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REVIEW ARTICLE OPEN ACCESS

# REVIEW ON FLOATING GASTRO-RETENTIVE DRUG DELIVERY SYSTEM

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## ABSTRACT:

A Controlled release dose forms have been widely utilised to enhance treatment with a number of significant medications. However, a number of physiological challenges, including the inability to contain and localise the system within the appropriate region of the gastrointestinal tract and the extremely fluctuating physiological conditions, pose challenges to the development processes. the way that the stomach empties. This variation could result in inconsistent bioavailability and turn around times to attain maximum plasma levels. This review of gastroretentive medication delivery methods was written with the intention of gather the most recent research, paying particular attention to the many gastroretentive methods that have recently pioneering approaches to oral controlled release medication delivery for site-specific administration.

We have compiled key parameters affecting stomach retention in order to better understand the physiological challenges involved in achieving it.Drugs that are absorbed largely in the upper portions of the gastrointestinal (GI) tract, such as the stomach, duodenum, and jejunum, benefit more from floating drug delivery systems (FDDS).

*Keywords* —Floating Drug Delivery System, Controlled release, Site specific target

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## INTRODUCTION

The most practical and preferable method of delivering any medicine to the systemic circulation is oral administration.The pharmaceutical industry has recently shown an increased interest in oral controlled release drug delivery to gain better therapeutic benefits, such as simplicity in administering doses, patient compliance, and formulation flexibility. Drugs with short half-lives and easy absorption from the gastrointestinal tract (GIT) are removed from the systemic circulation swiftly.

For these medications to have the desired therapeutic effect, frequent administration is necessary.The development of oral sustained-controlled release formulations is an effort to bypass this restriction by slowly releasing the drug into the gastrointestinal tract (GIT) and maintaining an effective drug concentration in the systemic circulation for an extended period of time. Such a drug delivery would be held in the stomach after

oral administration and release the medication in a regulated manner, allowing the drug to be constantly given to its absorption sites in the gastrointestinal system (GIT)

It is desirable to extend the drug delivery's stomach residence duration in order to provide an oral controlled release dosage form that is site-specific. Long-term stomach retention increases bioavailability, lengthens the time it takes for a drug to start working, decreases drug waste, and increases the solubility of drugs that are less soluble in high pH environments. Additionally, a prolonged GRT in the stomach may be helpful for local actions in the upper part of the small intestine, such as the treatment of peptic ulcers, etc.It is possible to target site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects by using a strategy called gastroretentive drug delivery.

Additional advantages of this prolonged retention ability include increased activity for medications with short half-lives, increased drug bio-availability, elimination of side effects, decreased dosing frequency, and drug preservation due to prolonged retention. improved solubility for medications that are less soluble in high pH environments, improved therapy, and the previously mentioned advantages. Ultimately, the patient's cooperation will be simple.

Several gastroretentive drug delivery strategies have been created during the past few decades, such as high density (sinking) systems that are retained in the stomach's bottom. Low density (floating) systems that induce stomach juice to be buoyant. mucoadhesive systems that cause bio-adhesion to stomach mucosa, swellable system that limit the amount of dose forms that can be emptied through the stomach's pyloric sphincter, magnetic systems, super porous hydrogel systems, etc.

## PHYSIOLOGY OF STOMACH

The stomach is anatomically separated into the Fundus, Body, and Antrum (pylorus). The body and fundus made proximal portion serve as reservoir for waste materials, as opposed to the antrum is where motions and acts are primarily mixed, as the propeller acts as a pump from gastric emptying actions. During a fast, gastric emptying happens along with feed state. However, the patent of motility is unique in two states. When fasting, a person's a sequence of electrical events occur during digestion, which circulate through the gut and stomach each two to three hours. This is known as the migrating or the digestive myoelectric cycle the further myoelectric cycle (MMC), divided into the four phases listed below, according to Washington and Wilson.

1. Phase I (base phase), which includes contractions, lasts for 40 to 60 minutes.
2. Phase II (pre-burst phase) lasts 40 to 60 minutes and is characterised by sporadic contractions and action potentials. The intensity and frequency gradually rise as the phase progresses.
3.Phase III's burst phase lasts 4 to 6 minutes. It has powerful and frequent contractions that are brief a nd recurrent. This wave causes all of the undigested material to was out of the stomach and into the small intestine. also known as the housekeeping wave.
4. Phase IV lasts 0 to 5 minutes and takes place between the third and first phases of two successive cycles.

The pattern of contractions switches from that of a fasted state to that of a fed state following the consumption of a mixed meal. In phase II of the fasting state, constant contractions are present in this pattern, which is also known as the digestive motility pattern. These contractions cause the size of the food particles that are driven into the pylorus in a suspension form to decrease (to less than 1mm) as a result. The fed state causes MMC to start later, which slows down the rate at which the stomach empties. Gastric emptying rates were determined by scintigraphic investigations, which showed that controlled release dose forms taken orally are primarily affected by two problems: a short gastric residence time and low gastric pH.

## FACTORS AFFECTION GASTRIC RETENTION

A number of factors can affect how long an oral dosage form stays in the stomach. Particles should be between 1 and 2 mm in size in order to pass

through the pyloric valve and enter the small intestine13. In a fed condition, the pH of the stomach ranges from 2.0 to 6.0 whereas it is fasting between 1.5 and 2.0. The pH of stomach contents rises to 6.0 to 9.0 when a substantial volume of water is taken orally. Since the liquid empties the stomach before enough acid can be produced, basic medications generally have a better chance of dissolving in a fed state than a fasted state. The viscosity, volume, and calorie content of meals have a significant impact on how quickly the stomach empties. Meal nutritional density influences how quickly the stomach empties. It is irrelevant whether or not the meal contains a lot of protein, fat, or carbohydrates. if the calorie content stays constant. However Calorie and acid content increases slow down stomach emptying period. biological aspects such as age, gender, body mass index (BMI), posture, and illness states (diabetes, Chron.s disease) has an impact on stomach emptying. When it comes to seniors individuals, stomach emptying is slowed.In general, women's stomach emptying is slower. compare to men. Stress speeds up while Depression causes a slowdown. The volume at rest of There are 25 to 50 ml of fluids in the stomach. impacts how quickly the stomach empties. The emptying happens faster when the volume is high.

Fluids consumed at body temperature pass through the stomach. quicker than warmer or cooler fluids. Studies have shown that a dose form's stomach emptying in Its size can also have an impact on fed state. Small size tablets pass through the stomach throughout the digestion process. phase while emptying the large-sized pills during the waves for housekeeping. There have radiolabelled method was used to show.

There are two types of gastric emptying a liquid, a digestible solid, and an indigestible solids. A suggestion was made that emptying of big Indigestible particles from the stomach were (91mm) depends on the gastrointestinal migratory complex. When there are liquids and indigestible substances un the stomach contracts between three and four times per minute causing the contents to be moved through Partially opened pyrolus Digestible solids larger than the pyloric aperture are thrown back, and myoelectric activity goes through numerous phases.when the size of the pyloric hole enlarges during the cleaning crew works and permits the sweeping of solids that are indigestible. Several formulation variables can impact the gastric residence period When compared to single unit formulations, which have problems, multiparticulate formulations show more consistent stomach emptying patterns. concept of "all or nothing." Food transit time is affected less by the units of multiparticulate formulation than it is by single unit formulation13. The size and shape of the dose unit can also affect how quickly the stomach empties. Tetrahedron-trans ring-shaped devices are said to have a longer gastric residence period than other shapes. As a formulation parameter, the dosage unit's width is also crucial. In comparison to a dosage form with a 9.9 mm diameter, one with a diameter of more than 7.5 mm exhibits a better stomach residence time. The rate at which the stomach empties also depends on a dose form's density. A buoyant dose form that floats has a density lower than the stomach juices. The dose unit stays in the stomach for a longer amount of time because it is not near the pyloric sphincter. Gamma scintigraphy has been used to examine the effects of buoyancy, posture, and the types of meals on the in-vivo mechanisms for emptying the stomach. These tests were conducted using floating and non-floating capsules of three distinct sizes, each with a diameter of 4.8 mm (small units), 7.5 mm, and 12 mm.

Large units of 9.9 mm and medium units of 4 were developed. Considering the differences between floating and non-floating dosage units Regardless of their sizes, it was determined that floating dose units float atop the gastric contents during their time in the gastrointestinal tract, while non-floating dosage units sink and stay in the bottom section of the stomach. While the non-floating forms remained close to the pylorus and were subjected to the pushing and retropelling waves of the digestive phase, the floating units farther from the gastro duodenal junction were shielded from the peristaltic waves during digestion. Additionally, it was shown that comparing floating and non-floating dosage forms, floating dosage forms had a longer stomach

residence time for small and medium dosage forms, but there was no discernible difference between the two types of dosage forms for big dosage forms. Because of the individuals' size, it was found that when they were held in the supine posture, the floating form could only prolong their stay for a short time; otherwise, buoyancy would no longer be an advantage for stomach retention. To compare how fed and unfed stages affected stomach emptying, a comparison was done. For these studies, a light breakfast was provided to every subject who remained seated, and a second group that was similarly fed received a series of meals at regular intervals. It was determined that when meals were provided when the previous digestive phase was still ongoing, the floating form buoyant in the stomach could hold its position for an additional digestive phase because it was carried by the peristaltic wave in the upper part of stomach.

## FLOATING DRUG DELIVERY SYSTEM

Hydrodynamically balanced system is another name for floating drug delivery systems (HBS). while the system is floating on the contents of the stomach, the medicine is released from the system gradually and at the preferred rate. After drug release, the remaining system is cleaned out of the stomach. This causes a higher GRT and a improved regulation of drug plasma fluctuation concentration.

## APPLICATION OF FDDS

Due to the limited absorption window in the upper region of the GIT , floating drug delivery offers numerous uses for medications with poor bioavailability. It keeps the dosage form in place and increases the bioavailability by improving the location of absorption.
The following is a summary of them.

### 1) Sustained Drug Delivery

HBS systems can stay in the stomach for extended periods of time, allowing the medicine to release gradually. With these approaches, the issue of a brief gastric residence period that arises with an oral CR formulation can be resolved. These systems can float on the gastric contents because of their bulk density of<1. These systems are not allowed to pass through the pyloric aperture because of their size, which is relatively considerable.Nicardipine hydrochloride sustained release floating capsules have recently been created and tested in vivo. Utilizing rabbits, the formulation was contrasted with commercially available MICARD capsules (8 hours) . In comparison to traditional MICARD, sustained release floating capsules showed a longer period of administration (16 hours) in plasma concentration time curves.
Similar to the previous example, a comparison study between the Madopar HBS and Madopar standard formulation was conducted, and it was discovered that while the medication was released up to 8 hours in vitro in the former case, it was essentially finished in less than 30 minutes in the latter

### 2) Site Specific Drug Delivery

These systems are especially beneficial for medications like riboflavin and thiamine that are specifically absorbed from the stomach or the proximal small intestine. furosemide. Most of the time, furosemide is absorbed from the duodenum comes after the stomach. According to reports a single, massive floating dose form with extended The development of stomach residence time and the bioavailability went up. AUC determined using the floating pills were almost 1.8 times as common as standard furosemide pills.
Misoprostol, a synthetic analogue of prostaglandin E1 utilised as a preventative of gastric ulcers brought on by the ingestion of NSAIDs, was designed as a bilayer-floating capsule for local distribution. Misoprostol could be delivered slowly to the stomach in order to obtain the optimal therapeutic levels and decrease drug waste.

### 3) Absorption Enhancement

Potential possibilities for formulation as floating drug delivery systems include medications with low

bioavailability due to site-specific absorption from the upper gastrointestinal tract, which would maximise their absorption. Comparing floating dosage forms (42.9%) to currently available LASIX tablets (33.4%) and enteric coated LASIX-long product (29.5%), a considerable improvement in bioavailability could be made.

## CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM

1) Single Unit Floating Dosage Systems
a) Effervescent system
b) Non-effervescent Systems
2) Multiple Unit Floating Dosage Systems
a) Effervescent Systems
b) Non-effervescent Systems
c) Hollow microspheres
d) Raft forming system

### 1. Single Unit Floating Dosage Systems

### a) Effervescent Systems (Gas-generating Systems)

These buoyant systems made use of matrices made of effervescent substances, polysaccharides like chitosan, and swellable polymers like HPMC. such as tartaric acid, citric acid, and sodium bicarbonate or compartments with liquids that gasify at the body temperature.

The ideal citric stoichiometric ratio For the production of gas, sodium bicarbonate and acid are according to reports, 0.76:1. The typical method for In order to create these systems, resin beads that are bicarbonate and ethylcellulose coating. The covering This, though insoluble, is porous and permits penetration of water. So, the release of carbon dioxide results in the stomach with floating beads (Fig: 4). utilised excipients These systems most frequently use HPMC, Carbopol®, polyvinyl acetate, and polyacrylate polymers Agar, calcium chloride, sodium alginate, and polyethylene polycarbonates, oxide.

### b) Non-Effervescent Systems:

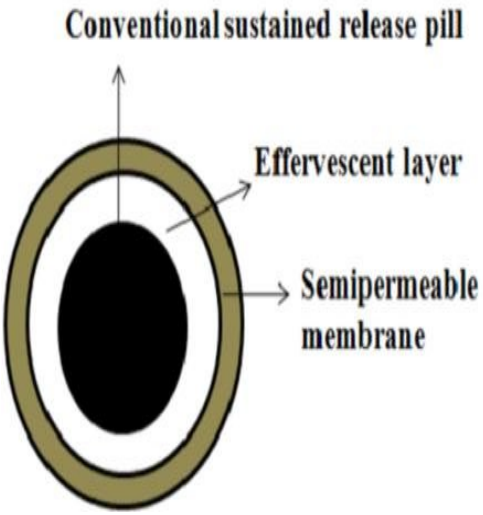
After swallowing, this type of system swells uncontrollably from ingestions of gastric fluid to the point where it hinders their departure from the stomach. Due to their propensity to remain ensconced close to the pyloric sphincter, these systems may be referred to as "plug-type systems." One of the processes used to create these dosage forms involves mixing the medicine with a gel that expands when it comes into touch with gastric fluid. These dose forms have buoyancy due to the air trapped by the inflated polymer. Alginate beads, micro porous compartment systems, colloidal gel barriers, and hollow microspheres are a few examples of this type of FDDS.
A fluid-filled floating chamber is an alternative form, which incorporates a gas-filled flotation chamber inside a microporous component that stores a medication.reservoir. At the top, there are openings or apertures. and bottom walls that the digestive tract passes through The medication is dissolved by fluid entering. the other two inside walls so that the undissolved matter has no contact with the fluid the medicine is still there. Possible fluids include air, any suitable gas, liquid, or suspended object under a partial vacuum solid with the right specific gravity and inert behaviour. The device can expand in size and continues to float for an extended period of time in the stomach. and the shell breaks down after the full release.is transferred to the gut and excreted there.
A 3-layer matrix is used in a more recent self-correcting floatable asymmetric configuration drug delivery device to regulate drug release. By creating a drug delivery system with an asymmetric configuration, the three-layer principle has been improved. This allows for zero-order release kinetics and modulation of the release extent by initially maintaining a constant area at the diffusing front with subsequent dissolution/erosion toward the end of the release process. The system was made to float to increase stomach residence time in

vivo, leading to a longer total transit time inside the environment of the gastrointestinal tract with maximum absorptive capacity and, as a result, improved bioavailability.
Drugs with a restricted window of absorption, pH-dependent solubility, and active transport absorption from either the proximal or distal region of the small intestine would fit this description.

## 2. Multiple Unit Floating Systems:

Despite intensive research and development into floating tablets and hydro dynamically balanced systems, these technologies have a significant drawback of high gastrointestinal transit time variations when taken orally Because of their all-or-nothing gastric regime, administered voiding nature In order to resolve this issue,Systems with several floating units were created, which decreases the variation in absorption between subjects, and reduces the likelihood of dose-dumping.
There are reports on the creation of multiple unit systems that are both effervescent and non-effervescent There has been a lot of research done, and scientists are The study of hollow microspheres, which are capable of improving and floating on gastric fluid stomach retention characteristics.




### a) Non-effervescent Systems:

Comparatively speaking to effervescent multiple unit systems, there were fewer reports of noneffervescent multiple unit systems in the literature. However, only a few researchers have mentioned the potential for creating such a system with indomethacin employing chitosan as the polymeric excipient. It is reported that an extrusion-prepared multiple unit HBS containing indomethacin as a model medication was created. Through the use of a needle, a mixture of the medication, chitosan, and acetic acid is extruded. Chitosan hydrates and floats in acidic solutions, and by adjusting the drug-polymer ratio, the desired drug release might be achieved.

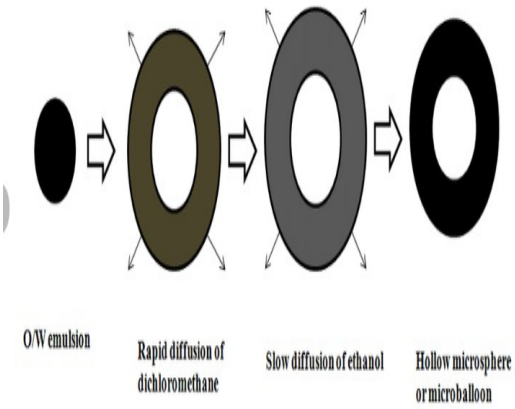
### c) Effervescent Systems (Gas-generating Systems):

Tetracycline Hcl-containing floating granules with prolonged release have been reported. The combination of grains Comprising drug granules in stages A and B, where A is the first stage. comprises 40 parts polyacrylic acid and 60 parts HPMC.and 20 parts of the medication, while B has 70 parts sodium. 30 parts tartaric acid and 30 parts bicarbonate. by 60 pieces stage A granule weight and 30 parts by weight of the Stage B grains are combined with a lubricant and placed within a capsule. The pill dissolves in dissolving media the shell disintegrates and releases the granules, which shown a floating period longer than 8 hours and persistent drug use an 80% release in roughly 6.5 hours.
There have been reports of floating pepstatin minicapsules with a diameter of 0.1 to 0.2 mm. These minicapsules have a covering on top of a central core. The sodium bicarbonate, lactose, and binder granules that make up the centre core are covered with HPMC polymer. The HPMC layer is covered with pepstatin. The system floats as a result of the gastric fluid's emission of CO2, and pepstatin stays in the stomach for an extended period of time. Alginates have drawn a lot of interest in the creation of several unit systems.

### d) Hollow Microspheres:

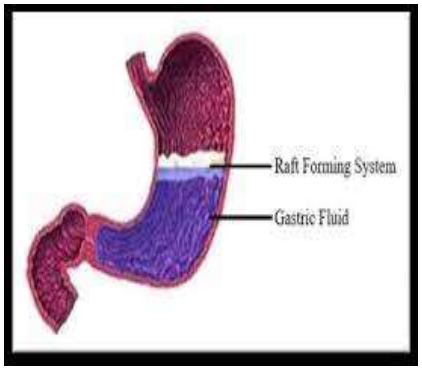
  

These buoyant systems are regarded as one of the most promising because to their distinct advantages.Using several unit systems and improved floating owing to the core empty region inside the microsphere. The fundamental methods used in their Simple solvent evaporation techniques are used in the preparation. and the process of solvent evaporation and diffusion. The kind of polymer, plasticizer, and solvents used in the formulation largely determine the drug release and superior floating qualities. polymers include Eudragit®, Polycarbonate, and Cellulose Acetate were hollow microspheres are prepared using this method, and the It is possible to control medication release by improving the The ratio of plasticizer to polymer and the amount of polymer. utilising floating microspheres with a sustained release Utilizing solvents, polycarbonate was created. evaporation process As model medications, aspirin, griseofulvin, and p-nitroaniline were employed.




## e) Raft Forming System:

Antacid delivery and medication delivery for GI infections and diseases have attracted a lot of attention thanks to raft forming mechanisms. The fundamental mechanism at work The development of viscous fluid is included in the raft formation. cohesive gel in touch with the stomach juices, where Each area of the liquid swells, creating a continuous A raft-style layer (Fig no: 3). The raft floats as a result of the buoyancy brought on by the production of CO2 and serve as a barrier to stop the reflux of gastric fluids like HCl and enzymes enter the oesophagus. Typically, the system contains alkaline bicarbonates and a gelling agent. or carbonates that are responsible for the formation to make the system that is less thick and floats atop the stomach juice




## MECHANISM OF FLOATING DRUG DELIVERY SYSTEM

Due to their lower bulk density than gastric fluids, floating drug delivery systems (FDDS) stay buoyant in the stomach without slowing down the rate at which the stomach empties. for a considerable amount of time. During the system's float on the stomach's contents (Fig no: 4) It is a drug. released from the system gradually and at the optimum rate. Following drug release, the residual system is emptied. from the abdomen. As a result, GRT is raised and improved regulation of medication plasma fluctuation concentration.

To ensure that the buoyancy retention principle is properly achieved, a minimum degree of floating force (F) is also necessary to keep the dose form consistently buoyant on the surface of the meal. A unique apparatus for calculating the resultant weight has been described in the literature to measure the floating force kinetics. The device works by continually measuring the force, F, needed to keep the submerged object in place (as a function of time).

When F is higher on the positive side, the object floats more effectively.

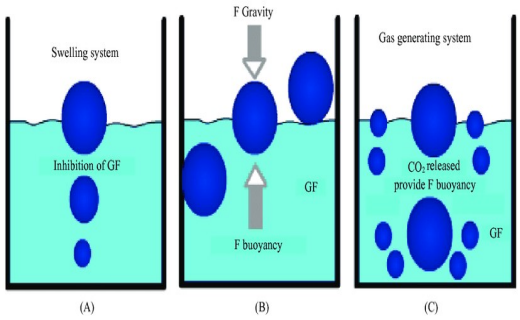
This device aids in FDDS optimization with regard to the stability and longevity of floating forces generated in order to avoid the negative effects of

unforeseen intra-gastric buoyancy capability fluctuations.

F = F buoyancy - F gravity
= (Df - Ds) gV

Where F is the total vertical force, Df is the fluid density, Ds is the object density, V is the volume, and g is the gravitational acceleration.




## FLOATING GASTRORETENTIVE PATENTS

| S.No | Type of formulation | Patent no | . Ref |
|---|---|---|---|
| 1 | Gastro retentive dosage form | U.S-7,413,752 . | Devane et al., 2008 |
| 2 | Multiple unit floating dosage form | European patent (EP) 10697 | Vanderbist et al., 2007. |
| 3 | Bilayer tablet | EP-002445 | Lohray et al., 2004. |
| 4 | Floating Tablet | U.S-66,352279 | Kolter et al., 2003. |
| 5 | Microspheres | U.S-6207197 | Illum et al., 2001. |
| 6 | 3-layer tablet | U.S-5780057 | Conte et al., 1998. |
| 7 | Foams (or) hollow bodies | U.S-5626876 | Muller et al., 1997. |
| 8 | Floating tablet | U.S-5169639 | Baichwal et al., 1992. |
| 9 | Granule | U.S-4844905 | Ichikawa et al., 1989 |
| 10 | Floating capsules | U.S-4814178,-79 | Sheth et al., 1989. |
| 11 | Tiny pills | U.S-4434153 | Urguhart et al., 1984. |
| 12 | Floating capsule | U.S-4126672 | Sheth et al., 1978 |
| 13 | Floating device | U.S-4055178 | Harrigan et al., 1977. |
| 14 | Empty globular shells | U.S-3976164 | Watanabe et al., 1976 |

## MARKETED FORMULATION OF FDDS

| *Brand Name* | *Drug (dose)* | *Company, Country* | *Remarks* |
|---|---|---|---|
| Madopar | Levodopa (100mg) Benserazide (25mg) | Roche products, USA | Floating CR capsule (Hydrodynamically Balanced Systems) |
| Valrelease | Diazapam (15mg) | Hoffmann La Roche, USA | Floating capsule |
| Liquid Gaviscon | Aluminium hydroxide (95mg) Magnesium carbonate (385mg) | Glaxosmithkline, India | Raft forming system |
| Topalkan | Al-MG antacid | Pierre fabre drug, France | Floating liquid alginate |
| Almagate float coat | Al-MG antacid | Pierre fabre drug, France | Floating liquid form |
| Conviron | Ferrous sulfate | Ranbaxy, India | Colloidal gel forming floating system |
| Cifran OD | Ciprofloxacin (1g) | Ranbaxy, India | Gas generating System |
| Cytotec | Misoprostat (100µg/200 µg) | Pharmacia, USA | Bilayer floating Capsule |

## LIMITATION OF FDDS

1) These systems need a lot of fluid in the stomach to float and function well while delivering drugs.
2) Unsuitable for medications with GIT solubility or stability issues
3) It may not be advisable to take medications like nifedipine, which is well absorbed throughout the GIT and undergoes first-pass metabolism.
4) Drugs that irritate the stomach mucosa are also not preferred or appropriate.
5) Drug compounds that are unstable in the stomach's acidic environment should not be integrated into the systems.
6) A full glass of water should be consumed after taking the dose form (200-250 ml).
7) Contrary to conventional medication dose forms, which are absorbed throughout the gastrointestinal tract, these systems do not significantly outperform them.

## CONCLUSION

With the aim of achieving continuous release and limiting the region of drug release to the stomach, numerous medications have recently been developed as floating drug delivery systems.
The idea of buoyant preparation gives a straightforward strategy. To produce prolonged drug release and enhanced stomach residence time for the dose form. The currently available polymer-mediated non effervescent and effervescent FDDS, which were developed using delayed stomach emptying and buoyancy principles, seem to be a very successful method for controlling oral drug administration.
The most crucial factor that must be taken into consideration when creating a floating drug delivery system is that the dosage form & density must be lower than that of stomach fluid. And therefore, it can be said that these dose forms work best for treating GIT related illnesses and getting a longer- lasting effect out of a medicine with a short half-life.

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