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FLOTING DRUGS DELIVERY SYSTEM

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ABSTRACT:

- Scientific and technological developments in the research and development of new drug delivery systems have been made in recent years by resolving physiological disorders, such as short gastric residence periods and unpredictable gastric emptying times. Dosage forms that can be hold within the stomach are called as Gastro-retentive Dosage Forms (GRDF). Multiple methods used in the prolongation of gastric residence time are floating drug delivery system, swelling and expanding system, polymeric bio-adhesive system, high density system and other delayed gastric emptying system. Medication-based disease treatment is entering a new era in which a increasing range of innovative drug delivery technologies are being used and are available for clinical use. Floating Drug Delivery Systems (FDDS) is one of the gastro-retentive dosage forms used to achieve extended duration of gastric residency. The aim of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with particular focus on the main floating mechanism to achieve gastric retention. Sustained oral release of gastrointestinal dosage types provides many benefits for drugs with absorption from the upper sections of the gastrointestinal tract and those that function locally throughout the stomach. This review includes the physiology, factors controlling gastric retention time, excipient variables influencing gastric retention, approaches to designing single-unit, hydro-dynamically balanced system and multi-unit floating structure, and aspects of their classification, formulation and evaluation are discussed in detail, and
few applications of these systems.

Keywords: Gastro retentive system, Floating drug delivery system, Classification, Mechanism, Methods, Evaluation.

INTRODUCTION:

- Drug delivery system represents pure crude form of the drugs either in solid, liquid or semi-solid form, which should be therapeutically efficient, safe and stable enough to deliver a required amount of the drug to the specified site in the body to reach instantly, to achieve the correct concentration and then retain the adapted concentration. Many of the drug delivery systems commercialized are oral drug delivery systems.1 Due to low treatment costs, increased patient compliance and ease of administration oral drug delivery is mostly preferred. Despite of multiple benefits, the frequency of dosing of a medication should be increased as it gets easily emptied from the stomach.[8]
- To overcome these barriers, the delivery of drugs must provide prolonged duration of gastric residence. Gastro retention contributes to an increase in bioavailability, an improvement in the duration of drug release, minimizes drug waste and improves drug solubility that is less soluble in a high environmental ph. Many drugs released in the stomach have the greatest therapeutic impact as they are continuously delayed and controlled in release. This type of drug delivery method would have comparatively less side effect and would eliminate the need for repeated dosages. in pharmaceutical dosage, the formulation of drugs in multilayered / bi-layered tablets is a innovative approach for providing the loading dose and maintenance dose in a tablet. This design allows for the preparation of extended release with an immediate release quantity of drug in one layer and an extended release proportion in the second, thereby retaining a prolonged blood level. The immediate release section will disintegrate rapidly after absorption, by supplying the initial dose of medication for immediate action where the matrix layer remains intact as it passes through the intestine most of the time, thus gradually dissolving from its exposed phases in this path, which helps to retain the blood level that was initially reached.
Typically, conventional controlled-release dosage forms prolong the release of drugs and do not have a rapid onset of action after oral usage. Accordingly, the layered tablets provide a pharmacokinetic benefit over conventional controlled release dosage forms as the drug is rapidly released from the rapid release layer leading to a rapid increase in drug plasma concentration accompanied by a continued release of the drug from the sustained release layer.

Drug Suitable for Gastro retentive Drug Delivery System:[9]

- The Drugs which are locally active in the stomach like Antacids, Misoprostol, etc.
- Drugs showing narrow absorption window in Gastro intestinal tract e.g. Riboflavin, Furosemide, etc.

- Drugs showing instability in the colonic environment e.g. Ranitidine HCl, Captopril
- Drugs which are effective against normal colonic microbes e.g. antibiotics against *Helicobacter pylori*.
- Drugs which have low solubility at high pH values e.g. Chlordiazepoxide, Diazepam

Drugs Unsuitable for Gastroretentive Drug Delivery System[9]

Drugs which have very limited solubility in the acid medium e.g. Phenytoin, etc.
Drugs enduring instability in the gastric environmental conditions e.g. Erythromycin, etc.
The Drugs which are mainly employed for their selective release in the colon e.g. 5-amino salicylic acid and corticosteroids, etc.

Floating Drug Delivery System:[2]

DEFINITION

Floating Oral Drug Delivery System (FDDS) are retained in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal
Fluids.
Floating drug delivery system (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.
While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system.
After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control fluctuations in plasma drug concentration

Basic GIT Physiology

Anatomically the stomach is divided in to three regions Fundus, Body and Antrum (pylorus).
The design and evaluation of FDDS is based on anatomy and physiology of GIT.
The stomach is J shaped dilated portion of the alimentary tract situated in the epigastria, umbilical and left hypochondriac regions of abdominal cavity.
The Gastrointestinal tract is essentially a tube about nine meters long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx), esophagus, stomach, small intestine (consisting of the duodenum, jejunum and ileum) and large intestine (consisting of the cecum, appendix, colon and rectum).

Mechanism of Floating Systems:[3]

While the system is floating on the gastric content the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F as a function of time that is required to maintain the submerged objects. The apparatus helps in optimizing FDDS with respect to stability to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.
F = F buoyancy - F gravity = (D f - D s) g v
Where, F = Total vertical force, Df = fluid density, Ds = object

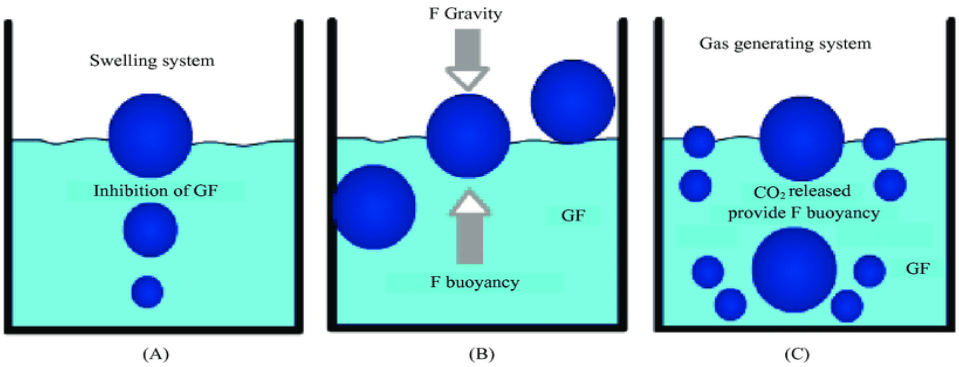

Fig: 1 Mechanism of Floating Systems[3]

CLASSIFICATION:[9] [10]

A. Effervescent FDDS

1. Gas generating system

2. Volatile liquid containing system

B. Non-Effervescent FDDS

1. Colloidal gel barrier system

2. Bi-layer floating tablets

3. Microporous compartment system

4. Floating Beads/ Alginate Beads

5. Micro balloons/ Hollow Microspheres

C. Raft forming system

- **Effervescent FDDS**

This system makes use of a floating chamber filled with water, vacuum, air, or inert gas. CO2 which is formed as a result of an effervescent reaction between the organic acid (citric acid) and the carbonate / bicarbonate salts can be introduced into the floating chamber. Such a system uses matrix prepared with swellable polymers such as chitosan-like polysaccharides, effervescent materials such as citric acid, sodium bicarbonate, and tartaric acid, or chambers containing a liquid that gasifies at the body temperature.

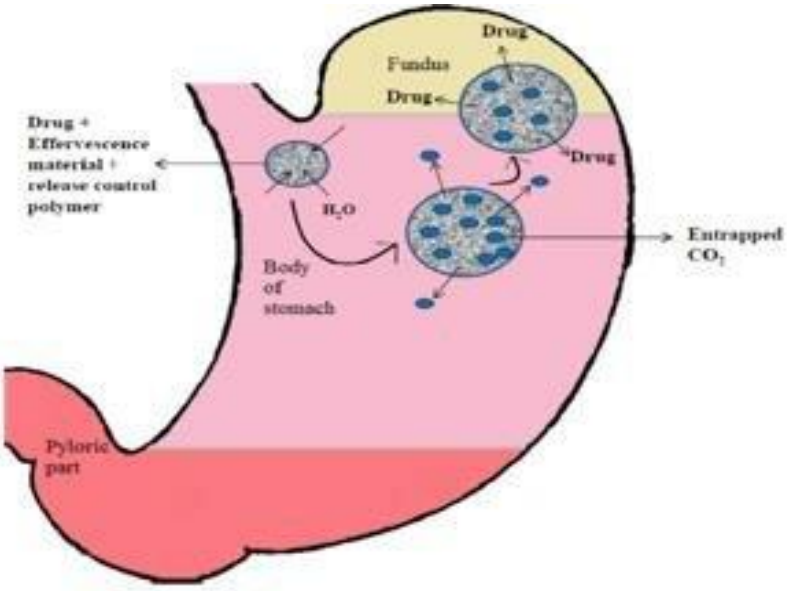

Figure 2: GRDDS based on effervescence.[1]

Gas generation system:

This buoyant delivery system uses effervescence reaction between citric acid / tartaric acid and carbonate / bicarbonate salts to release CO2 which further reduces its specific gravity and makes it float over chime.

Volatile liquid storage system:

These contain an inflatable chamber consisting of a liquid, e.g. cyclopentane, ether, which gasifies at body temperature to induce inflation of the chamber in the stomach. The system consists of two chambers the first chamber consisting of the drug, and the volatile liquid in the second chamber

- **Non-Effervescent FDDS**

In GI tract, the non-effervescent FDDS is based on the mechanism of polymer swelling or bioadhesion to the mucosal layer. The excipients most frequently used in non-effervescent FDDS are:

 Hydrophilic gums,

 Gel forming or highly swellable cellulose type hydrocolloids

 Polysaccharides and matrix forming materials such as polymethacrylate, polycarbonate, polystyrene, polyacrylate, as well as bioadhesive polymers such as Carbopol and Chitosan.

1. Colloidal gel barrier systems / Single layer floating tablets:[25]

Such systems contain a high degree of one or more gel forming, cellulose type hydrocolloids, polysaccharides, and polymers forming matrix, which are ex

FIGURE 3: SINGAL LAYER TABLET.[5]

2. Bi-layer floating tablets:

A bi-layer tablet comprises of two layers with first layer is the immediate release layer, which releases the initial dose from the system while the other is the sustained release layer which absorbs the gastric fluid, creating an impermeable colloidal gel barrier on its surface and retaining a bulk density of less than 1.

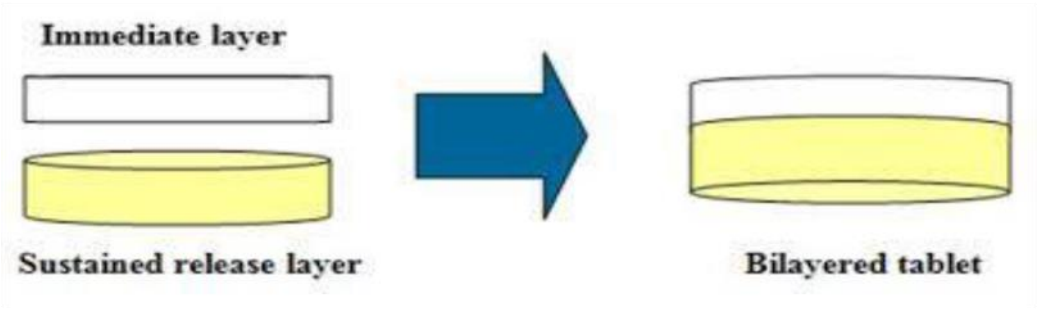

Figure 4: Bilayer tablet.[4]

3. Micro porous compartment systems:

This technology is based on a drug reservoir being encapsulated within a micro porous compartment with apertures along its top and bottom wal

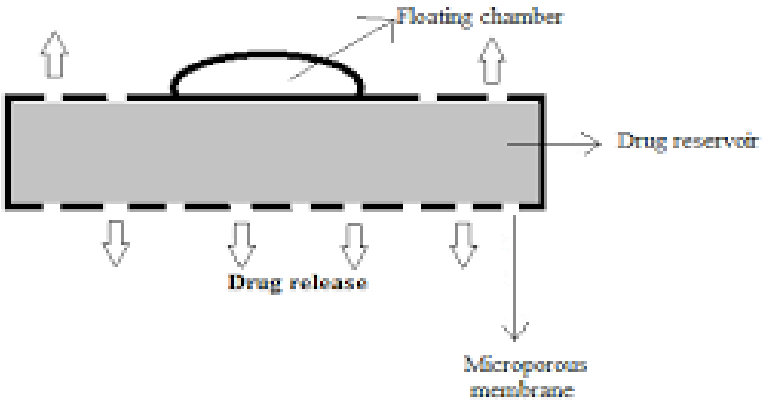

FIGURE 5: MICRO POROUS COMPARTMENT SYSTEM: [6].

4. Multi particulate system: Floating beads / Alginate beads:

Multi-particulate drug delivery systems are often oral dosage types consisting of a multiplicity of small discrete units.

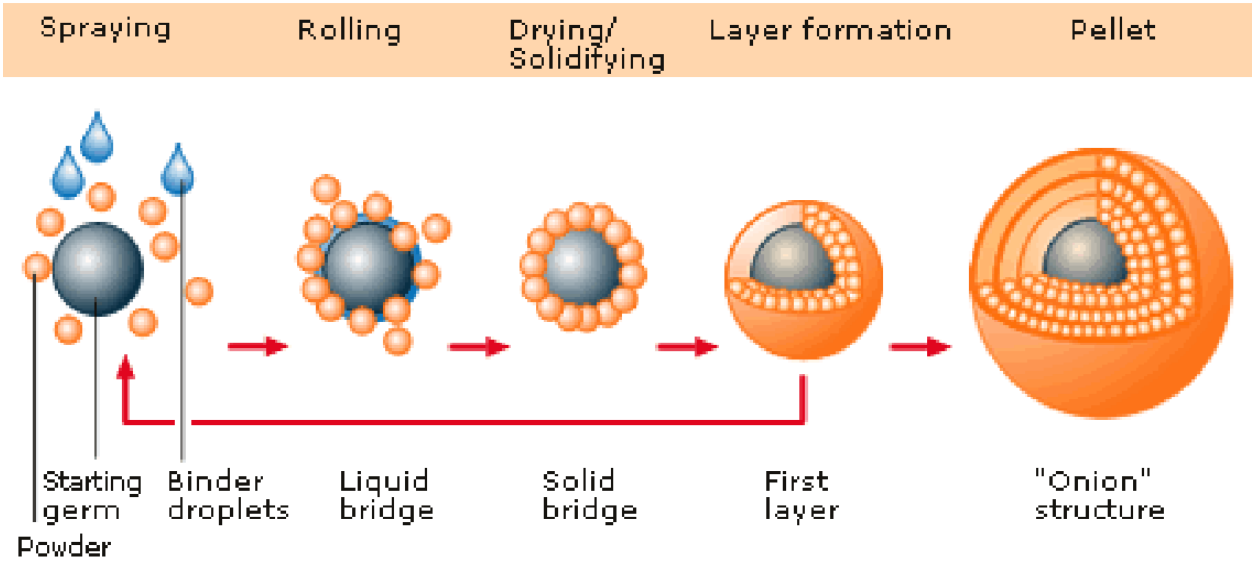

FIGURE 6: MULTY PARTICULAT SYSTEM [8].

5. Micro balloons/Hollow microspheres: Hollow microspheres, also known as micro balloons when immersed in aqueous media they were found to float *in vitro* for 12 hrs.

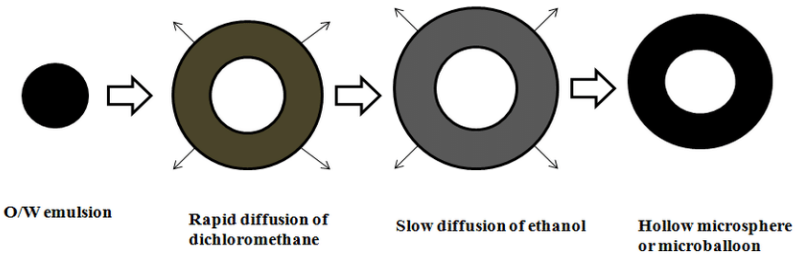

FIGURE 7: HOLLOW MICROSPHERES [7]

- **Raft Forming System[27][28]**

For the delivery of antacid and other medications for gastro-infection and gastro intestinal disorders, a Raft forming systems are mostly considered. Upon contact with gastric fluid the gel forming solution swells and creates a viscous compact gel containing an entrapped CO2 bubbles forming raft layer on top of gastric fluid that gradually releases the drug substance into

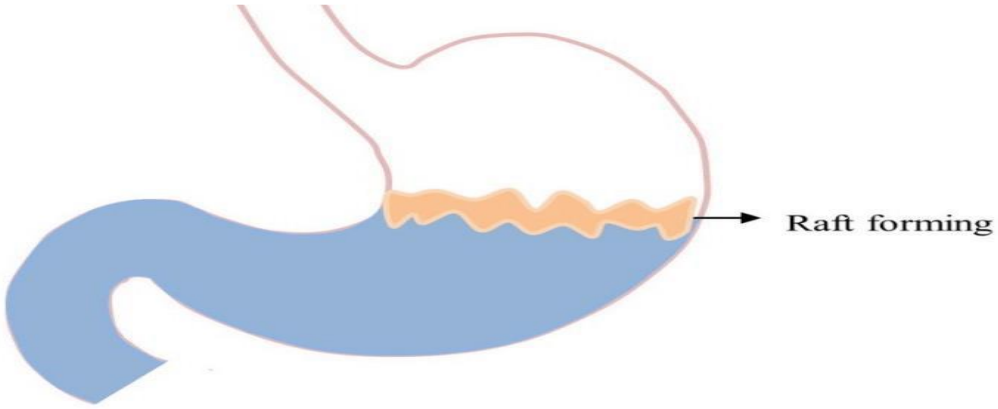

Figure 5: GRDDS based on Raft Forming System.1

Methods of Developing Floating Drug Delivery System:[10][11][12]

• Direct compression technique:
It means compressing tablets directly from powder content without altering the substance's physical structure itself. Dicalcium trihydrate phosphate, tricalcium phosphate, etc. are the most widely used carriers.

• Effervescent Technique:
An effervescent reaction between organic acid (citric acid) and bicarbonate salts will fill the floating chamber of the drug delivery system with inert gas (CO2).

• Wet granulation technique:
Involves wet powder massaging, milling or drying. Wet granulation shapes the granules by binding the powders together with an adhesive rather than compacting them.

• Ionotropic Gelation Technique:
Gelation of anionic polysaccharide sodium alginate, the primary polymer of natural origin, was accomplished with opposite charged calcium ions (counter-ions) with the objective of forming instantaneous micro particles.

• Solvent evaporation technique:
Continuous phase ability is inadequate to remove the entire amount of liquid dispersal solvent. Solvent evaporates from the dispersal surface to receive hardened microspheres.

• Spray Drying Technique:
Involves dispersing the core layer into the liquefied coating content and spraying the core coating mixture into the environment so that the coating is solidified by rapidly evaporating in which the coating material is solubilized

• Melt Solidification Technique:
his method involves emulsifying the molten mass in the aqueous phase followed by cooling it to solidify. Lipids, waxes, polyethylene glycol, etc. are the carriers used for this technique.

• Melt Granulation Technique:
This is the method that agglomerates the pharmaceutical powders using a meltable binder and does not use water or organic solvents for granulation.

Stomach Physiology:[13]

The stomach is an expanded digestive tube section present between the oesophagus and small intestine. The stomach is contracted in the empty state, and the mucosa and sub mucosa are thrown up into distinct folds called rugae.
Below are identified the four major types of secretary epithelial cells which cover the surface of the stomach and extend into gastric pits and glands.

- **Mucous cells:** secrete alkaline fluid.
- **Parietal cells:** secretes an acid that is hydrochloric acid.
- **Chief cells:** secrete pepsin, a proteolytic enzyme.

G cells: secrete the hormone gastic

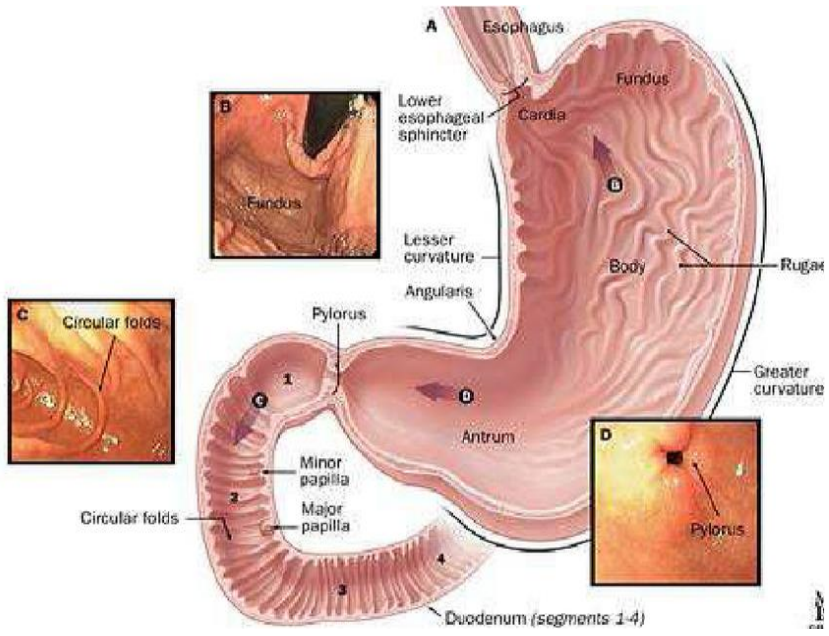

Figure 6: physiology of stomach

Advantages of FDDS [14]

1. Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine.

2. FDDS are advantageous for drugs meant for local action in the stomach eg: Antacids
3. FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhea to keep the drug in floating condition in stomach to get a relatively better response.
4. Acidic substance like aspirin causes irritation on the stomach wall when come in contact with it hence; HBS/FDDS formulations may be useful for the administration of aspirin and other similar drugs.
5. The FDDS are advantageous for drugs absorbed
through the stomach e.g.: Ferrous salts, Antacids

Disadvantages of FDDS[15]

1. Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.
2. Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergo significant first-pass metabolism, may not be suitable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.
3. One of the disadvantages of floating that they require a sufficiently high level of fluids in the stomach, so that the drug dosages form float
therein and work efficiently.

Limitations OF FDDS[16]

They require a sufficiently high level of fluids in the stomach for the drug Del float therein and to work efficiently.
Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluid. Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which insignificant first- pass metabolism, may not be desirable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability.
Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.

Evaluation of Floating Drug Delivery System[18][19][20]

Bulk Density:

It is the ratio of total mass of powder (m) to the bulk volume (Vo) of powder.
Db=m/Vo

Tapped Density:

It is the ratio of total mass of powder (m) to the tapped volume (Vi) of powder.
Dt = m/Vi

Compressibility Index:

The flow ability of powder can be evaluated via evaluating the bulk density (ρo) and tapped density (ρt) of powder and the rate at which it packed down. Compressibility index calculated by means of
Where,
ρo = Bulk density g/ml,
ρt = Tapped density g/ml.

Hausner's Ratio:

It is evaluated by means of taking Tapped density and it divided by Bulk density by the usage of following formula.
Hausner's Ratio= Tapped density / Bulk density

Angle of Repose:

The frictional forces in a loose powder or granules can be measured via angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The granules are allowed to flow through the funnel fixed to a stand at fixed height (h).
The angle of repose, then calculated by measuring the height and radius of the heap of granules formed.
Tan θ = (h/r)
θ= tan-1 (h/r)
θ = angle of repose
h = height of the heap
r = radius of the heap

Tablet Dimensions:

Thickness and diameter were measured using a calibrated Vernier Caliper. Three tablets of each formulation have been picked randomly and thickness were measured separately.

Hardness:

Hardness shows the capability of a tablet to face up to mechanical shocks while handling. The hardness of the tablets was evaluated using Monsanto hardness tester. It was expressed in kg/cm2. Three tablets have been randomly picked and hardness of the tablets was decided.

Friability test: [21]

The friability of tablets was evaluated by using Roche Friabilator. It was expressed in percent (%). Ten tablets had been to start with weighed (W) and transferred into friabilator. The friabilator were operated at 25 rpm for 4 minutes or run as much as 100 revolutions.

Application of Floating Drug Delivery System:[22][23][24]

Enhanced Bioavailability:
The bioavailability of riboflavin CR-GRDF is substantially increased compared with the administration of non GRDF CR polymeric formulations.

Sustained delivery of drugs:
Oral CR formulations experienced problems in the GIT like gastric residence time. HBS systems that can stay in the stomach for prolonged period of time and having a bulk density of less than 1 and can float on the gastric contents can usually overcome these problems.

Site specific drug delivery systems:
The controlled, gradual drug delivery to the stomach provides appropriate local therapeutic rates and reduces the systemic exposure of the drug. The dosing frequency can be decreased by extended gastric availability from a site driven drug delivery system. E.g. Furosemide and Riboflavin.

Improvement of Absorption:
Drugs with low bioavailability due to site specific absorption from the upper part of the GIT are possible candidates to be developed as floating drug delivery systems, by optimizing their
absorption.

Minimized adverse reaction at the colon:
Retention of the drug in the stomach in HBS minimizes the amount of drug entering the colon. Unwanted drug activity in the colon region can thus be avoided.

Reduced drug concentration fluctuation:
Continuous input of the drug following CR-GRDF administration creates concentrations of the blood drug within a narrower range compared with types of immediate release dosage forms

CONCLUSION:
Development of an efficient gastro retentive dosage form for stomach specific drug transport is an actual project. Accordingly, to produce the preferred gastro retention several strategies were used, out of which, the floating drug delivery system has emerged as the great promising approach. These systems offer the gain of better absorption of medication that are absorbed from the top part of stomach, which enhance the bioavailability and controlled delivery of many drugs with new and vital therapeutic options. This leads to less frequent dosing and more advantageous efficiency of the treatment. Good stability and better drug release as compared to other conventional dosage form make such system greater reliable. Drug absorption in GIT is a extraordinarily variable system and prolonging GI retention of the dosage form prolongs the time of drug absorption. Floating drug delivery system guarantees to be a technique for gastric retention. Although there are wide variety of complications to be labored out to gain extended GI retention, many companies are focusing in the direction of commercializing this approach. Wide variety of industrial product and patent issued in this field are evident of it.

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