

# GASTRO-RETENTIVE FLOATING DRUG DELIVERY SYSTEM

Authors: S.P. Budal, A. M. Gupta\*, D. R. Mundhada

Mr. Amit M. Gupta\*, Asst. professor, Miss. S.P. Budal, Research Scholar, Mr. D. R. Mundhada, Principal, Agnihotri Institute of Pharmacy, Wardha Maharashtra, India



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## Abstract:

The purpose of reviewing on Gastro-retentive floating drug delivery systems (GRDDS) was to compile the recent literature with special focus on the aim, principal mechanism of floatation and to achieve gastric retention and to deliver 'narrow absorption window' drugs. These reviews also focus on the various approaches used for the floating drug delivery systems. The floating drug delivery system can remain in the gastric region for several hours via floating mechanism on the gastric contents and hence significantly prolong the gastric residence time of the drugs. This review article is in pursuit of giving detailed information on the design, classification, approaches, factors, *In-vitro* and *In-vivo* evaluation parameters, advantages, disadvantages and the future potential of FDDS.

**Keywords:** Gastro retentive, floating drug delivery system

## Introduction

In oral route of drug administration firstly drug entered into stomach fluid, but main aim of floating drug delivery system to achieve buoyant system by making the dosage form less dense than gastric fluid to achieve floatation by addition of some density fillers. But many difficulties arise to retain dosage form in gastric fluid like Gastric emptying time normally 2-3 hours in humans and less solubility of drug in high pH environment which lead to incomplete release of the drug from the dosage form in lower part of intestine. Therefore sustain the release of drug from dosage form to achieve gastro retentive system. Once the dosage form retain in gastric fluid it reaches better drug absorption, enhance the bioavailability, solubility of drug which less soluble in intestinal pH and reduces drug waste.

Several approaches are currently used to increase the gastric retention of drugs like Mucoadhesive systems, Raft forming systems, Low density systems, Swelling and Expandable systems, Super porous hydrogel, Magnetic systems, Self unfolding systems, High density systems and floating dosage form. Floating tablets mainly matrix type that the drug remains incorporated in the matrix which comes in contact with the gastric fluid swells and the slow erosion of the drug takes place.<sup>1</sup>

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment.

The development of such systems is precluded by several physiological difficulties such as <sup>2</sup>:

- a) Inability to restrain and localize the drug delivery system within the desired range of gastrointestinal tract and
- b) Highly variable nature of gastric emptying process.

### **APPROACHES TO GASTRORETENTION**<sup>3</sup>

#### **Floating systems**

Floating drug delivery systems (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. Floatation of a drug delivery system in the stomach can be achieved by incorporating floating chamber filled with vacuum, air, or inert gas.<sup>4</sup>

### **CLASIFICATION OF FDDS**

#### **A) Single unit**

Single unit dosage forms are easiest to develop but suffers from the risk of losing their effects too early due to their all-or-none emptying from the stomach and, thus they may cause high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the gastro intestinal tract.<sup>5</sup>

#### **1. EFFERVESCENT SYSTEMS**

A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas. The gas in floating chamber can be introduced either by volatilization of an organic solvent or by effervescent reaction between organic acids and bicarbonate salts.

##### **1.1 Gas generating system**

These buoyant delivery systems utilize effervescent reaction between carbonate/ bicarbonate salts and citric/ tartaric acid to liberate CO<sub>2</sub>, which gets entrapped in the jellified hydrocolloid layer of the system, thus decreasing its specific gravity and making it float over chyme. These tablets may be either single layered wherein the CO<sub>2</sub> generating components are intimately mixed within the tablet matrix, or they may be bilayered in which the gas generating components are compressed in one hydrocolloid containing layer, and the drug in outer layer for sustained release effect. Multi-unit types of floating pills (Fig.No.3), which generate CO<sub>2</sub>, have also been developed.<sup>6</sup>

##### **1.2 Volatile liquid containing systems**

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid, e.g. Ether, Cyclopentane that gasifies at body temperature to cause the inflation of the chamber in the stomach. These devices are osmotically controlled floating systems containing a hollow deformable unit

that can convert from a collapsed to an expanded position, and returns to collapsed position after an extended period. A deformable system consists of two chambers separated by an impermeable, pressure responsive, movable bladder. The first chamber contains the drug and the second chamber contains volatile liquid. The device inflates, and the drug is continuously released from the reservoir into the gastric fluid. (Fig. No.4).<sup>7</sup>

Intragastric osmotically controlled drug delivery system consists of an osmotic pressure controlled drug delivery device and an inflatable floating support in bioerodible capsule. When the device reaches the stomach, bioerodible capsule quickly disintegrates to release the drug delivery system. The floating support is made up of a deformable hollow polymeric bag containing a liquid that gasifies at body temperature to inflate the bag. The floating support also contains a bioerodible plug that erodes after a predetermined time to deflate the support, which is then excreted from the stomach (Fig. No. 5).<sup>8</sup>

### **2. NON-EFFERVESCENT SYSTEMS**

#### **2.1 Colloidal gel barrier systems**

Hydro dynamically balanced system (HBSTM) contain drug with gel forming hydrocolloids meant to remain buoyant on the stomach contents. These systems incorporate high level (20 to 75 % w/w) of one or more gel forming highly swellable cellulose type hydrocolloids [for eg. Hydroxyethyl cellulose (HEC), Hydroxypropyl Cellulose (HPC) Hydroxypropyl Methyl Cellulose (HPMC), Sodium Carboxyl Methyl Cellulose (NaCMC) <sup>9</sup>, polysaccharides and matrix forming polymers such as Polycarbophil, polyacrylate and polystyrene, incorporated either in tablets or capsules. On coming in contact with the gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around its surface. (Fig. No.6)

This gel barrier controls the rate of the fluid penetration into the device and consequent release of drug <sup>9</sup>. A bilayered tablet can also be prepared to contain one immediate release and other sustained release layer (Fig.No.7)

Immediate release layer delivers the initial dose, whereas Sustained Release layer absorbs gastric fluid and forms a colloidal gel barrier on its surface. This results in system with bulk density lesser than that of gastric fluid and allows it to remain buoyant in the stomach for an extended period of time.<sup>10</sup>

#### **2.2 Microporous compartment system**

This technology is based on encapsulation of a drug reservoir inside a microporous compartment with aperture along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric mucosal surface

with undisclosed drug. In stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the aperture, dissolves the drug, and carries the dissolved drug for continuous transport across the intestine for absorption. The microproous compartment system is shown in (Fig.No.8).<sup>11</sup>

## B) Multiple units

Single unit formulations are associated with problems such as sticking together or being obstructed in gastrointestinal tract, which may have a potential danger of producing irritation. Multiple unit systems avoid the 'all-or-none' gastric emptying nature of single unit systems. It reduces the inter subject variability in absorption and the probability for dose dumping is lower.<sup>12</sup> Multiple unit formulations consist of following systems.

### 1. Effervescent system

-Floating microspheres

### 2. Non effervescent systems

## C) Raft forming systems:

The basic mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, where in each portion of the liquid swells forming a continuous layer called a raft. The raft floats because of the buoyancy created by the formation of CO<sub>2</sub> and act as a barrier to prevent the reflux of gastric Contents like HCl and enzymes into the esophagus. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of to make the system less dense and float on the gastric fluids.<sup>13</sup>

## FACTORS AFFECTING GASTRIC RESIDENCE TIME OF FDSS <sup>14</sup>

### 1. Formulation factors:

- a) Size of tablets
- b) Density of tablets
- c) Shape of tablets
- d) Viscosity grade of polymer

### 2. Idiosyncratic factors:

- a) Gender
- b) Age
- c) Posture
  - a. Upright position
  - b. Supine position
- d) Concomitant intake of drugs
- e) Feeding regimen

## POLYMERS USED IN FDSS <sup>15</sup>

List of Natural polymers used in floating drug delivery system

1. Guar gum

2. Pectin
3. Chitosan
4. Xantham gum
5. Psyllium husk starch
6. Alginates
7. Carrageenan
8. Karaya gum
9. Arabino galactose
10. Amylase

## Synthetic and Semi synthetic polymers used in floating drug delivery system

1. Hydroxyl propyl cellulose (HPC)
2. Methyl cellulose (MC)
3. HPMC (K4M, K15M, K100M etc)
4. HEC
5. Sodium Carboxyl methyl cellulose
6. Eudragit (RL100, L100, RS PO, RS EPO, S100) etc.
7. Polyvinyl alcohol (PVA)
8. Carbopol (934 P, 947 P)
9. Polyvinylpyrrolidone (PVP)

## Selection criteria for Drug Candidate for FDSS <sup>16</sup>

The drugs that would benefit from gastric retention are,

1. CNS drugs (for Parkinson disease, epilepsy, Alzheimer and migraine)
2. Anti-viral products (for HIV, herpes and hepatitis) and certain antibiotics
3. Anti-hypertension drugs
4. Anti-diabetic agents for Type 2 diabetes
5. Drugs for local treatment of GI infections, and gastric enzyme replacement.

## IN -VITRO AND IN-VIVO EVALUATION PARAMETERS OF STOMACH SPECIFIC FDSS

Different studies reported in the literature indicate that pharmaceutical dosage forms exhibiting gastric residence *in-vitro* floating behavior show prolonged gastric residence *in vivo*. Although, *in-vitro* floating behavior alone is not sufficient proof for efficient gastric retention so *In-vivo* studies can provide definite proof that prolonged gastric residence is obtained.

### 1) Hardness, friability, assay, content uniformity (Tablets)

These tests are performed as per described in specified monographs.

### 2) Floating lag time and total floating time determination

These tests are usually performed in simulated gastric fluid or 0.1N HCl maintained at 37 °C, by using USP dissolution apparatus containing 900 ml of 0.1M HCl as the dissolution medium.<sup>18</sup>

### 3) Drug release

The test for *in vitro* drug release studies are usually carried out in simulated gastric and intestinal fluids

maintained at 37 °C. Dissolution tests are performed using the USP dissolution apparatus. Samples are withdrawn periodically from the dissolution medium, replaced with the same volume of fresh medium each time, and then analyzed for their drug contents after an appropriate dilution.

#### 4) Drug loading, drug entrapment efficiency, particle size analysis, surface characterization, micromeritics studies and percentage yield (for floating microspheres and beads)

Drug loading is assessed by crushing accurately weighed sample of beads or microspheres in a mortar and added to the appropriate dissolution medium which is then centrifuged, filtered and analyzed by various analytical methods like spectrophotometry. The percentage drug loading is calculated by dividing the amount of drug in the sample by the weight of total beads or microspheres.<sup>19, 20</sup>

#### 5) Resultant weight determination

It operates by force equivalent to the force F required 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 quantify its floating or non floating capabilities. The magnitude and direction of the force and the resultant weight corresponds to the Victoria sum of buoyancy (F buoy) and gravity (F grav) forces acting on the objects as shown in the equal

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

$$F = df g V - ds g V = (df - ds) g V$$

$$F = (df - M/V) g V$$

In which the F is total vertical force (resultant weight of the object), g is the acceleration due to gravity, df if the fluid density, ds is the object density is the object mass and V is the volume of the object.<sup>14</sup>

#### 6) Weight gain and water uptake (WU)

Weight gain or water uptake can be studied by considering the swelling behavior of Floating dosage form. The study is done by immersing the dosage form in simulated gastric fluid at 37 °C and determining the dimensional changes like tablet diameter and/ or thickness at regular 1-h time intervals until 24 h, the tablets were removed from beaker, and the excess surface liquid was removed carefully using the paper. The swollen tablets were then reweighed and WU is measured in the terms of percent weight gain, as given by equation

$$WU = (W_t - W_o) \times 100 / W_o$$

In which  $W_t$  and  $W_o$  are the weights of the dosage form at time t and initially, respectively.<sup>21</sup>

#### 7) X Ray/Gamma scintigraphy

For *In-vivo* studies, X-Ray/Gamma Scintigraphy is the main evaluation parameter for floating dosage form. The formulation is administered by natural swallowing

followed by 50 mL of water. The radiographic imaging is taken from each animal in a standing position, and the distance between the source of X-rays and the animal should kept constant for all imaging, so that the tablet movement could be easily noticed. Gastric radiography was done at 30-min time intervals for a period of 5 h using an X-ray machine.<sup>22, 23</sup>

#### 8) Pharmacokinetic studies

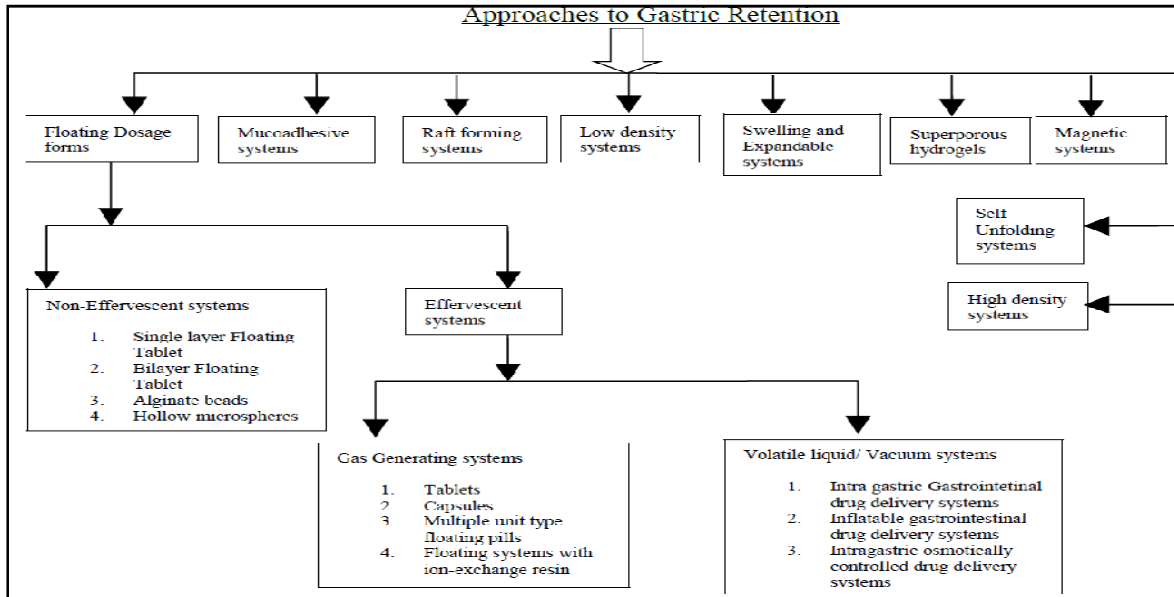
Pharmacokinetic studies include AUC (Area under Curve),  $C_{\text{max}}$ , and time to reach maximum plasma concentration ( $T_{\text{max}}$ ) were estimated using a computer. Statistical analyses were performed using a Student t test with p, 0.05 as the minimal level of significance.<sup>24</sup>

#### 9) Specific Gravity

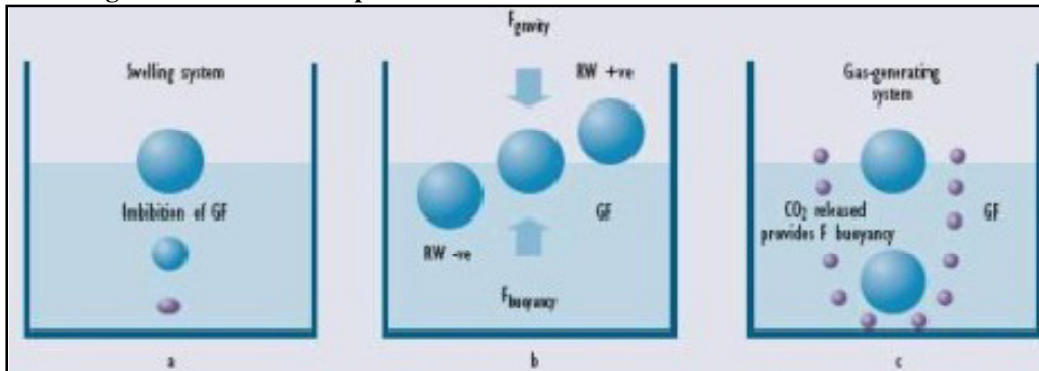
Displacement method is used to determine the specific gravity of floating system using benzene as a displacing medium.<sup>25</sup>

#### Advantages of floating dosage form<sup>14</sup>

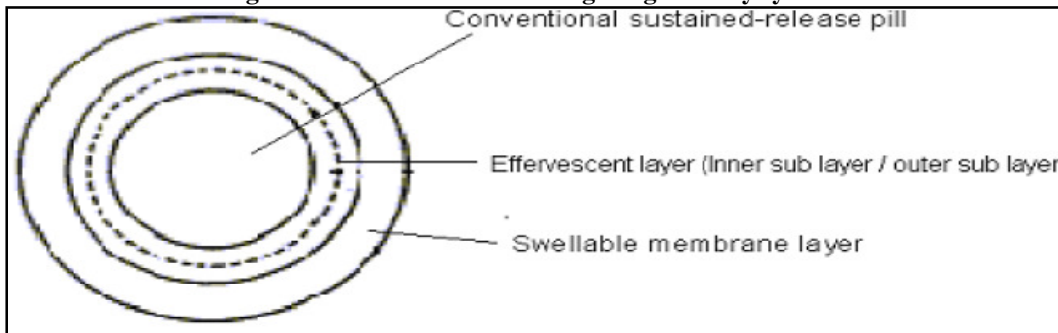
1. These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., riboflavin and Furosemide.
2. The fluctuations in plasma drug concentration are minimized, and concentration-dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.
3. The efficacy of the medicaments administered utilizing the sustained release principle of floating formulation has been found to be independent of the site of particular medicaments.
4. Complete absorption of the drug from the floating dosage form is expected even at the alkaline pH of the intestine. The dissolution of the drug in gastric fluid occurs and then the dissolved drug is available for absorption in the small intestine after emptying of the stomach contents.
5. Poor absorption is expected when there is vigorous intestinal movement and a shorted transit time as might occur in certain type of diarrhea. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.
6. Drugs that have poor bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. A significant increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric-coated LASIX-long product (29.5%).



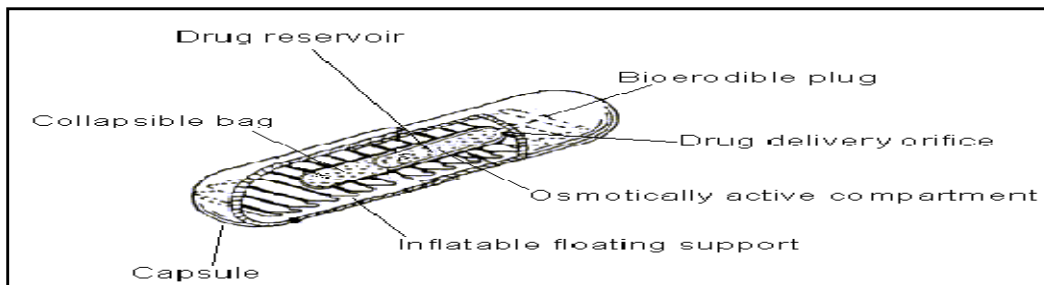
**Fig. No.1: Schematic representations of various Gastroretentive formulations.**



**Fig. No.2: Mechanism of floating drug delivery systems**



**Fig. No.3: Multiple unit oral floating dosage system**



**Fig. No. 4: Intra gastric osmotic controlled drug delivery system**

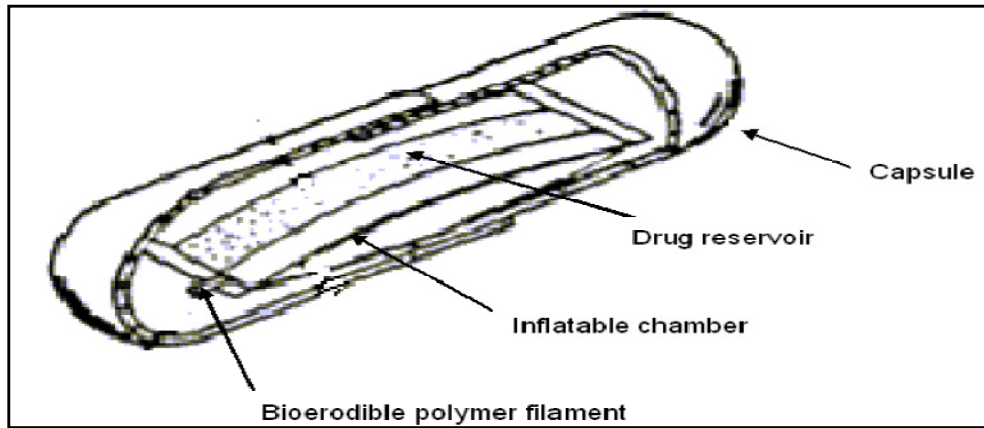


Fig. No. 5: Gastro inflatable drug delivery devices.

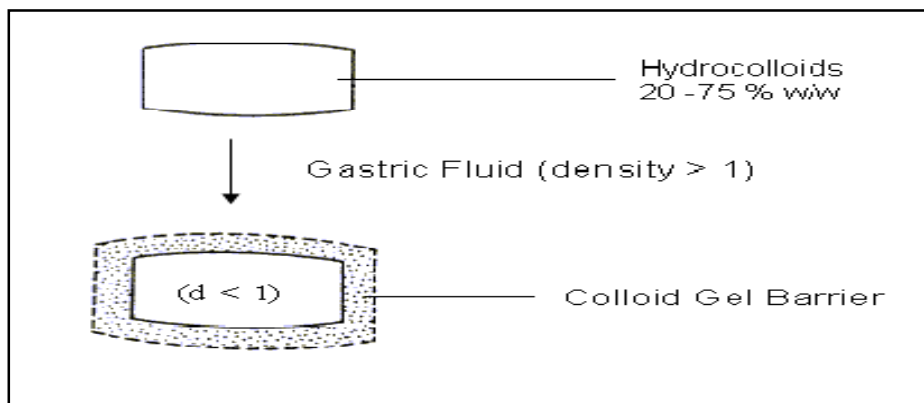


Fig. No. 6: Intragastric floating tablets

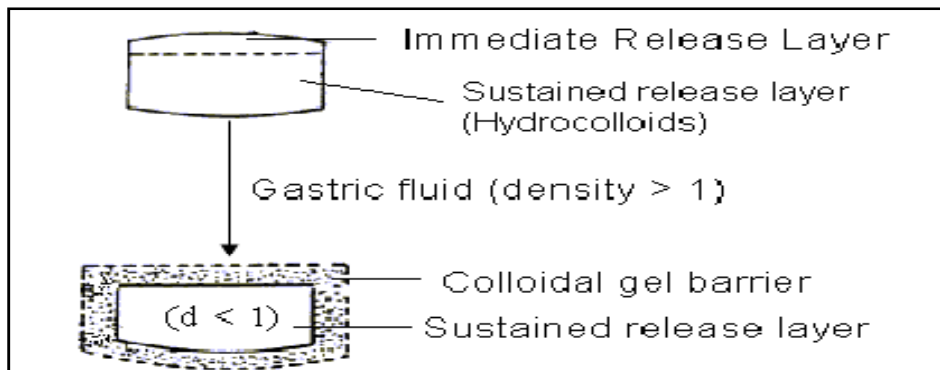


Fig. No. 7: Bilayer Intragastric floating tablet

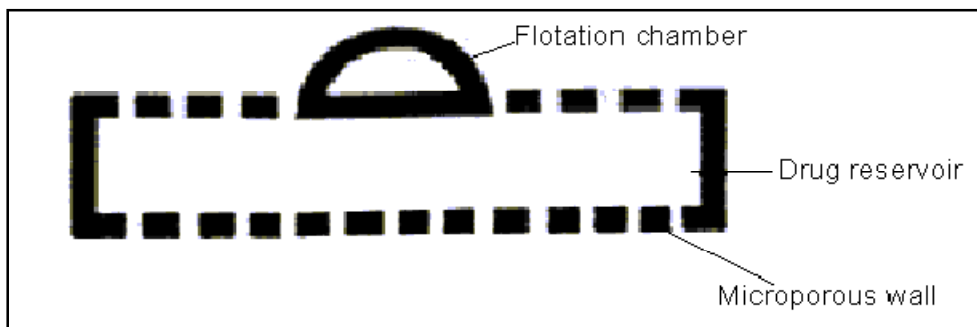


Fig. No. 8: Microporous Intragastric floating drug delivery device

Dosage forms	Drug used
<b>TABLETS/PILLS</b>	Chlorpheniramine maleate, Furosemide, Ciprofloxacin, Captopril, Amoxicillin trihydrate, Atenolol, Ampicillin, Acetaminophen, Aspirin, Ciprofloxacin, 5-Fluorouracil, Isosorbide Mononitrate, Diltiazem, Isosorbide Dinitrate, Nimodipine, Para Amino Benzoic acid, Piretanide, Prednisolone, Quinidine, Verapamil HCL, Riboflavin, Sotalol, Theophylline etc.
<b>CAPSULES</b>	Diazepam Propranolol Nicardipine
<b>MICROSPHERES</b>	Verapamil HCL Ketoprofen Ibuprofen
<b>GRANULES</b>	Diclofenac sodium Indomethacin
<b>FILMS</b>	Drug delivery devices Cinnarizine

**Table: Drugs Investigated In Floating Drug Delivery Systems<sup>17</sup>**

#### Disadvantages of FDDS<sup>26,27</sup>

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. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
4. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.

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