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Gastro-retentive Drug Delivery System- An Overview

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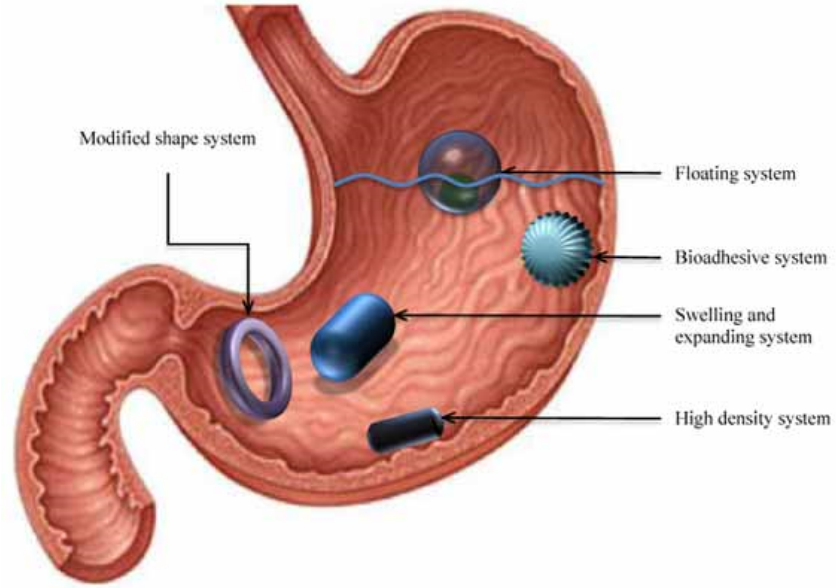


Abstract:
Gastro retentive drug delivery system (GRDDS) refers to systems in which the drug retained in the stomach for a prolonged period of time that improves the bioavailability of drug substances. The aim of any delivery system is to deliver a therapeutic amount of drug to the specific site in the body to obtain rapid and then maintain a requisite amount of drug. Oral controlled release drug delivery system furnishes the continuous oral delivery of drugs at predetermined and reproducible kinetics for a particular period during the course of GI transit. Various problems may arise in designing controlled release systems to improve absorption and to increase bioavailability. One of the problems is the inability to control the dosage form in the required area of the gastrointestinal tract. Additionally, the oral course has distinctive physiological issues, similar to a flighty gastric discharging rate that varies from individual to individual, a short gastrointestinal travel time (8– 12 h) and the nearness of a retention window in the upper small digestive system for some medications[3]. To prolong the retention of a formulation at the desired absorption site, various approaches were outlined, such as floating systems, expandable systems, bio adhesive systems and high-density systems.

Keywords: GRDDS, Absorption, Bioavailability, Gastric Emptying rate, gastro intestinal transit time.

Introduction:

Gastro retentive drug delivery system (GRDDS) refers to systems in which the drug retained in the stomach for a prolonged period of time that improves the bioavailability of drug substances. Generally, because of the alkaline pH, drugs are poorly soluble in the intestine, if the gastric residence may enhance the solubility before they are emptied, resulting in gastrointestinal absorption of drugs with narrow therapeutic absorption window. [1] Oral controlled release drug delivery system furnishes the continuous oral delivery of drugs at predetermined and reproducible kinetics for a particular period during the course of GI transit. Various problems may arise in designing controlled release systems to improve absorption and to increase bioavailability. One of the problems is the inability to control the dosage form in the required area of the gastrointestinal tract[2]. Moreover, the oral route has various physiological issues, like an unpredictable gastric emptying rate that differs from person to person, a brief gastrointestinal transit time (8–12 h) and the presence of an absorption window in the upper small intestine for many drugs[3]. To prolong the retention of a formulation at the desired absorption site, various approaches were outlined, such as floating systems, expandable systems, bio adhesive systems and high-density systems. The floating systems can be effervescent which liberate carbon dioxide gas when comes in contact with gastric fluid or non-effervescent one, which can be sub classified into hydro-dynamically balanced systems, alginate beads, hollow microspheres, raft systems incorporating alginate gels, super porous hydrogels, and magnetic systems[4]. Sustained drug delivery means not only to extend the duration of drug delivery but also involves certainty and reproducibility of drug release kinetics.
Sustained release dosage forms are acquiring widely acceptance over conventional dosage forms in the treatment of various acute and chronic conditions. Moreover, to enhance patient compliance, they minimize the occurrence and extremity of side effects and found it beneficial in ensuring constant therapeutic effects in the treatment of arthritis, angina pectoris, and hypertension etc[5].

Needs for Grdds[6,7]

The aim of any delivery system is to deliver a therapeutic amount of drug to the specific site in the body to obtain rapid and then maintain a requisite amount of drug.

- The gastro-retentive delivery system delivers the drug either at the stomach or intestine. It is acquired by keeping dosage form into the stomach and drug release is controlled to a particular site either in the stomach, duodenum, and intestine. Conventional oral delivery is generally used in the pharmaceutical field to treat diseases but, conventional delivery had many limitations and one of them is non-site specificity.
- Some drugs are absorbed in a particular site only so that extreme amount of drug reaches to the specific site.
- The pharmaceutical field is now directing towards drugs that are site specific.

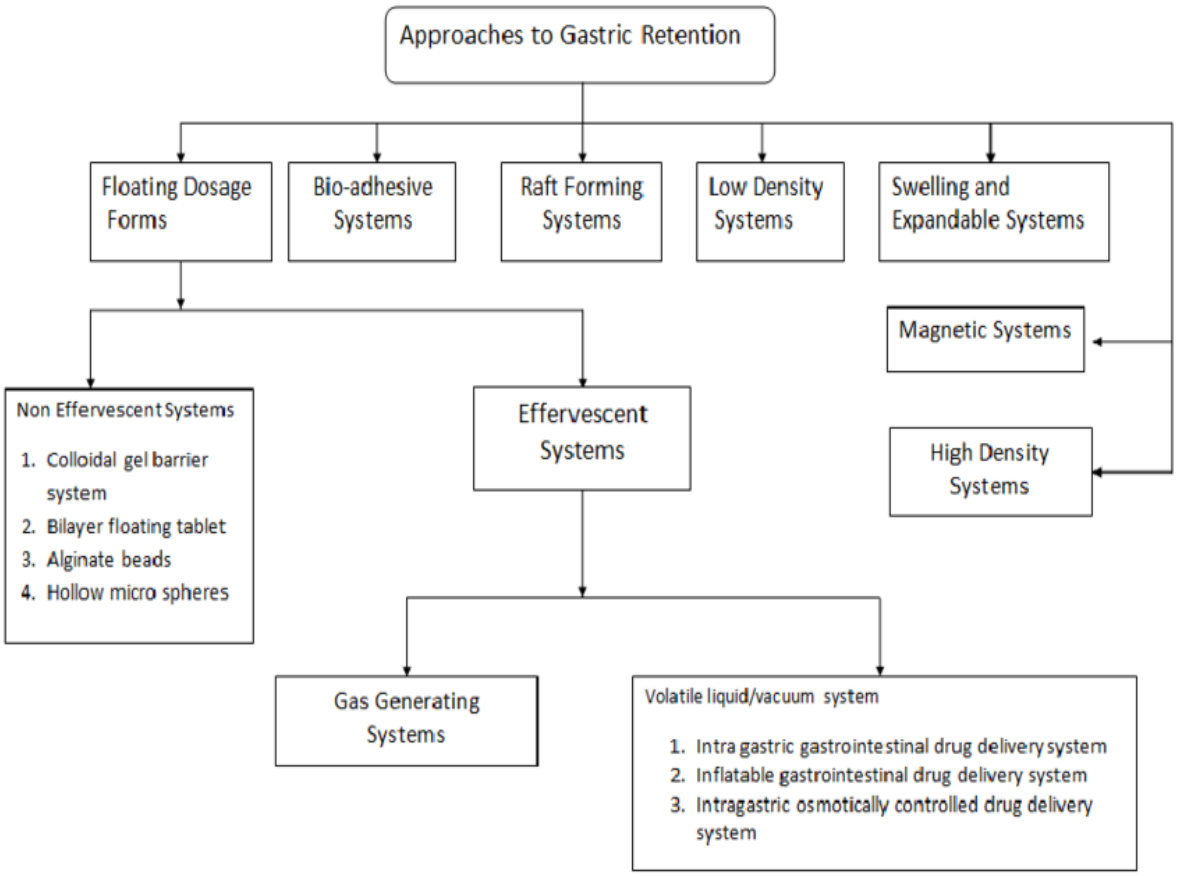
Different factors like temperature and viscosity of the meal, volume, and composition of the meal, emotional state of the individual, the pH of the stomach, body posture, etc. influence the gastric emptying of dosage forms.
Prolonged gastric retention of the drug is required in the following conditions:

- ✓ The optimum drug is absorbed from the stomach. E.g., Aspirin, Phenylbutazone, etc.
- ✓ The delayed release of drugs.
- ✓ Dissolution and absorption of the drug are triggered by the food. E.g., Griseofulvin.
- ✓ Drug show local effects within the stomach.
- ✓ Gastric fluids enable and enhance the disintegration and dissolution of the drug.

Conventional drug delivery system *Vs.* Gastroretentive drug delivery system[8]

Conventional drug delivery system	Gastroretentive drug delivery system
• High risk of toxicity • Less patient compliance • Not suitable for delivery of drugs with narrow absorption window in small intestine region • Not much advantageous for -Drugs having rapid absorption through GIT -Drugs which degrade in the colon -Drugs acting locally in the stomach -Drugs which are poorly at an alkaline pH • No risk of dose dumping	• Very low risk of toxicity • Improves patient compliance • Suitable for delivery of drugs with narrow absorption window in small intestine region • Very much advantageous for -Drugs acting locally in the stomach -Drugs which degrade in the colon -Drugs having rapid absorption through GIT • The possibility of dose dumping

Different approaches for grrds:[8]



Various dosage forms of GRDDS[9]

a. Floating microspheres Rosiglutazone, Cefpodoxime, Cefuroxime axitel, Nateglinide

b. Floating granules Lacidipine, Ranitidine, Simvastatin metoprolol atorvastatin

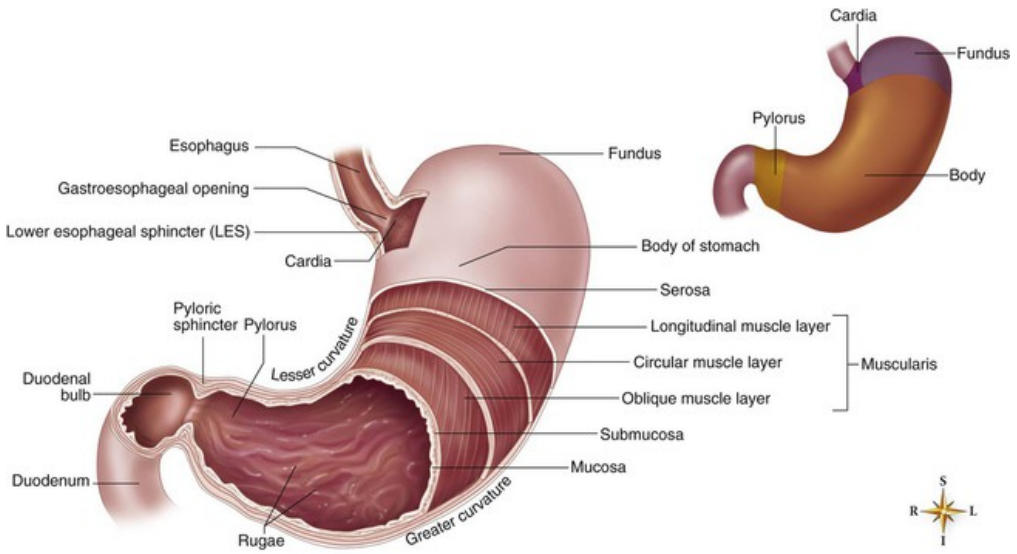
c. Films Cinnarizine

d. Floating capsules Celecoxib, Pioglutazone, diazepam, furosemide, misoprostol, L-dopa, Benserazide, ursodeoxycholic acid and Pepstatin

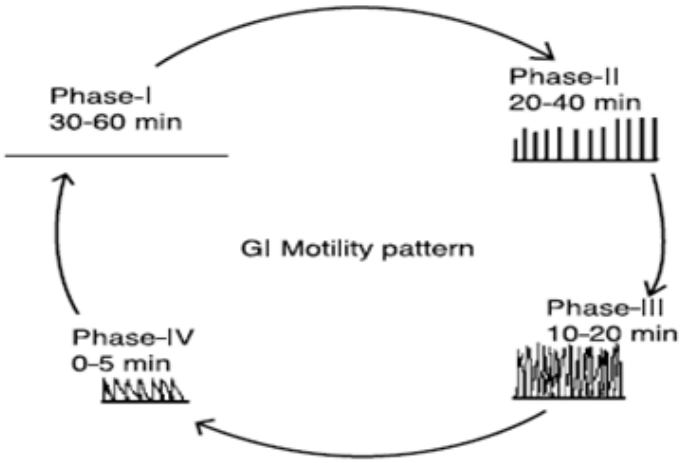
e. Floating tablets Alfuzosin, Losarten, propanolol, Ofloxacin, glipizide, Loratidine 6. Mucoadhesie system venlafaxine, famotidine, metformin, metopropalol

Physiology of stomach[10]

Anatomically the stomach is divided into three regions Fundus, Body and Antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested materials, whereas the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions. Gastric emptying occurs in both the fasting and fed states. During the fasting state, an interdigestive series of electrical events take place which cycle both through stomach and intestine every 2-3 hrs, which is called as inter digestive myoelectric cycle or migrating myoelectric cycle (MMC) which is further divided into four phases. After the ingestion of a mixed meal, the pattern of contractions changes from fast to that of the fed state which is also termed as digestive motility pattern.



1. Phase 1- (Basic phase) last from 30-60 minutes with rare contractions.
2. Phase 2- (Preburst phase) last for 20-40 minutes with intermittent action potential and contractions.
3. Phase 3- (Burst phase) last for 10-20 minutes which includes intense and regular contractions for short period.
4. Phase 4-last for 0-5 minutes and occurs between phase 2 and 1 of 2 consecutive cycles.



Commonly used drug in formulation of gastro retentive dosages forms[11]

DOSAGE FORMS	DRUGS
Floating Tablets	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerzine, Chlorpheniramine maleate, Ciprofloxacin, Diltiazem, Fluorouracil, Isosorbide dinitrate, Isosorbid mononitrate, p-Aminobenzoic acid(PABA), Prednisolone, Nimodipine, Sotalol, Theophylline, Verapamil
Floating Capsules	Chlordiazepoxide HCl, Diazepam, Furosemide, L-DOPA and Benserazide, Nicardipine, Misoprostol, Propranolol,
Floating Microspheres	Pepstatin Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfenadine, Tranilast
Floating Granules Powders Films	Diclofenac sodium, Indomethacin, Prednisolone Several basic drugs Cinnerzine

Classification of floating drug delivery system:

Based on the buoyancy mechanism, the floating system is classified as follows:
(A) Effervescent system

1. Gas generating system:-
This system is based on the mechanism of the liberation of CO_2 gas due to the reaction between sodium bicarbonate, citric acid and tartaric acid.[12]

These buoyant systems make use of matrices developed by swellable polymers like HPMC, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers comprising a liquid that gasifies at body temperature.[13]

2. The volatile liquid containing system:-
The GRT of a drug delivery system can be sustained by mixing an inflatable chamber which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also comprise of a bio-erodible plug fabricated by PVA, Polyethylene, etc. that slowly dissolve resulting in the inflatable chamber to liberate gas and crumble after a time to allow the spontaneous expulsion of the inflatable systems from the stomach[14].

(B) Non- effervescent system

1. Colloidal gel barrier system:-
Such a system comprises the drug with gel-forming hydrocolloids are designed to stay buoyant on the stomach content. Extended gastric residence time and the maximum amount of drug which reaches to absorption site in the form of the solution is ready for absorption. This system includes a high level of one or more gel-forming greatly soluble cellulose type hydrocolloids e.g. hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose (HPMC), polysaccharides and matrix-forming polymers i.e. polycarbophil, polyacrylate, and polystyrene. In presence of gastric fluid, the hydrocolloids in the system hydrated resulting in the formation of colloidal gel barrier over its surface

2. Microporous compartment system:-

This technology involves the encapsulation of a drug reservoir within a microporous compartment having pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment get entirely protected to avoid any direct exposure of undissolved drug to the gastric surface. In the stomach, the floatation chamber containing entrapped air resulting from the delivery system to float on to the gastric content. Gastric fluid penetrates through the aperture, dissolved the drug and transported the dissolved amount of drug for continual transport through the intestine for absorption[15].

i. **Floating microspheres[16]:-**
These systems are low-density systems having sufficient buoyancy to float on the gastric contents and retained in the stomach for an extended period. When the system floats over the gastric contents, the drug release is controlled to get the desired rate, which results in prolong gastro-retention time and decreases variations in plasma drug concentration

Polymers employed In Hollow Microspheres

a) **Hydrophilic polymers: -** gelatin, agar, egg albumin, starch, chitosan, cellulose derivatives; HPMC, DEAE cellulose.
b) **Hydrophobic polymers**
These include ethyl cellulose, polylactic acid, PMMA, acrylic acid esters etc.

ii. **Alginate floating beads:-**
Multiple units floating dosage forms have been designed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be formed by dropping a sodium alginate solution in to aqueous solutions of calcium chloride, resulting in precipitation of calcium alginate, then the beads are separated snap and frozen in liquid nitrogen, and freeze-dried at 40° for 24 h, leading to the formation of porous system, which can prolong a floating force over 12h.

iii. **Raft-forming system:-**
Raft-forming systems focus on the transportation of antacids and drug delivery for gastrointestinal infections and disorders. Floating Rafts have been used in the treatment of Gastric esophageal reflux

disease (GERD). The mechanism for raft formation is based the formation of viscous cohesive gel in contact with gastric fluids, where the swelling of each portion of liquid resulting in the formation of a continuous layer also termed as the raft, because of low bulk density created by the formation of CO_2 the raft is floated on the gastric fluid. Generally, the system consists of a gel-forming agent and alkaline bicarbonates or carbonates responsible for the liberation of CO_2 resulting from the system less dense and float over the gastric fluids. Numerous polymers, especially different polysaccharides, Alginic acid, alginates, and pectin are the most extensively used raft-forming agents. Other polysaccharides are also employed, including guar gum, locust bean gum, carrageenan, pectin, and isapgol[17].

Advantages of gastro retentive drug delivery system[18]

1. Increases patient compliance by reducing dosing frequency.
2. Bioavailability increases first pass effect because of the avoidance of variations in plasma drug concentration; a requisite plasma drug concentration is maintained by constant drug release.
3. Gastric retention time is enhanced because of buoyancy.
4. Absorption of drugs soluble in the stomach is enhanced.
5. Drug release is controlled for a prolonged period of time.
6. The drug is delivered to the specific site.
7. The microspheres release drug uniformly, due to which there is lesser evidence of dose dumping.
8. Sustained release effect results in the reduction of gastric irritation.
9. The drugs having short biological half-life drugs show better therapeutic effect.

Disadvantages of gastro retentive drug delivery system[19]

In all the severe gastric conditions the more conventional and reproducible floating properties will be achieved.

1. Drugs having stability and solubility issues in the stomach are not suitable for GRDDS.
2. Drugs having a higher risk of gastric irritation are not suitable for GRDDS E.g. NSAIDS.
3. Drugs having high first pass metabolism are not desired to design gastro-retentive dosage form. E.g. nifedipine.
4. Sufficiently high level of fluids is required for the system to float over gastric fluids and sufficient volume of water should be taken along with dosage form approx. 200-250ml.

Factors controlling the gastro retention of the dosage forms[20]

Physico-chemical factors:

1. pH-dependent absorption

According to pH-partition theory, the only unionized form of the drug has passive absorption throughout the GIT. So, acidic drugs or weak acidic drugs have remained unionized in acidic pH only, and as the gastric fluid has acidic pH, acidic drugs are more absorbed from stomach then intestine.

2. Higher solubility at acidic pH

Generally, at acidic pH, Weakly basic drugs shows good solubility, on the preparation of conventional SR dosage form of weakly basic drug they show better release profile inside the stomach but release rate will be reduced because of alkaline pH of the intestine. So, in case of sustain release dosage form i.e. GRDDS with these drugs and at acidic pH it is solubilized and then enters to the intestine in soluble form. E.g. Cinnarizine, Diazepam, Verapamil, Chlordiazepoxide.

3. pH-dependent stability

pH of stomach and intestine has a major influencing role in terms of stability of some drugs. Some are degraded at higher pH and stable at acidic pH and hence having lower absorption in intestine i.e. at alkaline pH e.g. captopril.

4. Drugs for local effect

In the stomach, there is a direct effect of antacids (e.g. aluminum and magnesium hydroxide) against acidity. So, when there is the requirement of SR effect and the drug releases in the intestine, on designing of conventional SR dosage form, in that situation it founds useless. So, there is the need for GRDDS such as direct acting antacids, the effect of other antacids like ranitidine is enhanced when it has maximum concentration. Misoprostol is a type of directly acting anti-ulcer agent having the effect on gastric mucosa.

Physiological factors:

1. **Mechanism of absorption:**

The absorption of some drugs takes place, mainly by active or facilitated transport mechanisms. These carriers or transporters are preferred in some particular area of GIT, can show specific sites for absorption.

2. **Microbial degradation**

The human colon comprises 400 different species of bacteria and has a bacterial content up to 10_{10} Bacteria per gram. These bacteria degrade some of the drugs which reduce the absorption in the colon. E.g. Ranitidine, Metformin.

3. **Effect of gender, posture, and age:**

It was found from previous studies that the females exhibit comparatively brief mean ambulatory GRT than males, and the gastric emptying in women was moderate than in men, the effect of posture on GRT, and found no remarkable difference in the mean GRT for individuals in vertically straight position, ambulatory and horizontal state. On the other hand, in a similar study, the floating and non-floating systems act differently. In the vertical position, the floating systems floated on the top of the GI content and persist for prolong duration, showing extended GRT. But in case of the non-floating units settled to the bottom part of the stomach and go through rapid emptying due to peristaltic contractions, and the floating units kept away from the pylorus. Although, in the horizontal position, the non-floating units of the same size takes more time for emptying floating units.

Biochemical factors:

1. **Secretory (efflux transporter):**

Secretory transporters mainly P-glycoproteins, having a tendency to collaborate with a wide variety of drugs. Its function is the reversion of the absorbed drug from the cytoplasm of enterocytes back into intestinal lumen resulting in lower bioavailability.

2. **Enzymatic degradation**

Some drugs are acting as substrates for some enzymes (Intestinal metabolic enzymes, Cytochrome p450-CYP3A, which are located in a specific region of GIT, can result in degradation of the drug at that site and form absorptive window.

So far many oral controlled drug delivery systems have been designed to extend drug release. The critical point in this aspect is that the drug has to be absorbed well all through the entire gastrointestinal tract.[21]

Gastroretentive DDS, on the other hand, are not suitable for drugs that:

- ✓ May cause gastric lesions, e.g. NSAIDS
- ✓ Are unstable in the strongly acidic environment of the stomach.
- ✓ Have very limited acid solubility e.g. phenytoin etc.
- ✓ Intended for selective release in the colon e.g. 5-aminosalicylic acid and corticosteroids.

EVALUATION OF FLOATING DRUG DELIVERY SYSTEM[23]

Evaluation of powder blend

a) The angle of Repose: - The maximum angle possible between the surface of the pile of the powder and the horizontal plane. Fixed funnel method was used for calculate. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a graph paper was placed. The powder was carefully allowed to pass through a funnel till the apex of the conical pile just touches the tip of the funnel. The angle of repose was then calculated using the formula,

$$\theta = \tan^{-1}(h/r)$$

Where, θ = angle of repose
h = height of pile,
r = radius of the base of the pile.

b) Bulk Density:- Bulk density can be defined as the ratio of the mass of the powder to its bulk volume. The bulk density based on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully taken into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density is represented in terms of gm/cc and is given by,

$$D_b = M / Vo$$

Where, D_b = Bulk density (gm/cc)
M =Mass of powder (g)
V_o = Bulk volume of powder (cc)

c) Tapped density: - An increment in bulk density which is achieved after mechanical tapping in measuring cylinder is termed as tapped density.[24]

Tapped density= Weight of powder taken/Tapped Volume

d) Hausner Ratio:- it measures the propensity of the powder to be compressed. Settling property and Interparticulate interaction can be measured by Hausner ratio.[24]

Hausner ratio= Tapped density/ Bulk density

Hausner ratio= Vo/Vf

Where, Vo= Unsettled apparent volume, V_f = Final tapped volume.

e) Carr's Index:- One of the useful measures that can be observed from bulk and tapped density determinations is the percent compressibility or the Carr's index, which is calculated by the following equation [25,]

$$\text{Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Evaluation of tablets:[26]

a. Drug-excipient interaction:- FTIR and HPLC techniques are used for drug-excipient interaction. The appearance of a new peak and/or disappearance of original drug or excipient peaks indicate the drug excipient interaction.

b. Floating lag time:- Time taken to comes out a tablet on the top of the surface after it is placed into the dissolution medium. It is measured in minutes or seconds.

c) Weight Variation Test:-Twenty tablets were randomly picked, and the individual tablet was weighed and the average weight was calculated. NMT two of the individual weights deviate from the average weight by 5% as per IP 2010 [27].

IP standards for weight variation test

The average weight of tablets	% deviation
80 mg or less	10
More than 80 mg but less than 250 mg	7.5
250 mg or more	5

d. Friability:-Roche friabilitaor apparatus is used to determine the friability. Six tablets were weighed and placed in the friabilator. The friabilator was operated at 25 rpm for four minutes. The tablets were then de-dusted and weighed. Friability limit is not more than 1%. %Friability was calculated acc.to the following equation[27]:

%Friability = (Initial weight – Final weight)/Initial weight * 100

e) Hardness:- It can be defined as the force exerted to break a tablet across the diameters of the tablet. This test is performed by placing a tablet between two anvils of hardness tester; force is exerted to the anvils and the pressing intensity that causes the tablet to break is noted. Hardness is also known as tablet crushing strength. Hardness testing gives an idea about the tablet has sufficient strength to withstand mechanical shocks of handling in the manufacture, packaging and shipping.[28]

f) Buoyancy studies:-The determination of floating behavior (buoyancy) of the tablets is based on the floating lag time. In a 100ml beaker containing 0.1N HCl, the tablets were placed to determine the floating lag time (time taken by the tablet to reach the surface) and total floating time (floating duration of the tablet).[29]

g) Dissolution Studies:- Usually in vitro dissolution test is performed by using USP paddle type apparatus. In vitro studies are generally monitored in SGF & SIF keeping them at a temperature of 37°C. At the beginning of each test, the tablet is placed in a basket. The basket is lowered before the rotation of paddle and the apparatus is immediately operated at 50 rpm. 0.1N HCl (900ml) is used as a dissolution media for release studies, during the entire process the assembly is maintained at 37±0.5 °C. Samples (5ml) are taken out at a particular time interval and replaced with dissolution media. The samples are then diluted with dissolution media and filtered through Whatman filter paper and assayed. The % release of drug was calculated and calibration curves can be plotted which represents the percentage release of drug with respect to time.

As floating dosage form not rotates may not give proper result and also not reproducible results. The similar problem occurs with swellable dosage form, as they are hydrogels may stick to the surface of vessel or paddle and gives irreproducible results. In order to prevent such problems; various types of modification in dissolution assembly made are as Follows. To prevent sticking at vessel or paddle and to improve movement of the dosage form, the method suggested is to keep paddle at the surface and not too deep inside dissolution medium[30].

List of commercialized gastro-retentive drug delivery system (GRDDS) [31]

Product	**Drug**	**Company**	**Technology**
Liquid Gaviscon®	Alginic acid and sodium bicarbonate	Reckitt Benckiser Healthcare, UK	Effervescent floating
Cipro XR®	Ciprofloxacin HCl and betaine	Bayer, USA	Erodible matrix-based system
Prazopress XL®	Prazosin hydrochloride	Sun Pharma, Japan	Effervescent and swelling-based floating system
Conviron®	Ferrous sulfate	Ranbaxy, India	Colloidal gel forming floating system Floating system
Cefaclor LP®	Cefaclor	Galenix, France	Floating system
Tramadol LP®	Tramadol	Galenix, France	Coated multi-layer floating and swelling system
Baclofen GRS®	Baclofen	Sun Pharma, India	Polymer-based swelling technology
Gabapentin GR®	Gabapentin	Depomed, Inc., USA	Polymer-based swelling technology
Proquin XR®	Ciprofloxacin	Depomed Inc., USA	Polymer-based swelling technology
Glumetza®	Metformin HCl	Depomed Inc., USA	Floating capsule
Madopar®	Levodopa and benserazide	Roche, UK	Floating capsule
Valrelease®	Diazepam	Roche, UK	Floating liquid alginate
Topalkan®	Aluminum and magnesium	Pierre Fabre Medicament, France	Bioadhesive tablets
Xifaxan®	Rifaximin	Lupin, India	Gastro-retention with osmotic system Foam-based floating system
Coreg CR®	Carvedilol	GlaxoSmithKline	Bilayer floating capsules
Inon Ace®	Simethicone	Sato Pharma, Japan	Floating tablets
Cytotec®	Misoprostol	Pharmacia/Pfizer Inc., USA	The gas generating floating tablets
Cifran OD®	Ciprofloxacin HCl	Ranbaxy, India	
Oflin OD®	Ofloxacin Ranbaxy, India Gas generating floating tablets	Ranbaxy, India	

Patents on GRDDS[32]

S. No	Patents	Patent no.
1.	Gastrorentevive dosage form systems and the process of preparation thereof.	US20140271871846
2	Gastrorentevive sustained and pulsatile drug delivery systems.	W02013051036 A1
3.	GRDDS and their dosage form their method of preparation using calcium carbonate.	W02014057086 A1
4.	A novel gastro retentive drug delivery of macrolide.	W02011125075 A3
5.	Gastrorentevive controlled release microsphere for improved drug delivery.	US6207197 B1
6.	Extended release gastro retentive oral drug delivery systems for valsartan.	EP2061438 A1
7.	GRDDS	W02009089665 A2
8.	GRDDS comprising an extruded hydratable polymer.	US8586083 B2

Conclusion:

Now a day's formulation and development of GRDDS products are one of the prime aspects of pharmaceutical research. From the above review, we conclude that GRDDS products by means of formulation and product design deliver the drug in a modified form different from that of the conventional dosage forms particularly at stomach region, significantly to drugs showing absorption at stomach site. The principle of buoyant preparation provides an easy and practical process to achieve enhanced gastric residence time for the dosage form and sustained drug release, a numbers of drug delivery systems are being formulated which focuses on releasing the drug at gastric region, these drug delivery systems have various advantages and disadvantages like their in-vitro in-vivo correlation is very less. In spite of its various limitations, serious efforts are being done to commercialize this delivery system.

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