDs [5].

Because of its many advantages, the oral route of administration has always been important in therapy. These formulations are appealing to patients for a variety of reasons, including their easily transportable, affordable, easy-to-store, and easily handled ingredients [6]. This oral method is used to administer 90% of medications. The most popular kind of solid dosage form is the tablet, which is divided into two categories: immediate release and modified release [7].

GRDDs, or gastroretentive drug delivery systems, are developed due to the inability of conventional systems to retain drugs in the stomach. Factors such as polymer types, dosage form composition, viscosity grade, molecular weight, and drug solubility affect the quality of GRDDs. The physicochemical nature of excipients also plays a crucial role in GRDDs [8].

Technologies, such as ultra-porous hydrogel systems, magnetic systems, unfoldable, extensible, or swellable systems, that stop the dosage forms from passing past the stomach's pyloric sphincter. Gastro retention is crucial for drugs whose alkaline pH degrades the gastrointestinal system, bioavailability by improving their solubility prior to emptying them [9].

Possible prospect for GRDDS:

1. Examples of medications that are mostly absorbed in the stomach are ampicillin.
2. Medication that is not well soluble in alkaline pH, such as furosemide and diazepam.
3. Medications have a limited window of absorption, such as methotrexate and levodopa.
4. Medication that acts locally in the stomach [10].

Benefits

GRDDS improve these drugs' bioavailability, therapeutic efficacy, potential dose reduction, and other benefits. In addition to these advantages, these systems offer other pharmacokinetic advantages such sustained therapeutic level maintenance over an extended length of time, which results in a decrease in therapeutic level [11]. Drugs with short half-lives and simple GIT absorption are swiftly eliminated from the bloodstream. After oral administration, the drug would remain in the stomach and be released via this method of drug delivery [12].

GRDD devices improve drug absorption by staying longer in the stomach than conventional site-specific drug delivery systems. This leads to improved bioavailability, decreased drug waste, and enhanced solubility of medications in high pH environments [13]. Due to their therapeutic advantages and ability to manage the timing and place of medicine release, oral dosage formulations for stomach retention are becoming more and more popular [14].

Why the need of GRDDS?

Regular dosage is required for some drugs since those that have been absorbed through the gastrointestinal tract (usually with short half-lives) are rapidly removed from the circulatory system. This method's capacity to distribute the medication in a controlled and reliable way eliminates variability in plasma drug concentration [15]. Reduced dosing frequency and longer-term medication release. Patient compliance is improved as a result. Ideal for drugs that degrade in the colon or bile duct, such as ranitidine hydrochloride.[16] Figure no. 1 demonstrates the reasoning for the application of GRDDS [17].



FigureNo1: Rationale for the use of GRDDS

Physiology of the Stomach

The human stomach is comprised of three anatomical areas, namely the fundus, the body, and the antrum (pylorus). After a meal, a stomach's normal capacity is about 1.5 liters, however it can vary between 250 and 500 milliliters between the phases between digestion [18]. While the antrum is the main location for mixing activity, the portion made up of the fundus and body acts as a reserve for any material that has not yet been digested. Through pushing, the antrum—the lower section—serves as a pump for stomach emptying. Pylorus controls the length of time that food remains in the stomach after being consumed and divides the stomach from the duodenum.

But between the fed and fasting stages, there are differences in the pattern of stomach motility.[19] There are cycles for both active and latent stomach motility. Four phases are included in each cycle, which lasts 90–120 minutes, as Table No. 1 [20] illustrates. From the oesophagus to the anus, the wall of the gastrointestinal system has a similar general structure, with notable local variations [16]. The term "migrating motor complex" (MMC) refers to the pattern of stomach motility [21].The delivery and subsequent ingestion of food cause an abrupt disruption in the MMC cycle, enabling the digestive phase to continue. The food is first kept in the upper part of the stomach, where phasic contractions progressively compress it [16].

Table1: Four phases of MMC [12]

PhaseS	Duration[min]	Description
Phase 1[basal phase]	30-60	Idlestatoeno contraction
Phase2 [pre-burst phase]	20-40	Contraction(Intermittent)
Phase 3[burst phase]	10-20	The excellent material migrates distally as a result of the regular contraction at the maximal frequency.
Phase4	0-5	Transition time (between phase 3 and phase1)

Stomach Functionalities [16, 22]

The following tasks are carried out by the stomach

Temporary preservation to enable the action of pepsins and digestive enzymes.

Pepsins are enzymes that break proteins down into polypeptides.

Non-specific antimicrobial defense provided by the stomach juice's hydrolytic acid. Ingesting stomach irritants like chemicals or germs can cause vomiting. Iron preparation for absorption: Iron salts, which are necessary for iron absorption in the small intestine, are dissolved in the stomach's acidic environment.

Approaches for achieving gastricretention [2, 16]

Figure 2 depicts some of the ways.

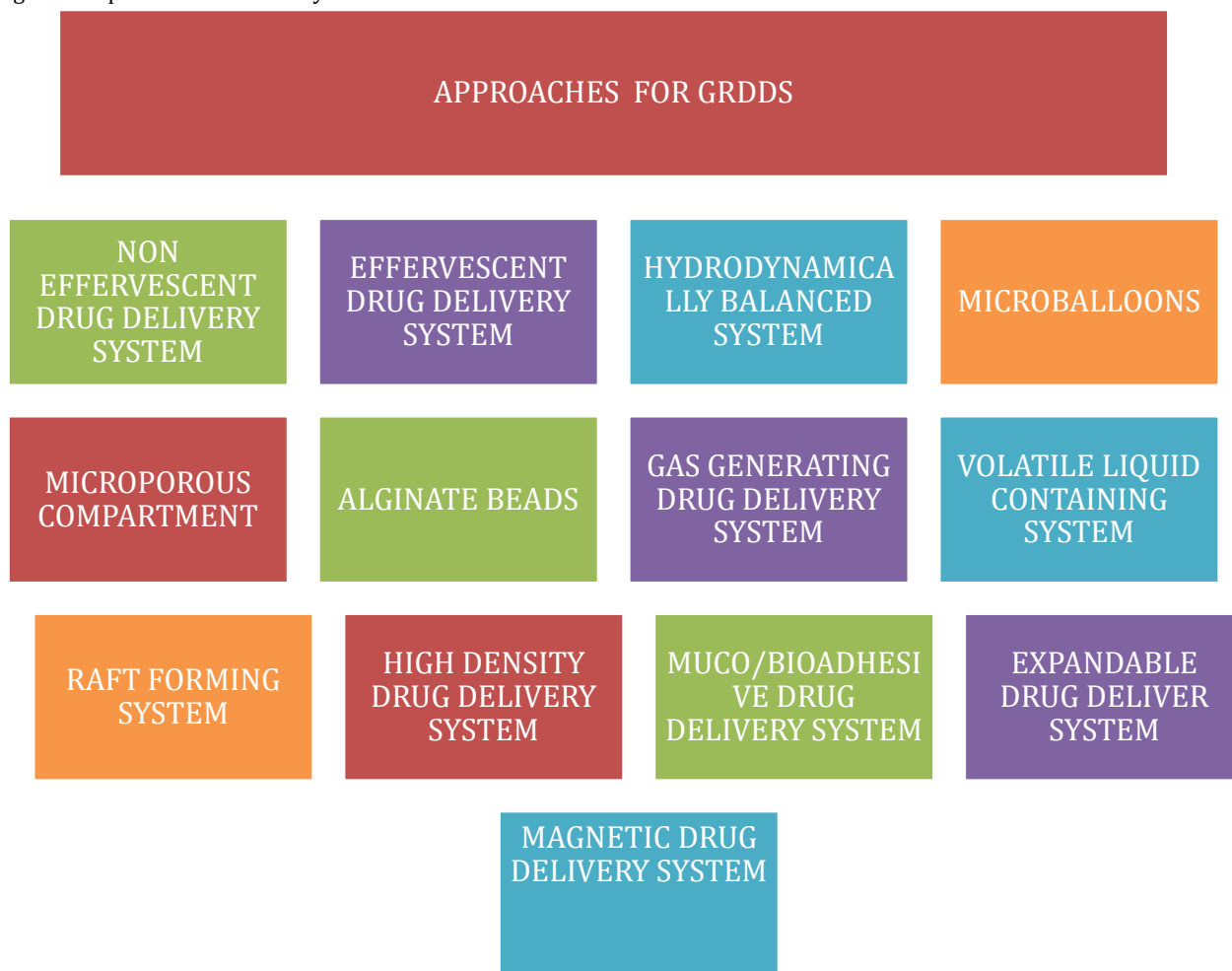


Figure 2: Approaches for GDDS

Non floating drug delivery system

High density (sinking) drug delivery system

The density of the formulation is higher than that of typical stomach contents. Density is increased to 1.5–2.4 gm/cm³ by the materials [23].

Bio adhesive or mucoadhesive drug delivery system

The delivery system's adherence to the stomach wall increases bioavailability by extending residence duration. Gliadin, carbopol, lecithin, chitosan, polycarbophil, and carboxymethyl cellulose are among the substances that are utilized for mucoadhesion [25]. The bioadhesive process may be aided by the contact between positively charged polymers and the negatively charged mucosal surface [8]. The stomach wall's propulsive force, however, is too great for the gastric mucoadhesive force to withstand. The constant creation of mucus and diluting of the stomach content is another drawback of this kind of system [7].

Magnetics System & expandable system

Using this procedure, a tiny magnet is integrated into the dosage form, and an additional magnet is positioned on the abdomen above the stomach. [24]

Floating Drug Delivery System

Effervescent System

Gas generating System

When the formulation is placed in the beaker, it sinks and rises to the surface due to the effervescent reaction between the carbonate/bicarbonate salts, citric/tartaric acid, and CO₂ [24].

Raft forming systems

These systems use effervescent excipients and gel-forming polymers to promote prolonged medication delivery. These systems work well at producing a localized effect because they function as a barrier between the stomach and the oesophagus. Consequently, the tool may be applied to the management of gastric reflux illness and peptic ulcers. A continuous layer known as a raft is formed when these systems come into contact with stomach contents because they expand and form a viscous cohesive gel [26, 27]. These systems are susceptible to MMC due to their limited mechanical strength [27, 29].

Non-effervescent system [30]

Hydrodynamically balanced system

They contain a high level of gel-forming polymers, ranging from 20-75% w/w in capsules or tablets. After taking these systems, a hydrocolloid enters the gastric juice, creating a gel barricade near its surface.[16,2]

Microporous compartment

The medication reservoir is contained inside a microporous chamber with pores along the length of its top and bottom walls [7].

Alginate beads

Calcium alginates, freeze-cured, can be used to create multi-unit floating dosage forms. After separation, the beads are frozen in liquid nitrogen and dried at 400°C for 24 hours [2, 16].

Factors controlling GRDDS [32, 33, 9]

Factors controlling GRDDS are enumerated below

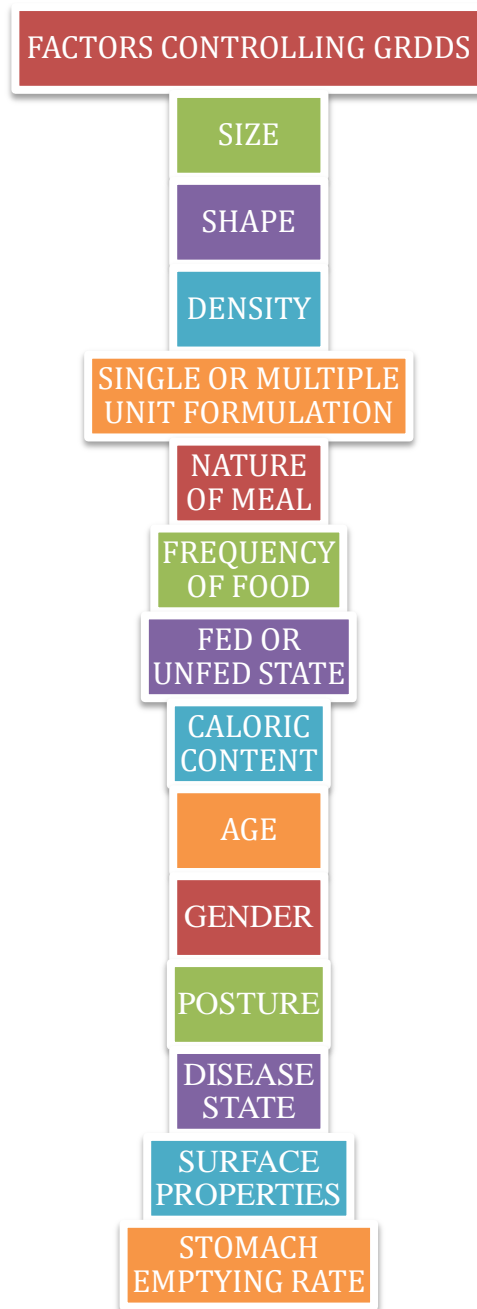


Figure 3: Factors affecting GRDDS

Advantages of Gastro-retentive Drug Delivery Systems

They can increase the bioavailability of medications with a limited absorption window or those that are unstable in the small intestine's alkaline environment [34]. The gastrointestinal system's several mechanisms related to drug absorption and transit work together to determine how much of a medicine is absorbed [35].

Sustained drug delivery/reduced frequency of dosing

When CR-GRDF is continuously and slowly added, the pharmacokinetics can flip-flop, allowing for a lower dosage frequency for medications with short biological half-lives. This characteristic improves therapy by increasing patient compliance [2].

Enhanced first-pass biotrans formation

Similar to the enhanced effectiveness of active transporters with capacity limited activity, the drug may be presented to the metabolic enzymes (cytochrome P450, specifically CYP3A4) in a sustained manner as opposed to by a bolus input, which may significantly increase the pre-systemic metabolism of the tested compound [36].

Reduced fluctuations of drug concentration

Continuous medication input following CRGRDF therapy leads to a decrease in pharmacological effect oscillations and the avoidance of concentration-dependent side effects linked to peak concentrations [37].

Minimization of fluctuations in drug concentration

It makes the evoked pharmacological effect of drugs more selective by activating several types of receptors at different dosages [2].

Targeted therapy in GIT.

Site-specific drug delivery

It is possible to use a floating dosage form, especially for medications that have few upper small intestine absorption sites [38]. Administering the medication to the stomach gradually and under control results in sufficient local therapeutic levels, while also minimizing systemic exposure to the drug [2].

Minimized adverse activity at the colon.

Disadvantages of Gastro-retentive Drug Delivery System [39]

- Not appropriate for medications that have problems with GI tract solubility or stability.
- Medications that cause irritation to the stomach mucosa are also inappropriate.
- Drugs like corticosteroids that only absorb certain parts of the colon. Targeting certain stomach locations with GRDDs might be challenging, particularly if the medication is given gradually. [34]
- The development and production of GRDDs can be more costly than those of other drug delivery systems.[7]

Methods of Preparation of Gastro-Retentive Multiparticulate System

Iontropic Gelation Method

The ability of poly electrolytes to cross link and form beads in the presence of opposing ions is what supports ionotropic gelation. The ionotropic gelation technique has become popular with the use of alginates, gellan gum, chitosan, and carboxymethyl cellulose for medication and cell encapsulation [38]. Natural poly electrolytes have some anions in their chemical structure, despite the fact that they cover the drug core and slow down the rate of release [41, 2].

Solvent Evaporation Method

Solvent evaporation techniques can be employed to create the hollow inner core of a floating multiparticulate dosage form. The polymer solution, which has been dissolved in an organic solvent, contains either dissolved or dispersed medication. The medication solution is then emulsified into an aqueous phase with the appropriate component (surfactants/polymer) to produce oil in water emulsion. The organic solvent is removed from the mixture [42,43], polymer precipitation occurs, creating holes and hollowing them out to give them their floating characteristics [44,2].

Melt Granulation Technique [45, 46, 2]

Using a technique called melt granulation; granules are created by using a solid binder that melts throughout the process, or a molten binder.

Principle of Meltgranulation

The granulation process is comprised of three distinct phases

- Wetting and nucleation, Wetting and Nucleation process
- Immersion
- Distribution
- Coalescence step
- Attrition and breakage

Polymeric Materials in Gastroretentive Formulations

Hydroxypropylmethyl Cellulose (HPMC)

The most often used hydrophilic carrier material in the production of oral controlled drug delivery systems is hydroxypropyl methylcellulose (HPMC) [48]. They are also used as a tablet binder and coating solution for extended-release tablets; the high viscosity grade is used for release retardant action [24].

Hydroxypropylcellulose (HPC) and hydroxyl ethylcellulose(HEC)

In order to gel and thicken biostructures that are intended to deliver hydrophobic medications, hydroxyethyl cellulose (HEC) is utilized [49]. Hydroxyethyl cellulose (HEC) has been included into multicomponent polymeric matrices to provide the necessary gastro-retentive properties, much like HPC [50].

Natural Gums

Drug release from swellable systems has been effectively controlled by the use of natural polymers as hydrocolloids in addition to synthetic cellulose ethers[51].

Guargum

In the pharmaceutical business, guar gum improves viscosity and functions as a disintegrant and binder when used in solid dosage forms [52].

Xanthan Gum

Xanthan gum is utilized in food, cosmetics, and topical and oral medication formulations because to its non-toxicity and non-irritating properties [53].

Crosslinkedpolyacrylates:

Carbomers, Carbopol® and Polycarbophyl(PCP)

The physical structure and chemical composition, crosslink density, crosslinking type, crosslinking solvent, network electrical charge, and physical appearance of different Carbopol® polymer grades affect their performance. For usage as controlled release polymers in matrix tablets, carbomers need polymer ratios between 3 and 30% [54].

Kollidon®SR

Kollidon® SR is a combination of povidone (poly(N-vinyl pyrrolidone)) and poly(vinyl acetate) (PVAc) that is primarily utilized as a matrix retarding agent. For the production of pH-independent sustained-release matrix tablets, direct compression or hot melt extrusion are the best options [56, 2].

Evaluation of gastro-retentive dosage form [2,57,58]

Buoyancy Lag Time-

It is measured to see how long it takes the dosage form to float on top of the dissolving liquid once it is submerged in it. The dissolving test may include measurements of these factors.

Specific Gravity / Density- Density may be computed by the displacement technique with benzene serving as the displacement medium.

Resultant Weight-Bulk density and floating time are the two essential components that determine buoyancy. However, as density fluctuates over time as a function of changes in the resultant weight, a single density measurement is insufficient to accurately describe buoyancy.

Particle Size and Shape

Light microscopy (LM) and scanning electron microscopy (SEM) are the most widely used techniques for seeing microparticles. In addition to instrumental methods, the size, shape, and morphology of the Multiparticulate may be characterized using laser light scattering and multisize Coulter counter [58].

Entrapment Efficiency -

The entrapment percentage may be computed by letting the washed multiparticulate lyse. Next, the active components of the lysate are identified in compliance with the monograph's specifications. To get the percentage of encapsulation efficiency:

$\% \text{Entrapment} = \frac{\text{Actual content}}{\text{Theoretical content}} \times 100$

In Vitro Release Studies

To fill the basket of the dissolving rate equipment, a weighted quantity of floating microspheres equivalent to the dosage of medication is taken. The dissolving fluid is maintained at $37 \pm 0.5^\circ\text{C}$ with a rotation speed that creates sink conditions during the drug release investigation [60].

In vivo Evaluation Test

Radiology

Uses X-rays extensively to examine inside body systems. The usage of barium sulphate is common. Radio Invisible Marker.

Scintigraphy

Similar to X-rays, emitting materials are integrated into dosage forms, and scintigraphy is used to take pictures. ^{99}Tc is a commonly used emission material [61].

Gastroscopy : Gastroscopy is the peroral endoscopy with fiber optics or video technology. The consequences of stomach expansion may be visually examined thanks to the use of gastroscopy [62].

Conclusion

Oral drug administration is common due to its ease of use. The Gastro-Retentive Drug Delivery System (GRDDS) prolongs the contact period with the stomach, enhancing bioavailability, solubility, therapeutic levels regulation, and reducing the need for repeated dosing, thereby

reducing the need for repeated dosing. FDDS is a method used to control the release of drugs from dosage forms, particularly those absorbed in the upper parts of the gastrointestinal tract (GI tract), such as the stomach, jejunum, and duodenum. Polymers are used for various purposes, including gelling, emulsifying, viscosity-enhancing, and rate-returning agents. However, more research is needed to overcome pharmaceutical and physiological barriers and develop efficient dosage forms. Future research should focus on precise control of drug input into the GI tract to optimize the toxicological and pharmacokinetic profile of pharmaceutical agents.

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Conflicts of Interests

There are no conflicts of interest.

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Authors Contributions

All the authors have contributed equally.

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