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FLOATING DRUG DELIVERY SYSTEM - A NEW ERA IN NOVEL DRUG DELIVERY SYSTEM

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Abstract

Floating drug delivery system provides local delivery to specific region like stomach and proximal small intestine and it's also shows better bioavailability and improved therapeutic activity and substantial benefits to patients. The objective of our review is to compile the recent advancements and literatures regarding the novel dosage form i.e. the floating drug delivery systems (FDDS) that can be retained in the stomach for a prolonged period of time and gives therapeutic action in a predetermined manner. Gastric emptying is a complex process and makes in vivo performance of the drug delivery systems uncertain. The floating drug delivery systems are useful approach to avoid this variability with increase the retention time of the drug-delivery systems for more than 12 hours. Effervescent and non-effervescent are two class of floating drug delivery system and can formulate either in single unit dosage form or in multiple unit dosage form. The methodologies used in the development of FDDS by formulating effervescent and non effervescent floating tablets based on buoyancy mechanism. By utilizing above feasible approaches it is possible to deliver drugs which have narrow therapeutic window. Our review article suggests that how the gastro retentive dosage forms (GRDFs) help to improve patient compliance and robustness.

INTRODUCTION

Pharmaceutical companies worked with different pharmaceutical product types include products of different administration route (e.g., oral to parenteral), new specific functionality/delivery systems (e.g., immediate release tablet to modified release tablet) and different dosage forms of the same administration route (e.g., capsule to tablet, solution to suspension) [1]. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation[2, 3]. Drugs with short half-lives and drugs that easily absorbed from gastrointestinal tract (GIT) are eliminated quickly from the systemic circulation. For these types of drugs the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT) [4, 2]. But oral sustained drug delivery formulations show some limitations connected with the gastric emptying time; variable and too rapid gastrointestinal transit could result in incomplete drug release from the device into the absorption window leading to diminished efficacy of the administered dose[5, 2]. Floating drug delivery system is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. This drug delivery system not only prolongs GI residence time but does so in an area of the GI tract that could maximize drug reaching its absorption site in solution and hence ready for absorption[6, 2]. (Table no. 1) enlists below shows the different dosage forms of FDDS with examples of various drugs.

Objective

The present study attempts to give an insight into the gastro retentive drug delivery systems, and gastric floating

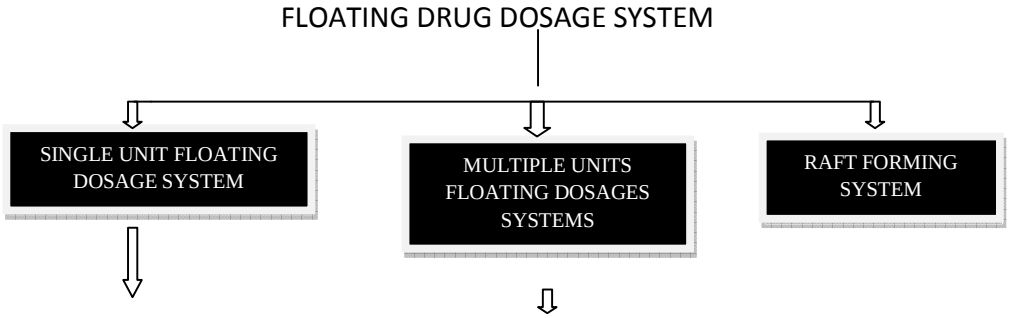
tablets, in particular. These have attracted the interest of many formulators due to their advantages over the conventional drug delivery systems, recently. The study highlights these advantages with reference to the various types of gastro retentive drug delivery systems, as well as provides an overview of the recent advances that have taken place in this arena [7].

Advantages [8,9,10]

1) The HBS formulations are not restricted to medicaments, which are principally absorbed from the stomach. Since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine e.g. Chlorpheniramine maleate.
2) The HBS are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.
3) The efficacy of the medicaments administered utilizing the sustained release principle of HBS has been found to be independent of the site of absorption of the particular medicaments.
4) Administration of a prolonged release floating dosage form tablet or capsule will result in dissolution of the drug in gastric fluid. After emptying of the stomach contents, the dissolve drug available for absorption in the small intestine. It is therefore expected that a drug will be fully absorbed from the floating dosage form if it remains in solution form even at alkaline pH of the intestine.
5) Certain types of drugs can benefit from using gastro retentive devices. These include:

- Drugs acting locally in the stomach;
- Drugs those are primarily absorbed in the stomach;
- Drugs those are poorly soluble at an alkaline pH;
- Drugs with a narrow window of absorption;
- Drugs absorbed rapidly from the GI tract; and
- Drugs those degrade in the colon.

Classification Of Floating System



1). Single Unit Floating Dosage Systems:-

a) Effervescent systems:

Effervescent floating drug delivery systems generate gas (CO_2), thus reduce the density of the system, and remain buoyant in the stomach for a prolonged period of time and release the drug slowly at a desired rate. The main ingredients of effervescent system include swell able polymers like chitosan, methyl cellulose and effervescent compounds such as citric acid, sodium bicarbonate, citric acid and tartaric acid [(11)]. Penners *et al* prepared an expandable tablet containing mixture of polyvinyl lactams and polyacrylates that swells rapidly in an aqueous environment and thus, stays in stomach over an extended period of time. In addition to this, gas-forming agents were also incorporated so as soon as the gas

Formed, the density of the system was reduced and thus, the system tended to float in the gastric environment [(12)]. M.Jaimini *et al.* prepared the effervescent floating tablet of famotidine. They found that the addition of gel-forming polymer methocel (K100 and K15M) and gas-generating agent sodium bicarbonate along with citric acid was essential to achieve in vitro buoyancy. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed [13].

b) Non effervescent system

Non-effervescent systems commonly use gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid [(14)]. Prior to formulation of floating tablets, nimodipine was incorporated into poloxamer-188 solid dispersion after which it was directly compressed into floating tablets. It was observed that by increasing the HPMC and decreasing the PEG 6000 content, a decline in *in vitro* release of nimodipine occurred . The main drawback of such system is "all or none" phenomenon. In such cases, there is a danger of passing of the dosage form to intestinal part at the time of house-keeper waves. To overcome this difficulty multiple, unit dosage forms are designed [15].

2) Multiple Unit Floating Systems:-

Multiple unit dosage forms may be an attractive alternate since they have been shown to reduce inter and intra-subject variability's in drug absorption as well as to lower the possibility of dose dumping. Various multiple unit floating systems have been developed in different forms, and using principles such as air compartment multiple unit system, hollow microspheres prepared by emulsion solvent diffusion method, beads prepared by emulsion gelation method. Use of effervescent and swellable polymer is another approach for preparing multiple unit FDDS [16].

a) Effervescent system

Ichikawa *et al* developed a new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into two sublayers to avoid direct contact between the two agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37ºC, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO_2 was generated by the neutralization reaction between the two effervescent agents, producing swollen pills

(like balloons) with a density less than 1.0 /ml.

b) **Non effervescent systems:**

Not many reports were found in the literature on non-effervescent multiple unit systems, as compared to the effervescent systems. However, few workers have reported the possibility of developing such system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion process is reported. A mixture of drug, chitosan and acetic acid is extruded through a needle, and the extrudate is cut and dried. Chitosan hydrates and floats in the acidic media, and the required drug release could be obtained by modifying the drug-polymer ratio[17].

c) Hollow Microspheres

Both natural and synthetic polymers have been used to prepare floating microspheres. Joseph *et al.* Developed a floating dosage form of piroxicam based on hollow polycarbonate microspheres. The microspheres were prepared by the solvent evaporation technique. Encapsulation efficiency of ~95% was achieved. *In vivo* studies were performed in healthy male albino rabbit.

3) Raft forming GF system

Raft forming systems have received much attention for the drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO_2. Usually, the system ingredients includes a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense and float on the gastric fluids . Jorgen et al described an antacid raft forming floating system. The system contains a gel forming agent (e.g. sodium alginate), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft), which when comes in contact with gastric fluids, the raft floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by

Acting as a barrier between the stomach and esophagus Jorgen et al described an antacid raft forming floating systems [19].

Approaches to design floating dosage forms

Two types of floating systems are available. These are single unit dosage forms and multiple unit dosage forms. Single-unit dosage forms are exemplified by hydrodynamic ally balanced systems capsules[20] and floating tablets [21, 22]. Multiple unit dosage forms include hollow microspheres (microballoons), granules, mini-tablets and pellets. In (Figure No. 4) listed below represented the multiple-unit effervescent (gas generating) oral floating drug delivery system and similarly (Figure No. 5) represented the working of a triple-layer system. Some marketed formulations of floating drug delivery system is also listed below in (table no. 2) [2, 3, 24, 25].

Bioadhesive or Mucoadhesive Drug delivery Systems:

Bioadhesive drug delivery systems are used as a delivery device within the human to enhance drug absorption in a site-specific manner. In this approach, bio adhesive polymers are used and they can adhere to the epithelial surface in the stomach.

Expandable, Unfoldable and Swellable Systems:

Unfoldable systems are made of biodegradable polymers. They are available in different geometric forms like tetrahedron, ring or planner membrane (4 - label disc or 4 - limbed cross form) of bioerodible polymer compressed within a capsule which extends in the stomach. Swellable systems are also retained in the gastro intestinal tract (GIT) due to their mechanical properties. An expanded gastroretentive form, and a final small form enabling evacuation following drug release from the device. (Figure 2) listed below which show the working principle of swellable systems [24, 3].

Super Porous Hydrogel Systems

In this approach to improve gastric retention time (GRT) super porous hydrogels of average pore size >100 micro miter, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores. They swell to a large size (swelling ratio: 100 or more) and

are intended to have sufficient mechanical strength to withstand pressure by gastric contraction [23, 3].

Magnetic Systems

This approach to enhance the gastric retention time (GRT) is based on the simple principle that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance [3].

Hydrodynamically Balanced Systems

These systems contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period [(25,3)]. (Figure No. 6) listed below represented hydrodynamically balanced system (HBS).

Ionotropic Granulation

In this multiple-unit floating system approach generally sodium alginate solution is dropped into aqueous solution of calcium chloride and causes the precipitation of calcium alginate. This is made by using Ca^{2+} and low methoxylated pectin (anionic polysaccharide) or Ca^{2+} low methoxylated pectin and sodium alginate [24, 3, 2].

Microporous Compartment System

This approach is based on the principle of the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the device were completely sealed to present any direct contact of the gastric surface with the undissolved drug [23, 3].

Factors affecting floating drug delivery system[8, 9, 10]

1. Density – gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density;
2. Size – dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm;
3. Nature of meal – feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric

emptying rate and prolonging drug release;

4. Age – elderly people, especially those over 70, have a significantly longer GRT;
5. Biological factors – diabetes and Crohn's disease, etc.

Limitations [8, 9, 10]

The major disadvantage of floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float. However this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach. Floating system is not feasible for those drugs that have solubility or stability problem in gastric fluids. The dosage form should be administered with a minimum of glass full of water (200-250 ml). The drugs, which are absorbed throughout gastro-intestinal tract, which under go first-pass metabolism (nifedipine, propranolol etc.), are not desirable candidate. Some drugs present in the floating system causes irritation to gastric mucosa.

Evaluation [(26)]

Evaluation parameters of floating tablets are similar with the evaluation parameters of simple tablet which can be administered easily through oral route such as:

a) angle of repose**,**
b) bulk density
c) percentage porosity,
d) weight variation,
e) Hardness and friability,
f) Drug content,
g) Dissolution studies.

Evaluation parameters of floating microsphere:

a) Particle size analysis, surface characterization (for floating microspheres and beads):

The particle size and the size distribution of beads or microspheres are determined in the dry state using the optical microscopy method. The external and crosssectional morphology (surface characterization) is done by scanning electron microscope (SEM) [31].

b) XRay/gamma scintigraphy:-

X-Ray/Gamma Scintigraphy is a very popular evaluation parameter for floating dosage form nowadays. It helps to locate dosage form in the gastrointestinal tract (GIT), by which one can predict and

correlate the gastric emptying time and the passage of dosage form in the GIT. Here the inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays.

CONCLUSION

Recently many drugs have been formulated as floating drug delivery systems with an objective of sustained release and restricting the region of drug release to stomach. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. The currently available polymer-mediated non effervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be a very much effective approach to the modulation of controlled oral drug delivery. The most important 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. And hence, it can be concluded that these dosage forms 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.

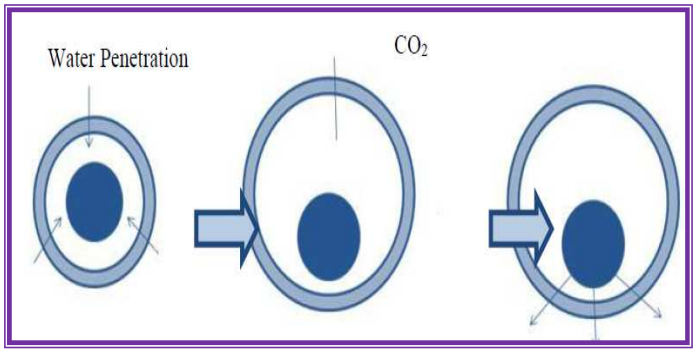


Figure 1 Working Principle of Effervescent Floating Drug Delivery System

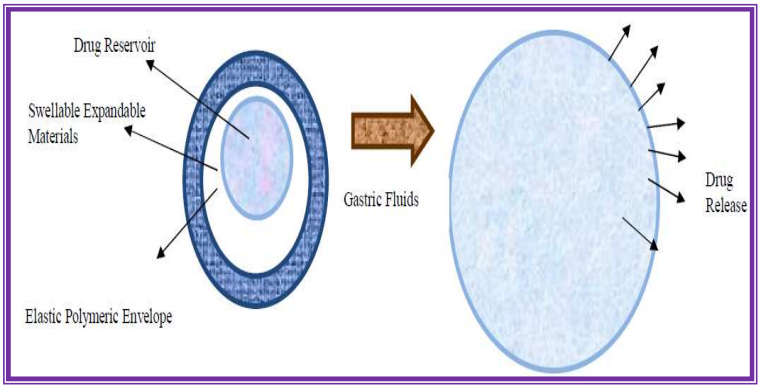


Figure 2 Working Principal of Swellable System

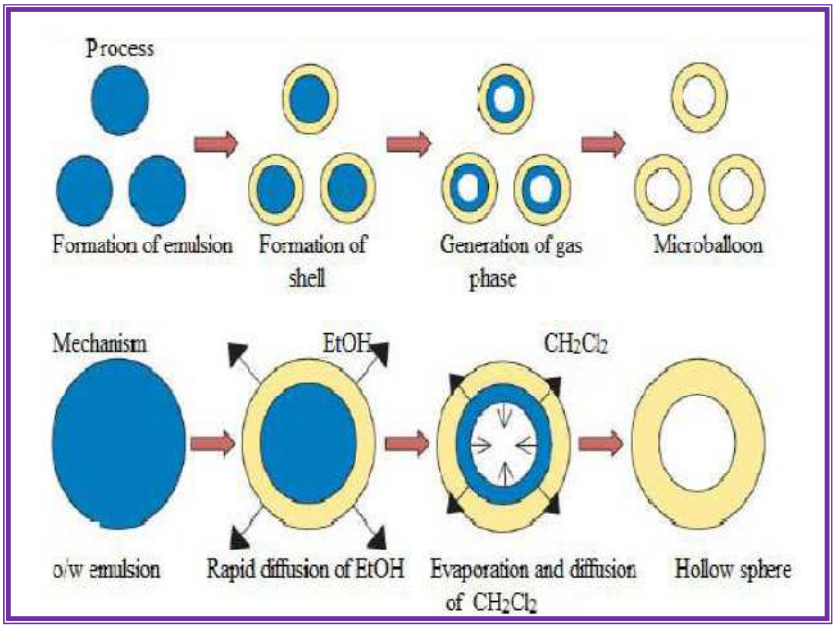


Figure 3 Preparation technique (Emulsion-Solvent Diffusion Method) And Mechanism of Microballon Formation

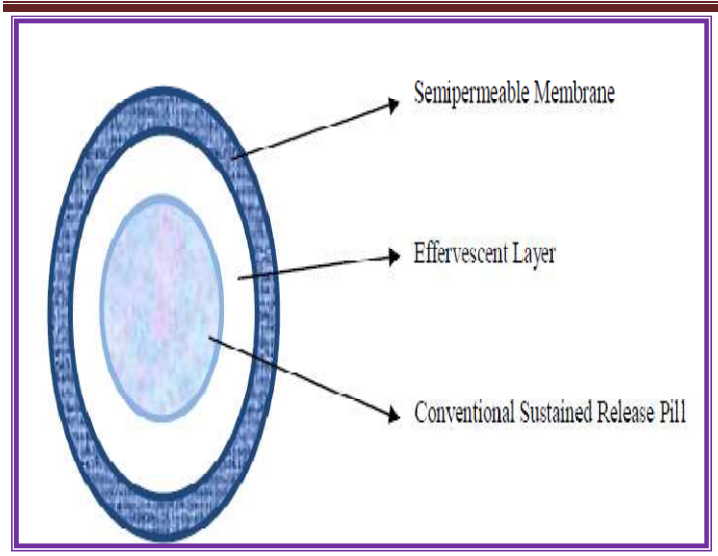


Figure 4 Multiple-Unit Effervescent (Gas Generating) Oral Floating Drug Delivery System

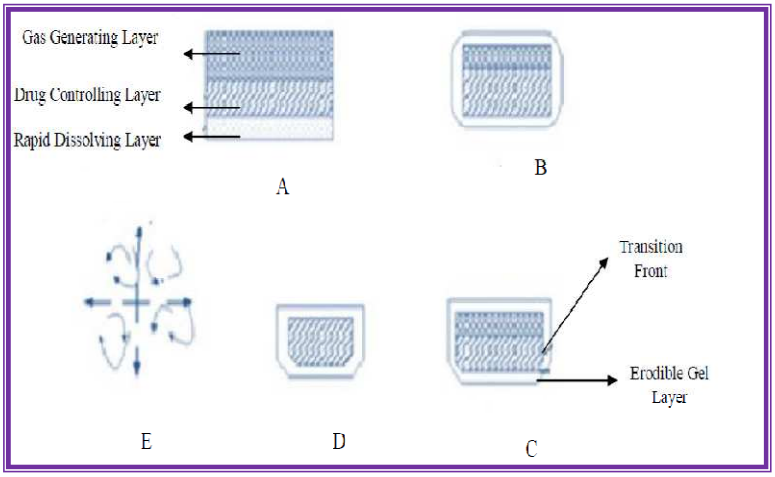


Figure 5 Working of Triple Layer System

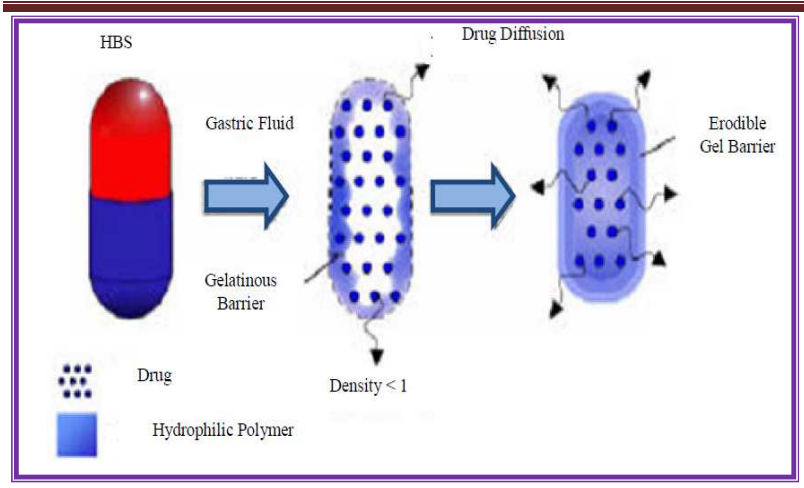


Figure 6 Hydrodynamic Balance System

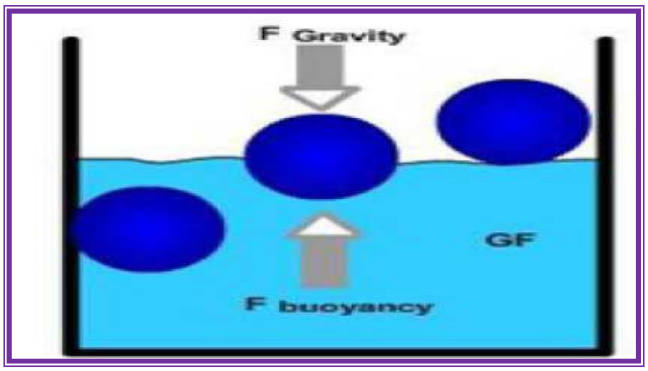


Figure 7 Effects of Various Forces on Floating System

Table 1

Dosage Forms Of FDDS With Examples Of Various Drugs [2,5]

Sr. No	Dosage Forms	DRUGS
1	Floating tablet	Acetaaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerzine, Diltiazem, Fluorouracil, Isosorbide dinitrate, Isosorbide mononitrate, p-aminobenzoic acid
2	Floating capsule	Furosemide, L-DOPA, Benserazide, Nicardipine, Misoprostol, Propanolol, Pepstatin
3	Floating microsphere	Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfinadine, Tranilast
4	Floating granules	Cinnerzine, p-aminobenzoic acid, prednisolon, quinidine gluconate.
5	Powders	Several basic drugs- Riboflavin phosphate, Sotalol, Theophylline
6	Film	Cinnerzine, p-aminobenzoicacid, prednisolon, quinidine gluconate
7	Multiple unit floating dosage form	Clarithromycin, p-aminobenzoic acid
8	Bilayer Tablet	Misoprostal
9	Foams/ Hollow Bodies	Ibuprofen
10	Floating controlled release capsule	Levodopa, Benserazide
11	Effervescent floating liquid alginate preparation	Aluminium hydroxide, Magnesium carbonate
12	Floating liquid alginate preparation	Aluminium-Magnesium antacid
13	Colloidal gel forming FDDS	Ferrous sulphate

Table 2

Marketed Formulation Of Floating Drug Delivery System: [2, 3, 24, 25]

Sr. No	Brand Name	Drug	Dosage Form
1	Topalkan	Aluminium - Magnesium Anta acid	Floating liquid Alginate Preparation
2	Liquid Gavison	Aluminium hydroxide, Magnesium carbonate	Effererescent Floating Liquid Alginate Preparation
3	Valrelease	Diazepam	Floating Capsule
4	Madopar	Levodopa, Benserazide	Floating Controlled Release Capsule
5	Cifran OD	Ciprofloxacin	Gas- generating Floating Tablets
6	Conviron	Ferrous sulphate	Colloidal Gel Forming Capsule
7	Cytotec	Misoprostal	Bilayer Floating Capsule
8	Amalgate Float Coat	Antacid	Floating Dosage form

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