

**FORMULATION AND EVALUATION OF GASTRO-RETENTIVE FLOATING TABLETS****Gupta Priya, Kesh Mugdha**

Department of Pharmaceutical Sciences, Jayoti Vidyapeeth Women's University, Jaipur, Rajasthan, India

**ABSTRACT**

In case of drugs which are less soluble at alkaline pH of intestine, conventional oral dosage forms having low bioavailability problems due to their rapid gastric transition from stomach. Moreover drugs which show their local action in stomach, get quickly emptied do not get sufficient residence time in stomach. Thus the result is frequency of dose administration in such cases is increased. To solve these problems, numerous efforts have been made to prolong the retention time of drug in stomach. Floating drug delivery system (FDDS) is one of the most significant methods in prolonging the retention time of drug in stomach. FDDS is low-density systems that have enough buoyancy to float over the gastric contents and remain buoyant in the stomach for a prolonged period of time without affecting the gastric emptying rate. The drug is released gradually at the desired rate while the system is floating on the gastric contents which outcomes in an improved control of the fluctuations in plasma drug concentration. This review provides the detailed summary of formulation and evaluation of gastro-retentive floating drug delivery system with their advantages over the conventional drug delivery system and also includes limitation.

**Key words:** Floating Drug Delivery System, Gastro-retentive Drug Delivery System, Gastric Retention, Gastric Residence Time, (GRT) and Plasma drug concentration.

**INTRODUCTION:**

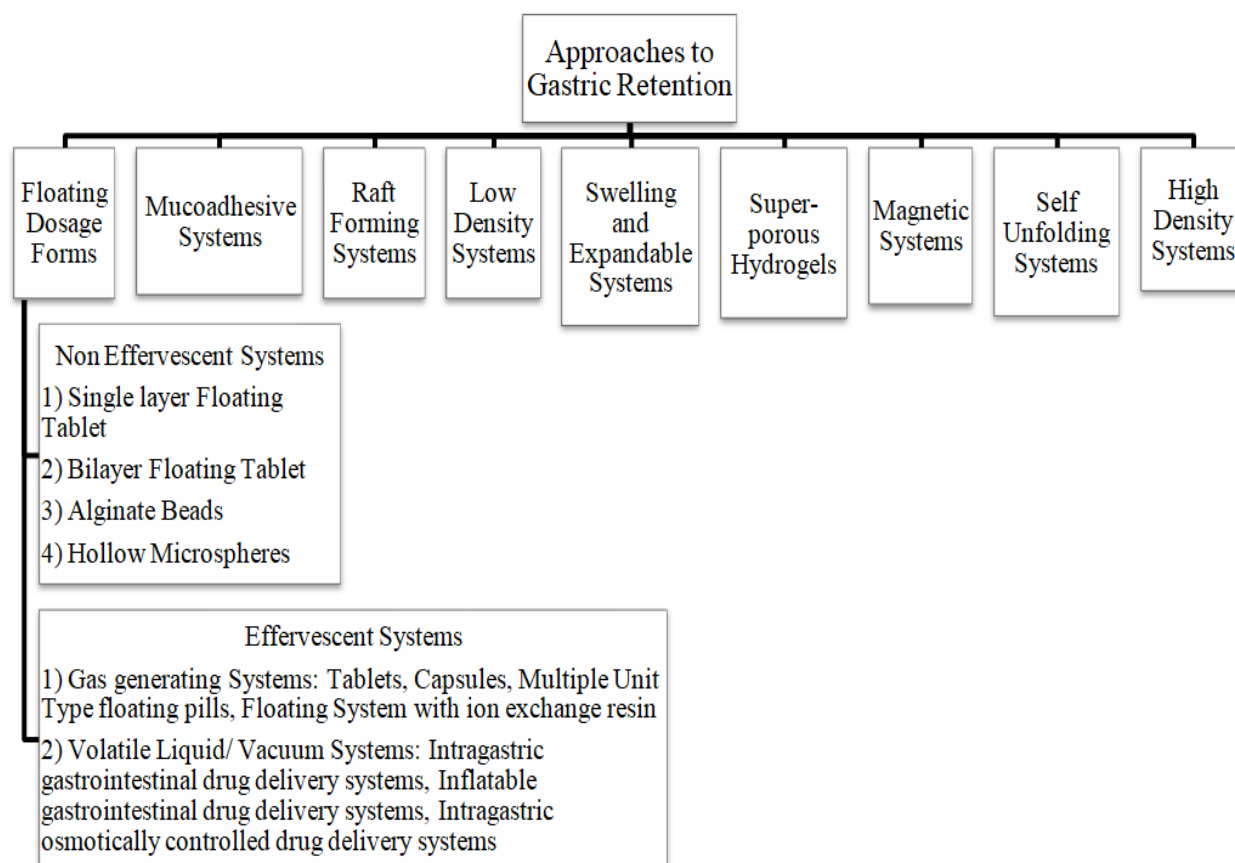
So far for human administration, oral formulations have made a major place among the various dosage forms established and the most preferable route of drug delivery. In most of the cases, the conventional oral delivery systems show partial bioavailability because of fast gastric-emptying time among many other reasons involved such as inability to restrain and locate the controlled drug delivery system within the desired region of gastro intestinal tract. <sup>[1, 2, 3]</sup> To overcome these problems oral controlled dosage form with gastro retentive properties were developed. Gastro-retentive dosage forms are appropriate for local drug delivery to the stomach and small intestine. Numerous approaches are available to increase gastric residence time of oral dosage form in the stomach which includes floating systems, swelling and expanding systems, bio adhesive systems, modified shape systems, high density

systems and other delayed gastric emptying devices. <sup>[4, 5, 6]</sup>

**GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS**

Gastro-retentive drug delivery systems (GRDDS) are those dosage forms that can be retained in the stomach. These are the systems which can persist in gastric region for several hours and significantly prolongs the gastric residence time of drug. After oral administration, such a delivery system would be retained in stomach. It will release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to absorption site in GIT. <sup>[7]</sup>

Their application can be advantageous in the case of drugs absorbed mainly from the upper part of GIT or are unstable in the alkaline medium of distal intestinal regions. They can also be used beneficially in the local therapy of the stomach.



**Graph 1:** Schematic representation of various gastro-retentive formulations

**ADVANTAGES** [8, 9]

- 1) Increase in bioavailability and efficiency of drugs and commercial usage of dosage.
- 2) Reduced factor of risk in resistance in antibiotics.
- 3) Improved release in case of short half-life drugs causes flip flop pharmacokinetics and also confirms patient compliance with reduced dosage frequency.
- 4) They are beneficial against limitations of the gastric retention time (GRT) as well as the gastric emptying time (GET). Because of lower bulk density than gastric fluids the system remains buoyant on gastric fluid.
- 5) These are effective in repairing stomach and small intestine related problems. It's attributed to the fact that gastro-retentive drug delivery sustains drug release and hence, avail local therapy in these organs.
- 6) This method provides with a systematic and controlled drug delivery system which

reduces chances of drug over exposure at the diseased site.

- 7) Providing a narrow curative index, the gastro-retentive dosage forms reduce variance in concentrations of drugs and effects.
- 8) Due to reduced counter activity by body this system supplies higher efficiency.

**DISADVANTAGES** [9, 10, 11, 12]

- 1) Increased level of fluids in the stomach is required.
- 2) Incompatible for such drugs as:
  - Drugs insoluble in gastric fluid
  - Causes G.I irritation
  - Inefficient in acidic environment
- 3) Drugs proposed for selective release in the colon.
- 4) Unpredictable adherence owing to state of constant renewal of mucus wall of stomach.

**Table 1:** SUITABLE DRUGS USED FOR GRDDS [9, 13]

S. No.	Suitable Drugs	Examples
1.	Drugs acting locally in the stomach.	Antacids, Anti-ulcer drugs, drugs against H. Pylori, Misoprostol, Clarithromycin, Amoxicillin.
2.	Drugs with narrow absorption window in Gastrointestinal tract (GIT).	Cyclosporine, Methotrexate, Levodopa, Repaglinidine, Riboflavin, Furosemide, Para-aminobenzoic Acid, Atenolol, Theophyllin,
3.	Drugs having unstable properties in the intestinal or colonic environment.	Captopril, Ranitidine HCl, Metronidazole, Metformin HCl.
4.	Drugs caused imbalance of normal colonic microbes.	Antibiotics against H. Pylori, Amoxicillin Trihydrate.
5.	Drugs having low solubility at high pH values.	Diazepam, Chlordiazepoxide, Furosemide, Verapamil HCl.

**Table 2:** UNSUITABLE DRUG USED FOR GRDDS [9, 14]

S. No.	Unsuitable Drugs	Examples
1.	Drugs having very limited acid solubility.	Phenytoin
2.	Drugs that exhibits instability in the gastric environment.	Erythromycin
3.	Drugs that are used for selective release in the colon.	5- amino salicylic acid and corticosteroids

**FACTORS CONTROLLING GRDDS** [9, 15, 16, 17]

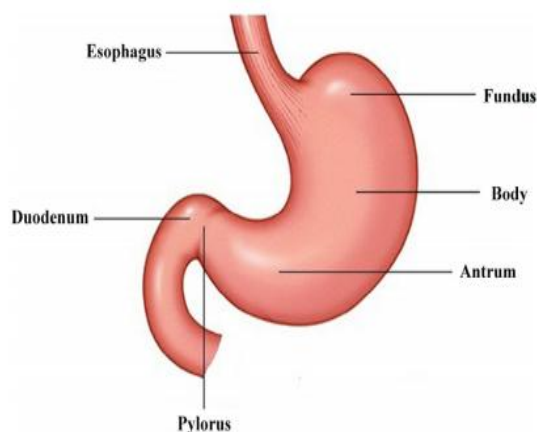
- Density: Dosage form with lower density can float to the surface in the gastric content. Suitable density required for floating property is less than  $1.0 \text{ gm/cm}^3$ .
- Size: Size should be more than 7.5 mm in diameter.
- Shape: Either round or spherical shaped dosage form exhibit better property than other shapes.
- Single or multiple unit formulation: Due to predetermined release profile multiple units are desirable.
- Fed or Unfed State: Gastric retention time is less during fasting condition due to rise in gastric motility.
- Nature of Meal: High amount of fatty acid and other indigestible polymers slow down the gastric retention time due to variation in gastric motility.
- Frequency of Feed: Low frequency of migrating myoelectric complex (MMC) contributes to GRT up to 400 times which in turn depends on the frequency of food intake.
- Caloric Content: A high protein and fat rich diet can increase GRT by 4 to 10h.
- Gender: Males have greater GRT than females.
- Age: GRT is more in geriatric patients and less in neonates and children. Age above 70 (>70) exhibit longer GRT.
- Posture: GRT can vary between supine and upright ambulatory states of the patient.
- Disease State: Gastric disease such as diabetes, chron's disease, hypothyroidism, hyperthyroidism, duodenal ulcers etc fluctuate the GRT.
- Concomitant Intake of Drug: Combination of some drugs along with gastric motility enhancers or depressants, affect GRT

## FORMULATION CONSIDERATIONS FOR GRDDS

[7]

1. Must have adequate drug loading capacity
2. Must regulate the drug release profile
3. Must have complete degradation and removal of the system once the drug release is over
4. Should not have effect on gastric motility including emptying pattern
5. Should not have other local adverse effects

## BASIC GASTROINTESTINAL TRACT PHYSIOLOGY



**Figure 1:** Diagram of human stomach [3]

Mainly stomach is divided into 3 sections:

1. Fundus- The proximal part.
2. Body- The reservoir for undigested material.
3. Antrum (pylorus)- The main site for mixing motions and act as a pump for gastric emptying by propelling actions. [18, 19, 20, 21]

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is different in the 2 states.

→ *During the fasting state:-* [18, 19, 22, 23]

An inter-digestive series of electrical events take place in which cycle both through stomach and intestine every 2 to 3 hours known as inter-digestive myoelectric cycle or migrating myoelectric cycle (MMC).

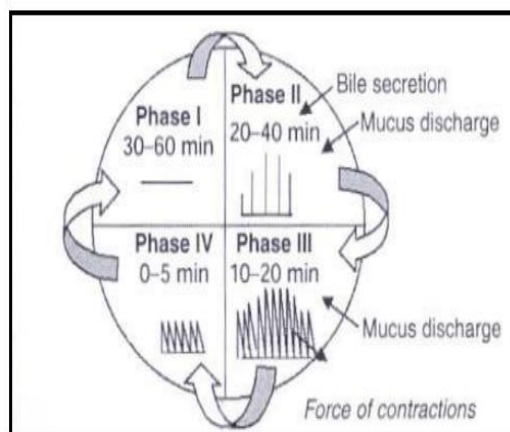
This is further divided into following 4 phases:

- i Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
- ii Phase II (pre-burst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the

intensity and frequency also increases gradually.

iii Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

iv Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.



**Figure 2:** Motility patterns of the GIT in the fasted state

→ *During the fed state:-* [18, 19, 22, 23]

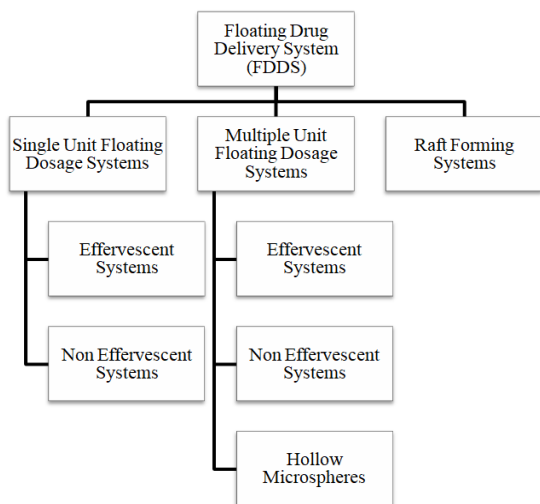
The pattern of contractions changes from fasted to that of fed state after the ingestion of a mixed meal known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in decreasing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.

## FLOATING DRUG DELIVERY SYSTEM (FDSS)

Floating systems or Hydrodynamically controlled systems are low-density systems that require adequate buoyancy to float over the gastric contents and stay buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. The drug is released gradually at the desired rate from the system while the system is floating on the gastric contents. The residual system is

emptied from the stomach after release of drug which results in an improved GRT and a better control of the fluctuations in plasma drug concentration. [19, 24]

**CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM (FDSS)** [18]



**Graph 2:** Schematic representation of classification of FDSS

**MECHANISM OF FLOATING SYSTEMS**

Floating drug delivery systems (FDSS) have a bulk density less than gastric fluids which help to remain buoyant in the stomach without disturbing the gastric emptying rate for a prolonged period of time. The drug is released slowly at the desired rate from the system while the system is floating on the gastric contents. The residual system is emptied from the stomach after release of drug which results in an improved GRT and a better control of the fluctuations in plasma drug concentration.

Besides a minimal gastric content needed to allow the accurate achievement of the buoyancy retention principle, a minimal level of floating force (F) is also essential to keep the dosage form reliably buoyant on the surface of the meal. A novel apparatus for determination of resultant weight has been reported to measure the floating force kinetics. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side. This apparatus helps in optimizing FDSS with respect to stability and

durability of floating forces produced. [18, 19, 21, 25, 26]

$$F = F_{\text{buoyancy}} - F_{\text{gravity}}$$

$$F = (D_f - D_s) gV$$

Where,

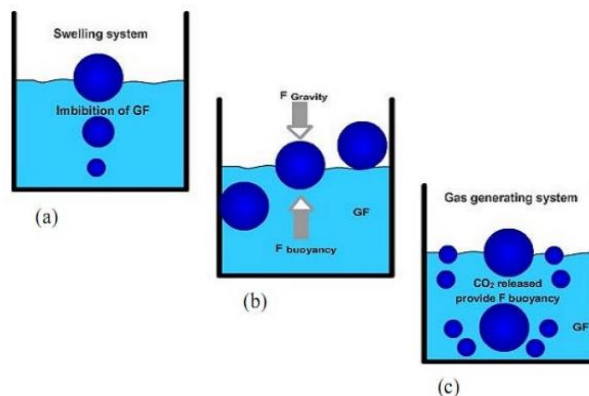
F = Total vertical force in N,

D<sub>f</sub> = Fluid density in Kg/m<sup>3</sup>,

D<sub>s</sub> = Density of object in Kg/m<sup>3</sup>,

V = Volume of the object m<sup>3</sup>,

g = Acceleration due to gravity m/s<sup>2</sup>. [18, 19, 25]



**Figure 3:** Mechanism of floating system, GF= Gastric fluid [25]

**ADVANTAGES OF FLOATING DRUG DELIVERY** [27, 28]

1. Improved bioavailability
2. Sustained drug delivery/reduced frequency of dosing
3. Targeted therapy for local ailments in the upper GIT
4. Decreased fluctuations of drug concentration
5. Enhanced receptor activation selectivity
6. Reduced counter-activity of the body
7. Prolonged time over critical (effective) concentration
8. Reduced adverse activity at the colon
9. Site specific drug delivery

**DISADVANTAGES OF FLOATING DRUG DELIVERY** [27, 29]

1. Need a high level of fluid in the stomach for drug delivery to float and work efficiently.

2. Not appropriate for drugs that have solubility or stability problem in GIT.
3. Drugs which is well absorbed along the entire GIT and undergoes first pass metabolism, may not be desirable.
4. Drugs which are irritant to gastric mucosa are also not desirable.
5. The drug substances that are unstable in the acidic environment of the stomach are not desirable.
6. The dosage form should be directed with a full glass of water (200-250 ml).

### **EVALUATION OF FLOATING DRUG DELIVERY SYSTEMS**

#### **1. Buoyancy / Floating Test:** <sup>[27, 30, 31]</sup>

The test for buoyancy is usually determined in 900 mL of simulated gastric (HCl/NaCl with 0.02% Tween 80, pH 1.2) or intestinal fluids (KH<sub>2</sub>PO<sub>4</sub>/NaOH buffer with 0.02% Tween 80, pH 7.4) maintained at 37°C using the USP dissolution apparatus. These fluids simulate the surface tension of human gastric juice (35–50 mN/m<sup>2</sup>). The amount of time the dosage form floats is termed the floating time.

#### **2. Swelling Study:** <sup>[27, 30, 31]</sup>

The swelling behavior of a dosage form is measured by studying its weight gain or water uptake. The dimensional changes can be measured in terms of the increase in tablet diameter and/or thickness over time.

Water uptake is measured in terms of percent weight gain, as given by the following equation-

$$\frac{W_t - W_0}{W_0} \times 100$$

W<sub>t</sub> = Weight of dosage form at time t

W<sub>0</sub> = Initial weight of dosage form

#### **3. In Vitro Drug Release Studies:** <sup>[27, 32]</sup>

The test for buoyancy and in vitro drug release studies are generally carried out in simulated gastric and intestinal fluids maintained at 37°C. In practice, floating time is determined by using the USP dissolution apparatus containing 900ml of 0.1 HCl as a testing medium maintained at 37°C. The time required to float

the HBS dosage form is noted as floating time. Dissolution tests are performed using the USP dissolution apparatus. Samples are withdrawn from time to time from the dissolution medium, replenished with the same volume of fresh medium each time, and then examined for their drug contents after a proper dilution.

#### **4. Resultant weight test:** <sup>[27, 30, 31]</sup>

An in vitro measuring apparatus has been considered to determine the real floating capabilities of buoyant dosage forms as a function of time. It operates by measuring the force equivalent to the force F necessary to keep the object totally submerged in the fluid. This force determines the resultant weight of the object when immersed and may be used to measure its floating or non-floating capabilities. The magnitude and direction of the force and the resultant weight corresponds to the vectorial sum of buoyancy (F<sub>buoy</sub>) and gravity (F<sub>grav</sub>) forces acting on the object as shown in the following equation-

$$F = F_{\text{buoy}} - F_{\text{grav}}$$

$$F = d_f gV - d_s gV = (d_f - d_s) gV$$

$$F = (d_f - M / V) gV$$

Here, F = the total vertical force (resultant weight of the object),

g = acceleration due to gravity,

d<sub>f</sub> = the fluid density, d<sub>s</sub> = the object density,

M = the object mass and

V = the volume of the object.

A positive resultant weight indicates that the force F is exerted upward and that the object is capable to float, whereas a negative resultant weight indicates that the force F acts downward and that the object sinks.

Apart from the In vitro release, duration of floating and in vivo gastro-retention tests, the multiple unit dosage forms are also evaluated for- <sup>[27, 33]</sup>

i Morphological and dimensional analysis with the help of scanning electron microscopy (SEM). The size can also be measured using an optical microscope.

ii % yield of microspheres-

$\frac{\text{Weight of microspheres obtained} \times 100}{\text{Total weight of drug and polymer}}$

Total weight of drug and polymer

iii Entrapment efficiency-

$\frac{\text{Practical amount of drug present} \times 100}{\text{Theoretical drug content}}$

Theoretical drug content

In vivo methods: [27, 32, 33]

(a) X-Ray method/Gamma Scintigraphy:

It is a very popular evaluation parameter for floating dosage. It helps to locate dosage form in the g.i.t. and by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT.

(a) Pharmacokinetic studies: [27, 34]

Pharmacokinetic studies are the integral part of the in vivo studies and several works has been done on that. Sawicki studied the pharmacokinetics of verapamil, from the floating pellets containing drug, filled into a capsule, and compared with the conventional verapamil tablets of similar dose (40 mg). The  $t_{\max}$  and AUC values for floating pellets were comparatively higher than those obtained for the conventional verapamil tablets. No much difference was found between the  $C_{\max}$  values of both the formulations, suggesting the improved bioavailability of the floating pellets compared to the conventional tablets. An improvement in bioavailability has also been observed with piroxicam in hollow polycarbonate microspheres administered in rabbits.

**APPLICATION OF FDDS** [19, 21, 35]

**1. Sustained drug delivery:**

FDDS can persist in the stomach for long periods and hence can release the drug over a prolonged period of time. These systems have bulk density of  $<1$ , as a result of which they can float on the gastric contents.

**2. Site specific drug delivery:**

These systems are particularly advantages for drugs that are precisely absorbed from stomach or the proximal part of the small intestine.

Absorption enhancement:

Drugs that have poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, there by maximizing their absorption.

**3. Minimized Adverse Activity at the Colon:**

Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented.

**4. Reduced Fluctuations of Drug Concentration:**

Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

### **RECENT ADVANCEMENT IN FDDS**

**1. Osmotic Regulated systems:** [27, 36]

It is consist of osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device.

**2. PVA-PVP Spray Dried Tablets:** [27, 37]

These tablets display immediate floating for 24 hours with almost no lag time and do not sink. The exceptionally good compressibility of spray dried PVA-PVP combination makes it possible to produce mechanically stable oral DF, even with extremely low pressure.

**3. Ion exchange resins Beads:** [27, 38]

Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resulted beads are then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of stomach, an exchange of chloride and

bicarbonate ions take place. As a result of this reaction carbon dioxide is released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to uncoated beads, which will sink quickly.

Micro particles: <sup>[27, 39]</sup>

This approach is created on low-density foam powder. These floating microcapsules produced by emulsion solvent evaporation technique containing polypropylene foam powder, polymers and model drug. Drug release increases rate significantly increases with different types of polymers

**Table 3:** POLYMERS USED FOR GASTROINTESTINAL RETENTION TIME <sup>[19, 40]</sup>

Polymers and other ingredients	Examples
Hydrocolloids (20%-75%)	Acacia, Pectin, Chitosan, Agar, Casein, Bentonite, Veegum, HPMC (K4M, K100M and K15M), Gellan gum (Gelrite®), Sodium CMC, MC, Calcium alginate, Eudragit S100, Eudragit RL, Propylene foam, Eudragit RS, ethyl cellulose, poly methyl methacrylate, Carbopol, $\beta$ Cyclodextrin, CMC, Polyethylene glycol, polycarbonate, PVA, Polycarbonate, Sodium alginate, HPC-L, CP 934P, HPC, Eudragit S, Metolose S.M. 100, PVP, HPC-H, HPC-M, HPMC K15, Acrylic polymer, E4 M.
Inert fatty materials (5%-75%)	Beeswax, fatty acids, long chain fatty alcohols, Gelucires® 39/01 and 43/01.
Effervescent agents	Sodium bicarbonate, citric acid, tartaric acid, Di- SGC (Di-Sodium Glycine Carbonate), CG (Citroglucine).
Release rate accelerants (5% - 60%)	Lactose, Mannitol
Release rate retardants (5%-60%)	Dicalcium phosphate, Talc, Magnesium stearate
Buoyancy increasing agents (upto80%)	Ethyl cellulose
Low density material	Polypropylene foam powder (Accurel MP 1000®).

**Table 4:** GENERALLY MANUFACTURED MARKETED PRODUCTS <sup>[27, 41]</sup>

S.No.	Brand Name	Drug(Dose)	Company, Country	Remarks
1.	Modapar®	Levodopa(100mg), Benserazide(25 mg)	Roche Products, USA	Floating CR capsule
2.	CifranOD®	Ciprofloxacin (1 gm)	Ranbaxy, India	Gas generating Floating table
3.	Valrelease®	Diazepam (15 mg)	Hoffmann- LaRoche, USA	Floating Capsule
4.	Liquid Gavison®	Al hydroxide (95 mg), Mg carbonate (358 mg)	GlaxoSmith Kline, India	Effervescent floating Liquid alginate preparation
5.	Cytotec®	Misoprostal (100 mcg/200 mcg)	Pharmacia, USA	Bilayer floating capsule
6.	Topalkan®	Al-Mg antacid	Pierre Fabre Drug, France	Floating liquid Alginate preparation

## **FUTURE ASPECTS** <sup>[19, 42]</sup>

Gastro-retentive floating dosage form provides various future potential. Delayed gastric emptying time results in the decreased fluctuations in the plasma level of drug. Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailability. Buoyant delivery system considered as an advantageous approach for the treatment of gastric and duodenal cancers. The floating concept can also be utilized in the development of various anti-reflux formulations. Developing a controlled release system for the drugs, which are potential to treat the Parkinson's disease. This system can also be useful to discover the eradication of *Helicobacter pylori* by using the narrow spectrum antibodies. Day after day the FDDS shows more promise for a bright future.

## **CONCLUSION**

Gastro-retentive floating drug delivery systems have plenty of benefits over the other drug delivery system. As this system provides a dosage form which is stable with sustained release. The principle of hydrodynamically balanced systems preparation provides a basic and practical approach to accomplish improved gastric residence time for the dosage form and sustained drug release. The most significant criteria which has to be looked into for the productions of a floating drug delivery system is that the density of the dosage form should be less than that of gastric fluid. FDDS serve the best in the treatment of diseases related to the GIT and for extracting a prolonged action from a drug with a short half- life. FDDS promises to be a potential approach for gastric retention.

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