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A REVIEW ON FLOATING DRUG DELIVERY SYSTEM AS A PART OF GRDDS

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ABSTRACT

A lot of scientific and technological advancements have been made in the drug delivery research in the recent years. Physiological problems like short Gastric Residence Time (GRT) and the unpredictable Gastric Emptying Time (GET) were overcome with the use of floating dosage forms which provide opportunity for both local and systemic drug action. Several approaches are currently being used in the prolongation of GRT, which includes the Floating Drug Delivery Systems (FDDS), also known as Hydrodynamically Balanced System (HBS). The purpose of this overview is to compile the recent advancements with special emphasis on the mechanism of floatation. In this overview we have discussed the variables affecting gastric retention, approaches to design single unit and multiple unit floating systems and the applications of such system with future trends. Market survey has been also done and also current situation regarding FDDS is focused.

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Key Words

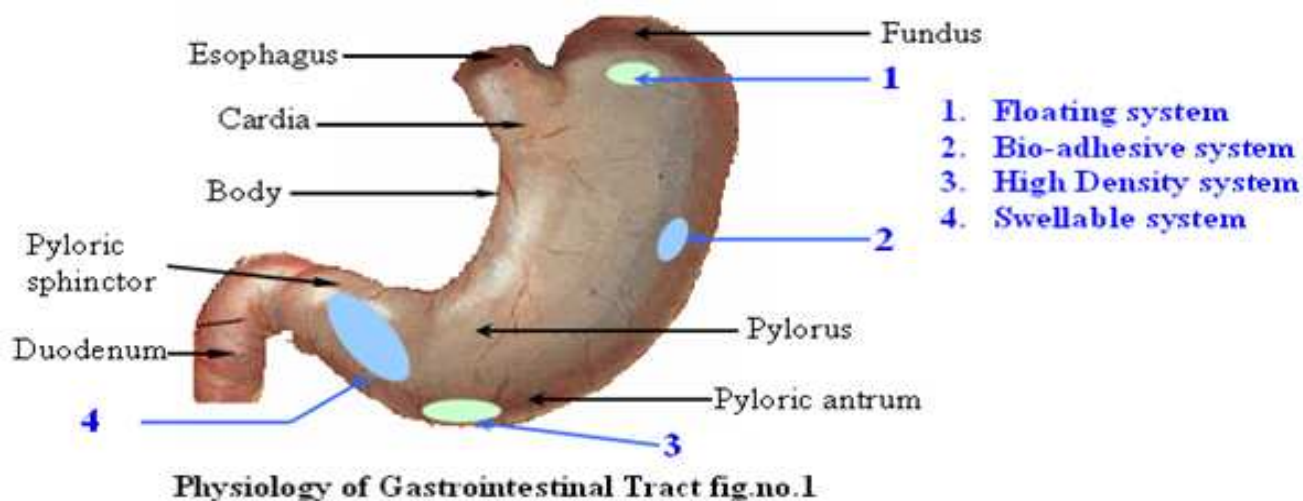
Floating Drug Delivery, Get,
Grt, Hbs, Fdds etc.

INTRODUCTION

Oral Dosage Form

Oral delivery of the drug is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in the formulations. From immediate release to site-specific delivery, oral dosage form has really progressed. It is evident from the recent scientific and patented literature that an increased interest in novel dosage forms that are retained in the stomach for prolong and predictable period of time exist today in academic and industrial research groups. Various attempts have been made to develop Gastroretentive delivery systems.

Over the past three decades, the pursuit and exploration of devices designed to be retained in the upper part of the gastrointestinal (GI) tract has advanced consistently in terms of technology and diversity, encompassing a variety of systems and devices such as floating systems, raft systems, expanding systems, swelling systems, bioadhesive systems and low-density systems. This technology benefits drugs that have a narrow window of absorption in the stomach and upper GI tract.

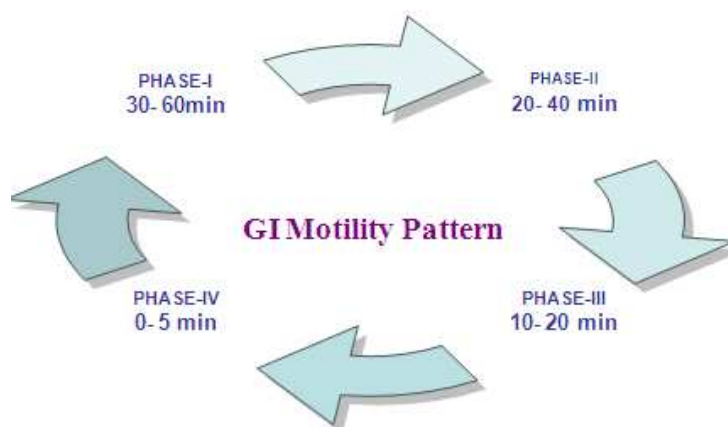


Gastrointestinal tract physiology

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.

Under fasting conditions, the stomach is a collapsed bag with a residual volume of approximately 50ml and contains a small amount of gastric fluid (pH 1–3) and air. The mucus spreads and covers the mucosal surface of the stomach as well as the rest of the GI tract. The GI tract is in a state of continuous motility consisting

of two modes, interdigestive motility pattern and digestive motility pattern. The former is dominant in the fasted state with a primary function of cleaning up the residual content of the upper GI tract. The interdigestive motility pattern is commonly called the 'Migrating Motor Complex' ('MMC') and is organized in cycles of activity and quiescence. Each cycle lasts 90–120 minutes and consists of four phases. The concentration of the hormone motility in the blood controls the duration of the phases. In the interdigestive or fasted state, an MMC wave migrates from the stomach down the GI tract every 90–120 minutes. A full cycle consists of four phases, beginning in the lower esophageal sphincter, gastric pacemaker, propagating over the whole stomach, the duodenum and jejunum, and finishing at the ileum.



Four phases of GI motility:

Phase I (basal phase) - lasts from 40 to 60 minutes with rare contractions.

Phase II (preburst phase) - lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

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.

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

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing 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.

Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate.

Gastro retention systems

Gastro retentive 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. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

Requirements of gastric retention

Physiological factors in the stomach, it must be noted that, to achieve gastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms. To function as a gastric retention device, it must resist premature gastric emptying. Furthermore once its purpose has been served, the device should be removed from the stomach with ease.

Need For Gastro Retention:

Drugs are absorbed from the proximal part of the gastrointestinal tract (GIT).

Drugs are less soluble or are degraded by the alkaline pH they encounter at the lower part of GIT.

Drugs are absorbed due to variable gastric emptying time.

Local sustained drug delivery to stomach and proximal Small intestine for treat certain conditions.

Particularly useful for the treatment of peptic ulcers caused by H. Pylori Infections.

Factors Affecting Gastric Retention:

Density: GRT is a function of dosage form buoyancy that is dependent on the density.

Size: Dosage form units with a diameter of more than 7.5mm are reported to have an increased GRT compared with those with a diameter of 9.9mm.

Shape of dosage form: Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (kpsi) are reported to have

better GRT 90% to 100% retention at 24 hours compared with other shapes.

Single or multiple unit formulation: Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co- administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

Fed or unfed state: under fasting conditions:

GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

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.

Caloric content: GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.

Frequency of feed: the GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC.

Gender: Mean ambulatory GRT in males (3.4 ± 0.6 hours) is less compared with their age and race matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, height and body surface.

Age: Elderly people, especially those over 70, have a significantly longer GRT.

Posture: GRT can vary between supine and upright ambulatory states of the patient.

Concomitant drug administration:

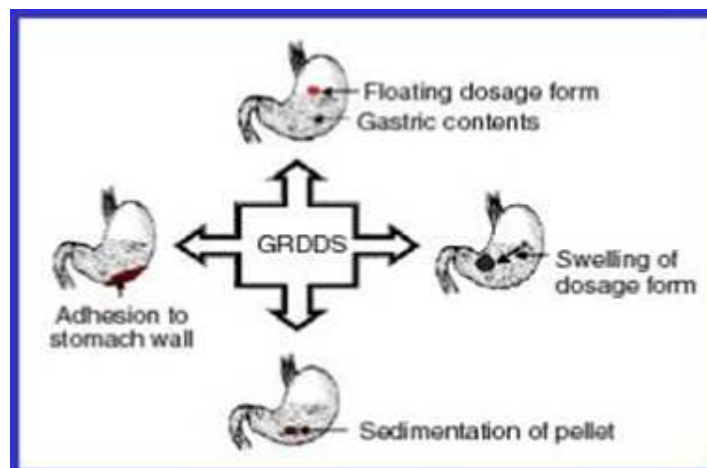
Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride.

Biological factors: Diabetes and Crohn's disease.

Approaches to Gastric Retention:-

Various approaches have been pursued to increase the duration of oral dosage form in the stomach, including

floating systems, swelling and expanding system modified shape system, high density systems and other delayed gastric emptying devices. (Magnetic systems super porous – biodegradable hydrogel systems).



Hydrodynamically balanced systems (HBS):

Incorporated buoyant materials enable the device to float.

Raft systems:

Incorporate alginate gels – these have a carbonate component and, upon reaction with gastric acid bubbles form in the gel, enabling floating.

Swelling type:

This type of dosage form is such that after swelling, this product swells to extent that prevents their exit from the stomach through the pylorus. As a result, the dosage form retained in the stomach for a longer period of time. These systems may be referred to as a “Plug type system”, since they exhibit tendency to remain lodged in the pyloric sphincters.

Bioadhesive or mucoadhesive systems:

They are used to localize a delivery device within the lumen and cavity of the body to enhance the drug absorption process in a site-specific manner. The approach involves the use of bioadhesive polymer that can be adhere to the epithelial surface of the GIT. The proposed mechanisms of bioadhesive is the formation of hydrogen and electrostatic bonding at the mucus polymer boundary.

Modified shape systems:

They are non-disintegrating geometric shapes molded from silastic elastomer or exuded from polyethylene blends and extended the GTT depending on the size, shape and flexural modulus of the drug delivery device.

High density formulations:

They include coated pellets, and have density greater than that of the stomach content (1.004 gm/cm³). This is accomplished by coating the drug with a heavy inert material such as barium sulphate, ZnO, titanium dioxide. This formulation of high-density pellet is based on assumption that heavy pellets might remain longer in

the stomach, since they are position in the lower part of the antrum.

Other delayed gastric emptying approaches of interest include sham feeding of digestible polymers or fatty acid salts that changes the motility pattern, of the stomach to a fed stage thereby decreasing the gastric emptying rate and permitting considerable prolongation of the drug release. But some of this has certain drawbacks, which could limit their uses described in the following table:

Formulations	Drawback
Incorporation of passage delaying food excipient such as fatty acids	Affect the emptying mechanism of the entire content
Bio adhesive drug delivery systems	Adhesive is non specific Efficiency is limited by the possible interaction with food.
Biodegradable and non biodegradable (swelling) formulation in which the size and shape retain in the dosage form.	Present the hazard of permanent retention and might lead to serious life threatening effects if multiple dosing is predicted.

Floating Drug Delivery Systems (FDDS):-

Floating systems, first described by Davis in 1968, have bulk density lower than that of the gastric fluid, and thus remain buoyant in stomach for prolong period. Floating drug delivery systems are classified depending on the use of 2 formulation variables: EFFERVESCENT and NON-EFFERVESCENT SYSTEMS.

Effervescent Floating Dosage Forms:-

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. The device may also consist of a bioerodible plug made up of PVA, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach. (Figure__A and B) developed

floating capsules composed of a plurality of granules that have different residence times in the stomach and consist of an inner foamable layer of gas-generating agents.

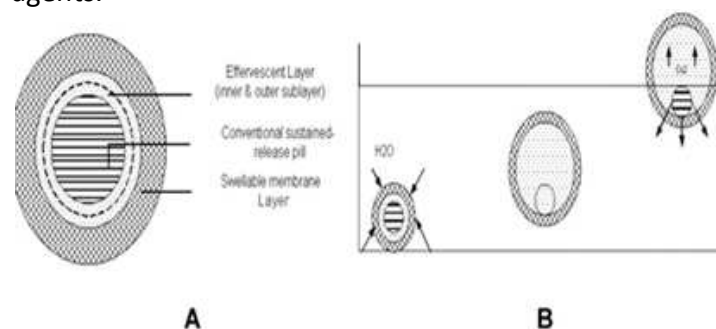


Fig. no. 4 - (A) Multiple-unit oral floating drug delivery system. (B) Working principle of effervescent floating drug delivery system.

This layer was further divided into 2 sublayers, the outer containing sodium bicarbonate and the inner containing tartaric acid. This layer was surrounded by an expansive polymeric film (composed of poly vinyl acetate [PVA and shellac], which allowed gastric juice to pass through

and was found to swell by foam produced by the action between the gastric juices and the gas-generating agents. It was shown that the swellable membrane layer played an important role in maintaining the buoyancy of the pills for an extended period of time.

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO₂, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme.

Gas-generating Systems:

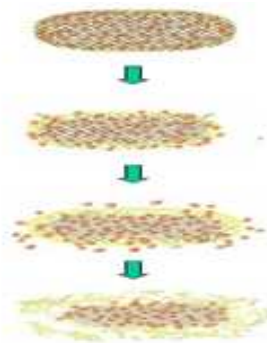


Fig. no. 5 - HBS - Mode of action

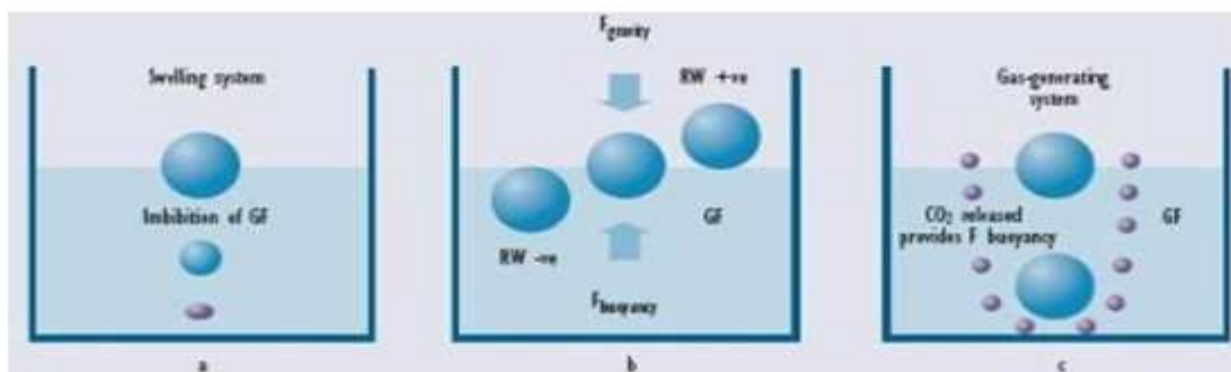


Fig. no. 6 - The Mechanism of Floating Systems

Non-effervescent systems:

Colloidal gel barrier systems
Hydrodynamically balance system (HBS™) was first design by Sheth and Tossounian in 1975. Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids. e.g. HEC,

HPMC, NaCMC, Polysaccharides and matrix forming polymer such as polycarboxylic, polyacrylates and polystyrene, incorporated either in tablets or in capsule. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the sweller polymer maintains a density less than unity and confer buoyancy to this dosage forms.

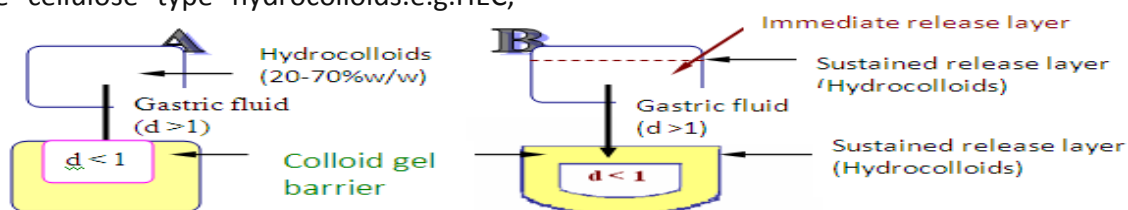


Fig. no. 7 - Intragastric floating tablets.

Microporous Compartment System

This technology is based on the encapsulation of drug reservoir inside a Microporous compartment with aperture along its top and bottom wall. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolved drug. In stomach the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the apertures, dissolves the drug, and carries the dissolved drug for continuous transport across the intestine for absorption.

Alginate beads

Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping a sodium alginate solution into aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated, snap and frozen in liquid nitrogen, and freeze dried at -40°C for 24 hours, leading to the formation of porous system, which can maintain a floating force over 12 hours.

Hollow microspheres

Hollow microspheres (microballons), loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40°C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 hours in vitro.

APPLICATION OF FLOATING DRUG DELIVERY SYSTEM:

Recent study indicated that the administration of Diltiazem floating tablets twice a day may be more effective compared to normal tablets compared to normal tablets in controlling the B.P of hypertensive patients.

Modapar® HBS containing L-Dopa and Benserazide, here the drug was absorbed over a period of 6-8 hours and maintained substantial plasma concentration for Parkinsonian patients. Cytotech® - containing Misoprostol, a synthetic prostaglandin –EL analogue, for prevention of gastric ulcer caused by non-steroidal anti-inflammatory drugs (NSAIDs).

As it provides high concentration of drug within gastric mucosa, it is used to eradicate *H.pylori* (a causative organism for chronic gastritis and peptic ulcers).

5-fluorouracil has been successfully evaluated in the patients with stomach neoplasm.

Developing HBS dosage form for tacrin provide better delivery systems and reduced its GI side effects.

Treatment of gastric and duodenal ulcer.

MERITS:

The delivery of drugs with narrow absorption window in the small intestinal region.

Longer residence time in stomach could be advantageous for local action in the upper part of the small intestinal. i.e. treatment of peptic ulcer.

Improved bioavailability is expected for drugs that are absorbed readily upon release in the GI tract. These drugs can be delivered ideally by slow release from the stomach.

Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose e.g. Furosemide .

Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics. e.g. b-lactam antibiotics (penicillins and cephalosporins).

Retention of drug delivery systems in the stomach prolongs overall Gastrointestinal transit time thereby increasing bioavailability of sustained release delivery systems intended for once-a-day administration. e.g. Ofloxacin.

DEMERITS:

There is certain situation where gastric retention is not desirable. Aspirin & NSAID are known to cause G.I. lesions & slow release of such drug in stomach is unwanted.

Those that have multiple absorption sites in the gastrointestinal tract.

Those that is not stable at gastric pH.

Those which gets degraded due to gastric enzymes.

Drug reported to be used in formulation of dosage form.

Sr.No.	Dosage forms	Drugs
1.	Floating microspheres	Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Terfenadine and Tranilast
2.	Floating granules	Diclofenac sodium, Indomethacin and Prednisolone
3.	Films	Cinnarizine
4.	Floating Capsules	Chlordiazepoxide hydrogen chloride, Diazepam, Furosemide, Misoprostol, L-Dopa, Benserazide, Ursodeoxycholic acid and Pepstatin

Marketed formulations.

Name	Type and Drug	Remarks
MadoparHBS (PropalHBS)	Floating capsule, Levodopa and benserazide	Floating CR capsules
Valrelease	Floating capsule, Diazepam	Floating Capsules
Topalkan	Floating Antacid, aluminum and magnesium mixture	Effervescent floating liquid alginate preparation
Amalgate Float Coat	Floating antacid Floating gel,	Floating dosage form
Convicon	Ferrous sulphate	Colloidal gel forming FDDS
Cifran OD	Ciprofloxacin (1 gm)	Gas generating floating form
Cytotech	Misoprostol (100 mcg/200 mcg)	Bilayer floating capsule
Liquid Gaviscon	Mixture of alginate	Suppress gastro esophageal

		reflux and alleviate the heart burn
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FUTURE POTENTIAL

Floating dosage form offers various future potential as evident from several recent publications. The reduced fluctuations in the plasma level of drug results from delayed gastric emptying.

Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently there by maximizing their absorption and improving their absorption and improving their absolute bioavailability.

Buoyant delivery system considered as a beneficial strategy 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.

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