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REVIEW ARTICLE

Recent Development in Floating Delivery Systems for Gastric Retention of Drugs An Overview

M. Uddin*, P. B. Rathi, A. R. Siddiqui, A. R. Sonawane, D. D. Gadade

Department of Pharmaceutics, Shri Bhagwan College of Pharmacy, Aurangabad, India.

ABSTRACT

The present review on floating drug delivery systems (FDDS) is aimed to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. The recent developments of FDDS such as physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. This review also summarizes the in vitro techniques, in vivo studies to evaluate the performance and application of floating systems, and applications of these systems. It is concluded that, these systems are useful to resolve several problems encountered during the development of a pharmaceutical dosage form

KEYWORDS: floating drug delivery systems, single unit, multiple units, *in vitro* and in *vivo*

INTRODUCTION

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 a prolonged period. Floating systems can be of effervescent or non effervescent in nature. In effervescent gas generating excipients, e.g., bicarbonate salts and acidic ingredients are used that can form CO_2 in the presence of gastric acid. Also, volatile organic solvents have been introduced into the floating chamber to generate gas at physiological temperature.

Gastroretentive dosage forms extend significantly the period of time over which the drugs may be released. Thus, they not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage forms. This application is especially effective in delivery of sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. To address this, oral administration of sparingly soluble drugs is carried out frequently, often several times per day. As a mechanism to override this problem, erodible, gastro retentive dosage forms have been developed that provide continuous, controlled administration of these drugs at the absorption site. In addition, these dosage forms are useful for delivering drugs incorporated into vesicles such as liposomes, nanoparticles, proteinoid microspheres and pharmacosomes etc. The drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems. Furthermore, other drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract, drugs undergoing first pass metabolism will not benefit from incorporation into a gastric retention system. It requires sufficient high level of fluids in the stomach for the drug delivery to float.

MECHANISM OF FLOATING SYSTEMS

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Among these, the floating dosage forms have been most commonly used. 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 (given in the Figure 1 (a)), the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the

*Corresponding author: **M. Uddin** / *Email:* minhajuddin21@gmail.com

literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side (Figure 1(b)). This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations

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

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

Where,

F = Total vertical force in N,

D_f = Fluid density in Kg/m^3,

D_s = Density of object in Kg/m^3,

V = Volume of the object m^3,

g = Acceleration due to gravity m/s^2.

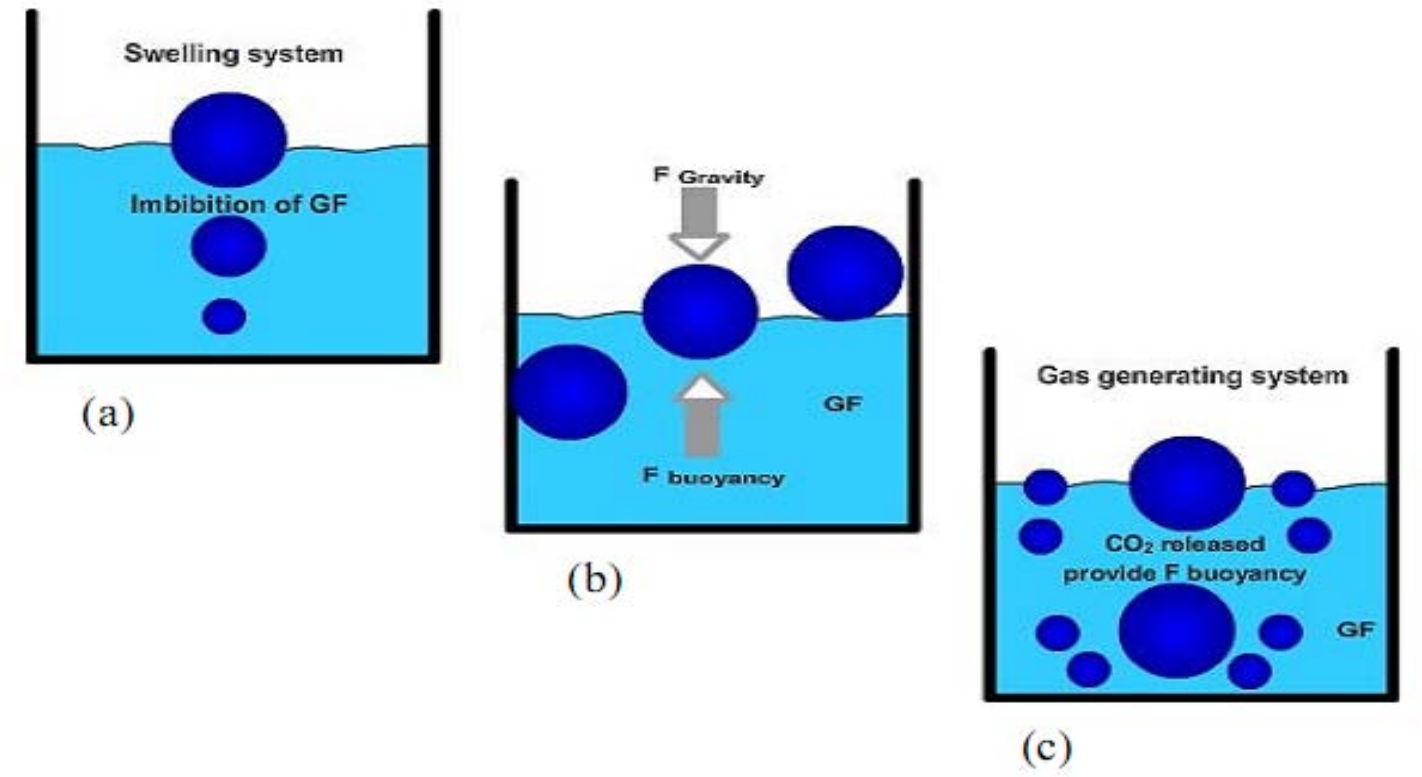

Figure1: Mechanism of floating system, GF= Gastric fluid

TYPES OF FLOATING DRUG DELIVERY SYSTEMS (FDDS)

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are:

A. Effervescent System, and

B. Non- Effervescent System.

A. EFFERVESCENT SYSTEM

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature.

THESE EFFERVESCENT SYSTEMS FURTHER CLASSIFIED INTO TWO TYPES

I. Gas generating systems

Ii. Volatile liquid/vacuum containing systems.

I. GAS GENERATING SYSTEMS:

1. INTRA GASTRIC SINGLE LAYER FLOATING TABLETS OR HYDRODYNAMICALLY BALANCED SYSTEM (HBS)

These are as shown in Fig.2 and formulated by intimately mixing the CO2 generating agents and the drug within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach.

This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration

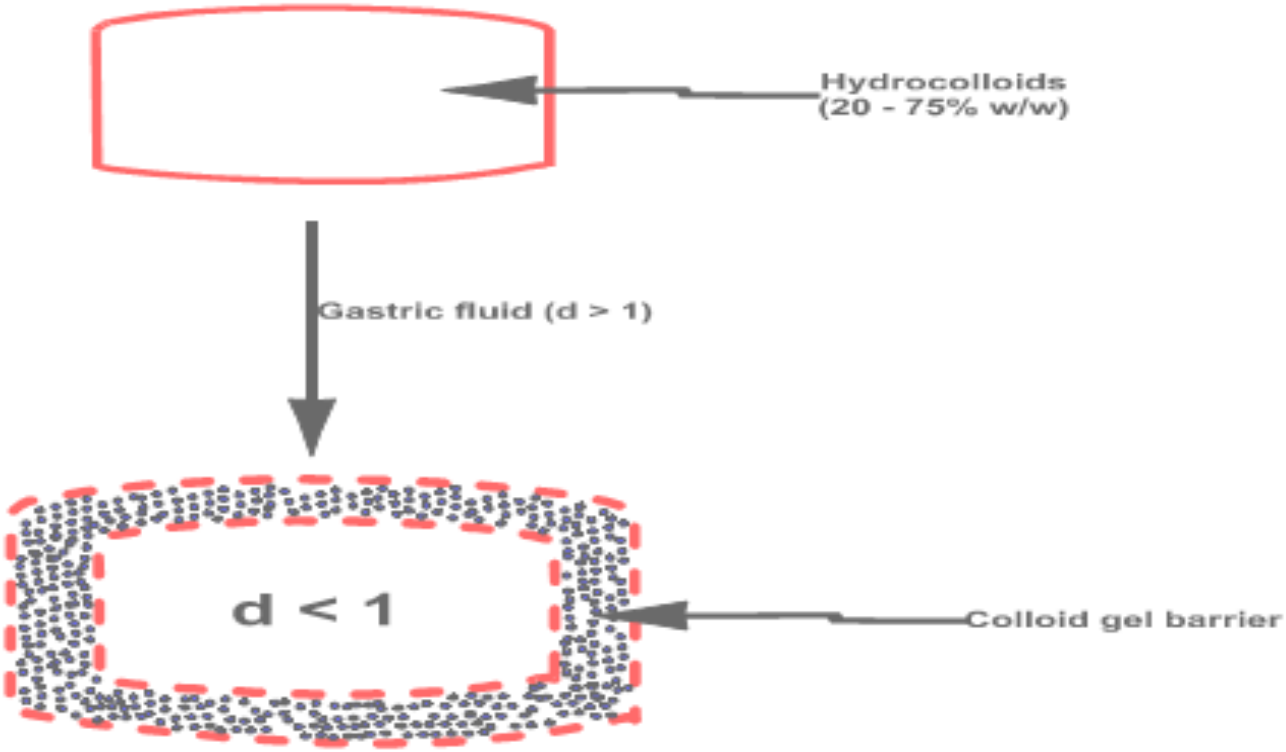

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Figure2: Intra Gastric Single Layer Floating Tablet

2. Intra Gastric Bilayer Floating Tablets:

These are also compressed tablet containing two layers, **(I)** Immediate release layer and **(II)** Sustained release layer.

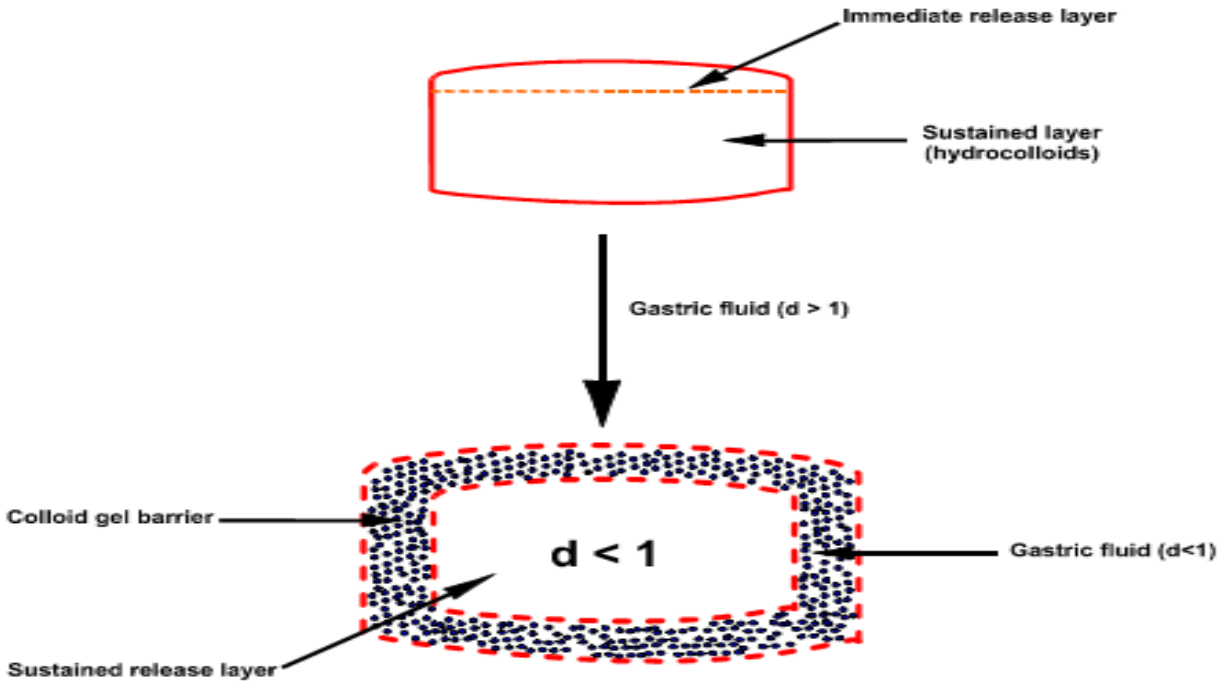

Figure3: Intragastric Osmotically Controlled Drug Delivery System

3. MULTIPLE UNIT TYPE FLOATING PILLS

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO2 within the system.

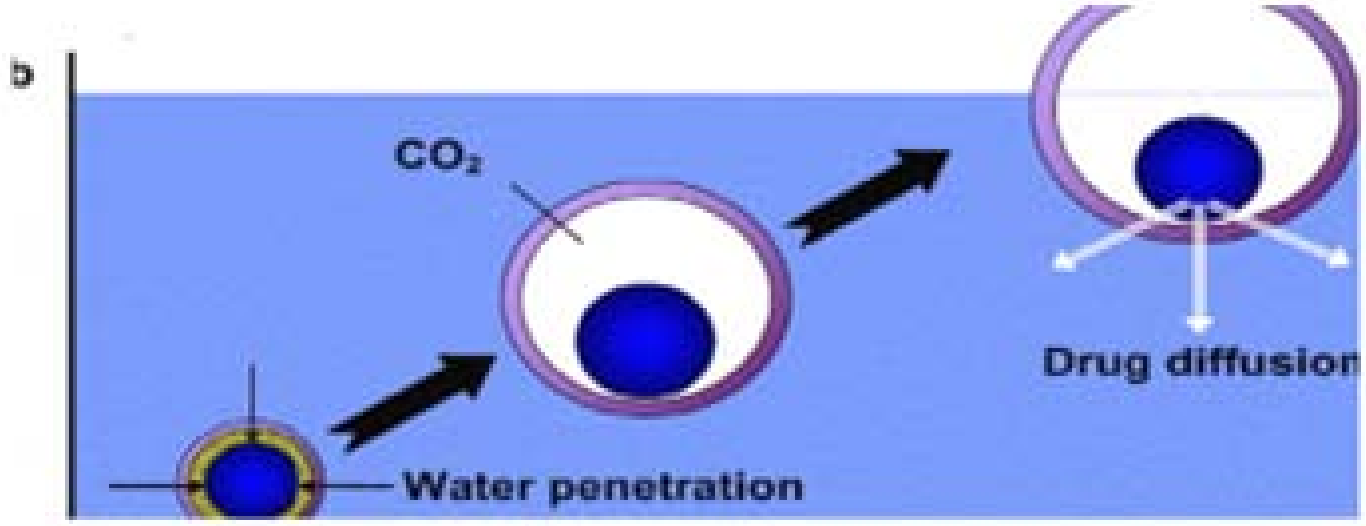

Figure4: Gas generating system

II. VOLATILE LIQUID / VACUUM CONTAINING SYSTEMS

1. INTRAGASTRIC FLOATING GASTROINTESTINAL DRUG DELIVERY SYSTEM:

This system can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microprous compartment, as shown in Fig. 5

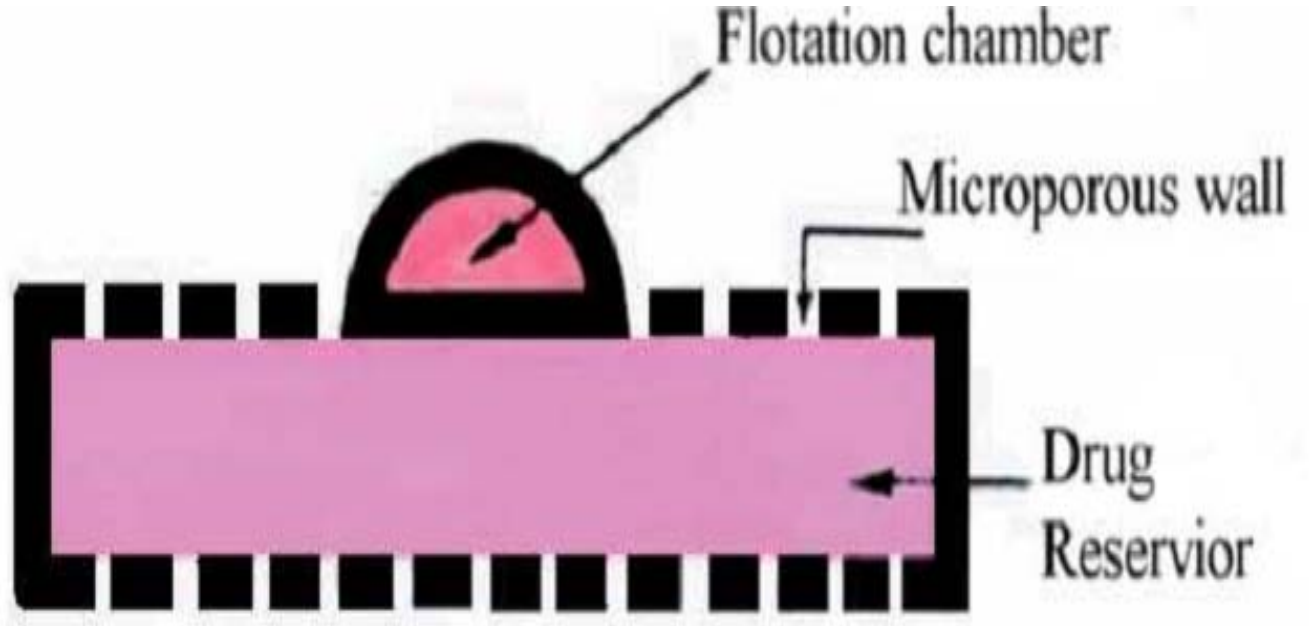

Figure 1: Intra Gastric Floating Gastrointestinal Drug Delivery Device

2. INFLATABLE GASTROINTESTINAL DELIVERY SYSTEMS

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid. This system is shown in Fig. 6.

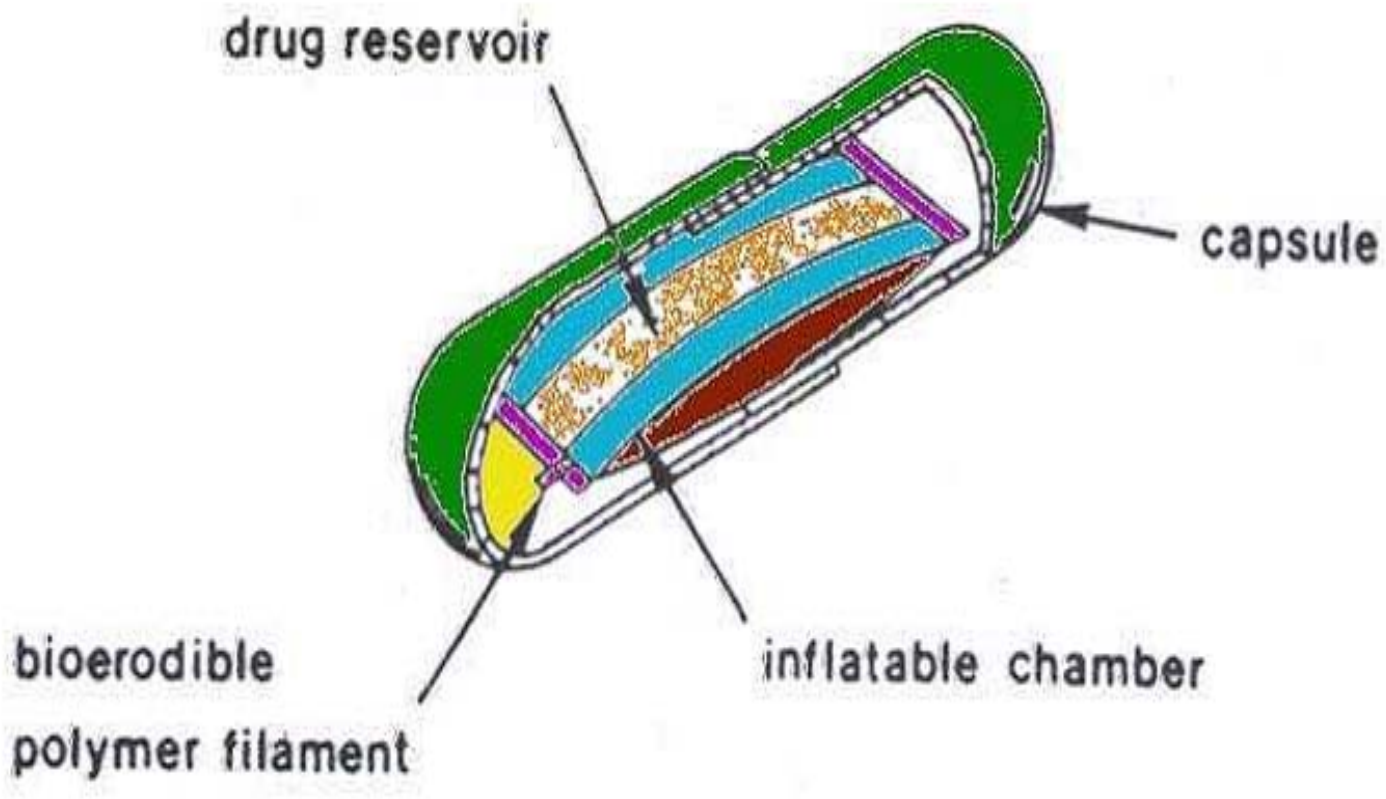

Figure 2: Inflatable Gastrointestinal Delivery System

2. INTRAGASTRIC OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEM

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastirc osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi permeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice. The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach. This system is shown in Fig.7.

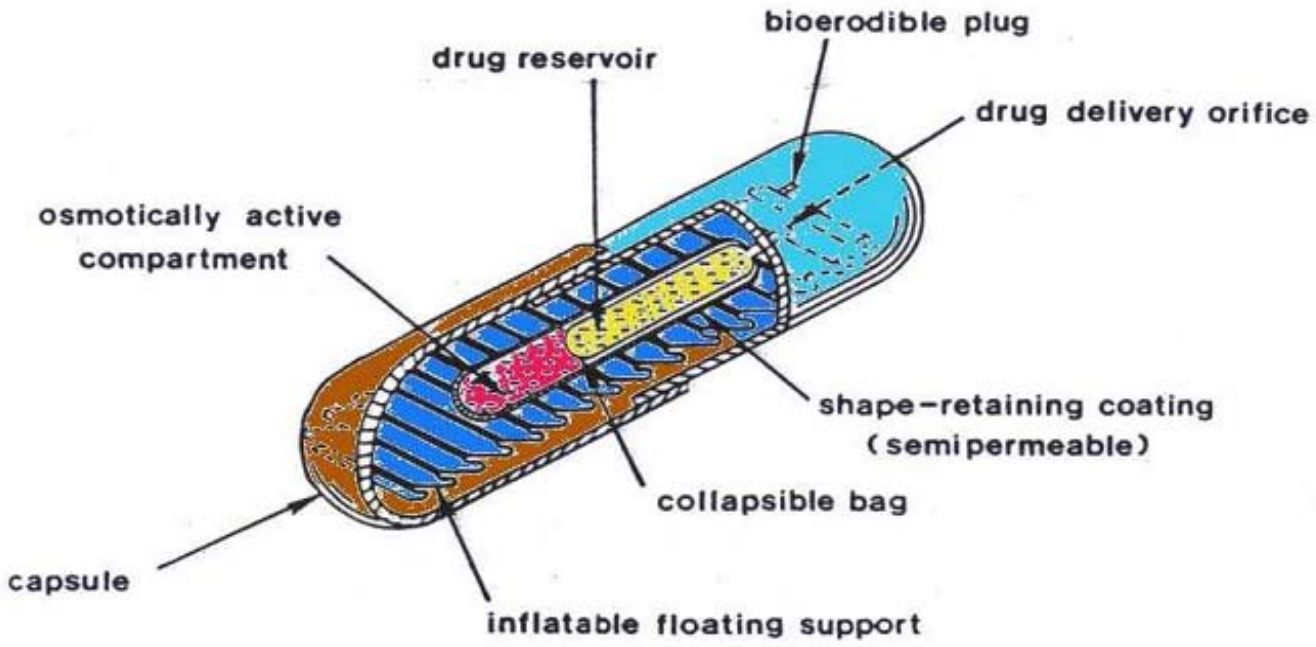

Figure 3: Intragastric Osmotically Controlled Drug Delivery System

B. NON EFFERVESCENT SYSTEMS

The Non-effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol. The various types of this system are as:

1. SINGLE LAYER FLOATING TABLETS

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

2. BILAYER FLOATING TABLETS

A bilayer tablet contain two layer one immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach

3. ALGINATE BEADS

Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence, time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hour.

4. HOLLOW MICROSPHERES

Hollow microspheres (microballoons), loaded with drug 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 400C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug. The microballoons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours in vitro.

SELECTION CRITERIA OF DRUG CANDIDATE FOR GRDF

1. Drugs required exerting local therapeutic action in the stomach: e.g. Misoprostol, 5-Flurouracil, antacids and antireflux preparations, anti *Helicobacter pylori* agents and certain enzymes.

2. Drugs exhibiting site-specific absorption in the stomach or upper part of the small intestine: e.g. Atenolol, Furosemide, Levodopa, *p*-Aminobenzoic acid, Piretanide.
3. Drugs unstable in lower part of GI tract: e.g. Captopril.
4. Drugs insoluble in intestinal fluids (acid soluble basic drugs): e.g. Chlordiazepoxide, Chlorpheniramine, Cinnarizine, Diazepam, Diltiazem, Metoprolol, Propranolol, Verapamil
5. Drugs with variable bioavailability: e.g. Sotalol hydrochloride and Levodopa

FACTORS AFFECTING THE FLOATING AND FLOATING TIME DENSITY

Floating is a function of dosage form buoyancy that is dependent on the density. Shape of dosage form: - Tetrahedron and ring shaped devices with flexural modules of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better floating, 90% to 100% retention at 24 hours compared with other shapes

CONCOMITANT DRUG ADMINISTRATION

Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride; can affect floating time.

FED OR UNFED STATE

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours.

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 AND FEEDING FREQUENCY

Floating can be increased by four to 10 hours with a meal that is high in proteins and fats. The floating can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

AGE

Elderly people, especially those over 70, have a significantly longer; floating.. Disease condition such as diabetes and crohn's disease etc also affect drug delivery.

POSTURE

Floating can vary between supine and upright ambulatory states of the patient.

There are several commercial products available based on the research activity of floating drug delivery (Table 1).

Name	Type and Drug	Remarks	Company Name
Madopar HBS (Propal HBS)	Floating Capsule, Levodopa and Benserazide	Floating CR Capsule	Roche Product, USA
Valrelease	Floating Capsule , Diazepam	Floating Capsule	Hoffmann-LaRoche, USA
Topalkan	Floating Antacid, Aluminium and Mg Mixture	Effervescent Floating liwuid alginate preparation	Pierre Fabre Drug, France
Conviron	Ferrous Sulphate	Colloidal gel forming FDDS	Ranbaxy, India
Citran OD	Ciprofloxacine (1gm)	Gas Generating Floating Form	Ranbaxy, India

Table1: Commercial Gastroretentive Floating Formulation

Sr. No.	Product	Active Ingredient	Reference No.
1	Valrelease	Diazepam	2
2	Topalkan	Aluminium Mag Antacid	3
3	Almagate Flatcoat	Antacid	4
5	Liquid Gavison	Alginic Acid and Sodium Bicarbonate	5

Table 2 Marketed Preparation of Floating Drug Delivery System

EVALUATION OF FLOATING DRUG DELIVERY SYSTEMS

Various parameters[2] that need to be evaluated in gastro-retentive formulations include floating duration, dissolution profiles, specific gravity, content uniformity, hardness, and friability in case of solid dosage forms. In the case of multiparticulate drug delivery systems, differential scanning calorimetry (DSC), particle size analysis, flow properties, surface morphology, and mechanical properties are also performed. The tests for floating ability (Table 2) and drug release are generally performed in simulated gastric fluids at 37ºC.

In vivo gastric residence time of a floating dosage form is determined by X-ray diffraction studies, gamma scintigraphy, or roentgenography (Table 3).

Drug (Polymer Used)	Floating Media/Dissolution Medium and Method	Ref
Pentoxyfillin (HPMC K4 M)	500 mL of artificial gastric fluid pH 1.2 (without pepsin) at 100 rpm using USP XXIII dissolution apparatus. The time taken by the tablet to emerge on the water surface (floating lag time) and time until it floats on water surface was measured.	6
Amoxicillin beads, (Calcium alginate)	For dissolution: 900 mL of deaerated 0.1 M HCl (pH 1.2) at 37ºC ± 1ºC in USP XXII dissolution tester at 50 rpm.	7
Ketoprofen (Eudragit S100 Eudragit RL)	20 mL of simulated gastric fluid without pepsin, 50 mg of floating microparticles in 50-mL beakers were shaken horizontally in a water bath. % age of floating micro particles was calculated. For dissolution: 900 mL of either 0.1 N HCl or the phosphate buffer (pH 6.8) at 37ºC ± 0.1ºC in USP dissolution apparatus (I) at 100 rpm.	8
Verapamil (Propylene foam, Eudragit RS, ethyl cellulose, poly methyl meth acrylate)	30 mL of 0.1 N HCl (containing 0.02% wt/wt Tween 20), pH 1.2. Floatation was studied by placing 60 particles into 30-mL glass flasks. Number of settled particles was counted	9
Captopril (Methocel K4M)	900 mL of enzyme-free 0.1 N HCl (pH 1.2) in USP XXIII apparatus II (basket method) at 37ºC at 75 rpm.	10
Theophylline (HPMC K4M, Polyethylene oxide)	0.1 N HCl in USP XXIII Apparatus II at 50 rpm at 37°C. Its buoyancy to upper 1/3 of dissolution vessel was measured for each batch of tablet.	11
Furosemide (β Cyclodextrin, HPMC 4000, HPMC 100,CMC, Polyethylene glycol)	For dissolution: continuous flow through cell gastric fluid of pH 1.2, 45–50 m N/m by adding 0.02% Polysorbate 20 (to reduce the surface tension), the flow rate to provide the sink condition was 9mL/min.	12
Aspirin, Griseofulvin, p-Nitro Aniline (polycarbonate, PVA)	For dissolution: 500 mL of simulated gastric and intestinal fluid in 1000-mL Erlenmeyer flask. Flasks were shaken in a bath incubator at 37^0C.	13
Piroxicam (microspheres)(Polycarbonate)	For dissolution: 900 mL dissolution medium in USP paddle type apparatus at 37^0C at 100 rpm	14
Ampicillin (Sodium alginate)	For dissolution: 500 mL of distilled water, JP XII disintegration test medium No.1 (pH 1.2) and No.2 (pH 6.8) in JP XII dissolution apparatus with paddle stirrer at 50 rpm	15
Diclofenac (HPC-L)	An aliquot of 0.1 g of granules was immersed in 40 mL of purified water in a vessel at 37°C. Dried granules were weighed and floating percentage of granules was calculated. For dissolution: flow sampling system (dissolution tester: DT-300, triple flow cell) followed by 900 mL of distilled water in JP XII with paddles at 37 ^{0}C ± 0.5^{0}C	16

	at 100 rpm.	
Sulphiride (CP 934P)	For dissolution: 500 mL of each JP XII disintegration test medium No. 1 (pH 1.2) and No. 2 (pH 6.8) in JP XII dissolution apparatus at 37º C at 100 rpm.	17
Amoxicillin trihydrate (HPC)	For dissolution: 500–1000 mL (adequate to ensure sink conditions) of citrate/phosphate buffer of variable pH or solution of HCl (pH 1.2) in Erweka DT 6 dissolution tester fitted with paddles.	18
Ibuprofen, Tranilast (Eudragit S)	For dissolution: 900 mL dissolution medium (disintegration test medium No. 1 (pH 1.2) and No. 2 (pH 6.8) as specified in JP XI and as corresponding to USP XXI, paddle method at 37ºC at 100 rpm.	19
Isardipine (HPMC)	For dissolution: Method 1: 300 mL of artificial gastric fluid in a beaker, which was suspended in water bath at 37ºC agitated by magnetic stirrer and by bubbling CO_2 free air. Method 2: 500/1000 mL of 0.1 M HCl and surfactant lauryl sulfate dimethyl ammonium oxide with rotating paddle at 50 rpm.	20
Potassium chloride (Metolose S.M. 100, PVP)	For dissolution: tablet was mounted onto the perspex holder except one face of the matrix was set flush with one face of the holder at 37ºC and the other face of the tablet was prevented from the dissolution media by a rubber closure; good mixing was maintained in the receiver by a magnetic stirrer at 100 rpm.	21
Verapamil (HPC-H, HPC-M, HPMC K15)	For dissolution: water in USP XXIII dissolution apparatus (method II) at 50 rpm.	22
PABA (Ethyl cellulose HPC-L)	70 mL of 50 mM acetate buffer with various pH (1–5) or viscosity (25–115 cps) in a 100-mL beaker at 37°C, 100 rpm. % age of floating pills was calculated. For dissolution: 50 mM acetate buffer (pH 4) in JP XI dissolution tester with paddles at 37ºC at 100 rpm.	23
Tetracycline, metronidazole, bismuth salt (Polyox, HPMC K4)	900 mL of 0.1 M HCl (pH 1.8) in USP dissolution apparatus at 50 rpm. The duration of floatation was observed visually.	24
Tranilast (Acrylic polymer, Eudragit RS)	Microballoons were introduced into 900 mL of disintegrating fluid solution no 1 (pH 1.2) containing Tween 20 (0.02% wt/vol) in USP XXII apparatus at 100 rpm . Percentage buoyancy was calculated.	25
Sotalol	Lag time required for the tablet to start floating on the top of the basket in dissolution apparatus was measured	26
Furosemide	Tablet were placed in a 400-mL flask at pH 1.2 and both the time needed to go upward and float on surface of the fluid and floating duration were determined.	27
Calcium carbonate (HPMC K4M, E4 M and Carbopol)	A continuous floating monitoring system was conceived. The upward floating force could be measured by the balance and the data transmitted to an online computer. Test medium used was 900 mL simulated gastric fluid (pH 1.2) at 37ºC.	28

Table3: Invitro Floating and Dissolution Performance

Drug (Polymer)	Method	Ref
Tranilast (Eudragit S (BaSo4))	Two healthy male volunteers administered hard gelatin capsules packed with microballons (1000 mg) with 100 mL water. X-ray photographs at suitable intervals were taken.	26
Isardipine (HPMC)	Twophases: PhaseI(fastedconditions): Five healthy volunteers (3 males and 2 females) in an open randomized crossover design, capsules ingested in sitting position with 100 mL of tap water. Phase II (fed states): Four subjects received normal or MR capsules in a crossover design after standard breakfast. Venous blood samples were taken in heparinized tubes at predetermined time intervals after dosing.	21
PABA+ Isosorbide dinitrate	Six healthy beagle dogs fasted overnight, then administered with capsules with 50 mL of water at 30 minutes after the meal. Control study: same amount of control pills without the effervescent layer were administered in the same protocol. The experimental design: Crossover design, 1-week washout time, plasma samples were taken by repeated venipuncture at upper part of the leg.	21
Hydrogel composites	Dogs (50 lbs) kept fasted and fed conditions. In each experiment (fed or fasted) 300 mL of water was given before administration of the capsules; X-ray pictures were taken.	4
Amoxycillin trihydrate	Six healthy fasted male subjects were selected; serum drug levels were compared in a single-dose crossover study following administration of tablets/capsules.	8
Floating beads	Gamma scintigraphy: In vivo behavior of coated and uncoated beads was monitored using a single channel analyzing study in 12 healthy human volunteers of mean age 34 yrs (22–49).	5
Pentoxyfillin	Four healthy beagle dogs (fasted for 24 hours). Tablet was administered with 100 mL of water for radiographic imaging. The animal was positioned in a right lateral/ventrodorsal recumbency	7
Furosemide	Six healthy males (60–71 kg) aged between 25 and 32 years for X-ray detection. Labeled tablets were given to subjects with 200 mL of water after a light breakfast, following ingestion. Gastric radiography revealed the duration for which the tablet stayed in stomach was determined	6
Polystyrene Nanoparticles	Dosing solution was administered to male SD strain rats fasted overnight The radioactivity was measured with a gamma counter or a β counter (small intestine was cut into 10-cm portions).	7
Piroxicam	Nine healthy male albino rabbits weighing 2.2–2.5 kg were divided into 3 groups and were fasted for 24 hours. First batch: fed with 20 mg of Piroxicam powder in a gelatin capsule. Second batch: 67% oxicam loaded piroxicam microspheres (~20mg of drug). Third batch: 7 mg of piroxicam and 67% piroxicam-loaded piroxicam microspheres (~20 mg of drug).	15
Furosemide	Six healthy males (60–71 kg) aged between 25 and 32 years for X-ray detection. Labeled tablets were given to subjects with 200 mL of water after a light breakfast, following ingestion. Gastric radiography	28

	revealed the duration for which the tablet stayed in stomach was determined.	
Sulphiride	Three 3.5-kg white male rabbits 10 mg of the drug/kg body weight were administered in a crossover manner with a 14-day washout period between dosing. Both IV and oral dosage form were given.	17

Table 1: *In vivo* Evaluation

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

SUSTAINED DRUG DELIVERY

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.

Recently sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours) Similarly a comparative study between the Madopar HBS and Madopar standard formulation was done and it was shown that the drug was released up to 8 hours in vitro in the former case and the release was essentially complete in less than 30 minutes in the latter case.

SITE-SPECIFIC DRUG DELIVERY

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, eg, riboflavin and furosemide. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets.[34] A bilayer-floating capsule was developed for local delivery of misoprostol, which is a synthetic analog of prostaglandin E1 used as a protectant of gastric ulcers caused by administration of NSAIDs. By targeting slow delivery of misoprostol to the stomach, desired therapeutic levels could be achieved and drug waste could be reduced.

ABSORPTION ENHANCEMENT

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%).[34]Miyazaki *et al* conducted pharmacokinetic studies on floating granules of indomethacin prepared with chitosan and compared the peak plasma concentration and AUC with the conventional commercially available capsules. It was concluded that the floating granules prepared with chitosan were superior in terms of decrease in peak plasma concentration and maintenance of drug in plasma. Ichikawa et al developed a multiparticulate system that consisted of floating pills of a drug (p- amino benzoic acid) having a limited absorption site in the gastrointestinal tract. It was found to have 1.61 times greater AUC than the control pills. The absorption of bromocriptine is limited to 30% from the gastrointestinal tract, however an HBS of the same can enhance the absorption. It was also studied that if metoclopramide is co delivered with bromocriptine, the side effects associated with high doses of bromocriptine can be prevented and the dosage from becomes therapeutically more potentialIn few cases the bioavailability of floating dosage form is reduced in comparison to the conventional dosage form. In a recent study 3 formulations containing 25 mg atenolol, a floating multiple-unit capsule, a high-density multiple-unit capsule, and an immediate-release tablet were compared with respect to estimated pharmacokinetic parameters. The bioavailability of the 2 gastroretentive preparations with sustained release characteristics was significantly decreased when compared with the immediate-release tablet. This study showed that it was not possible to increase the bioavailability of a poorly absorbed drug such as atenolol using gastroretentive formulations In some cases the reduction in bioavailability is compensated by advantages offered by FDDS, for example a hydrodynamically balanced system of L-dopa provided

better control over motor fluctuations in spite of reduced bioavailability of up to 50% to 60% in comparison with standard L-dopa treatment. This could be attributed to reduced fluctuations in plasma drug levels in case of FDDS. Cook et al concluded that iron salts, if formulated as an HBS, have better efficacy and lesser side effects. FDDS also serves as an excellent drug delivery system for the eradication of *Helicobacter pylori*, which causes chronic gastritis and peptic ulcers. The treatment requires high drug concentrations to be maintained at the site of infection that is within the gastric mucosa. By virtue of its floating ability these dosage forms can be retained in the gastric region for a prolonged period so that the drug can be targeted. Katayama et aldeveloped a sustained release (SR) liquid preparation of ampicillin containing sodium alginate, which spreads out and aids in adhering to the gastric mucosal surface. Thus, the drug is continuously released in the gastric region. Yang et aldeveloped a swellable asymmetric triple-layer tablet with floating ability to prolong the gastric residence time of triple drug regimen (tetracycline, metronidazole, clarithromycin) of *Helicobacter pylori*–associated peptic ulcers using HPMC and PEO as the rate-controlling polymeric membrane excipients. Results demonstrated that sustained delivery of tetracycline and metronidazole over 6 to 8 hours could be achieved while the tablets remained floating. It was concluded that the developed delivery system had the potential to increase the efficacy of the therapy and improve patient compliance.

Floating microcapsules of melatonin were prepared by ionic interaction of chitosan and a surfactant, sodium dioctyl sulfosuccinate that is negatively charged. The dissolution studies of the floating microcapsules showed zero-order release kinetics in simulated gastric fluid. The release of drug from the floating microcapsules was greatly retarded with release lasting for several hours as compared with nonfloating microspheres where drug release was almost instantaneous. Most of the hollow microcapsules developed showed floating over simulated gastric fluid for more than 12 hours. Sato and Kawashima developed microballoons of riboflavin, which could float in JP XIII no 1 solution (simulated gastric fluid). These were prepared by an emulsion solvent technique. To assess the usefulness of the intragastric floating property of the developed microballoons of riboflavin, riboflavin powder, nonfloating microspheres of riboflavin, and floating microballoons of riboflavin were administered to 3 volunteers. Riboflavin pharmacokinetics was assessed by urinary excretion data. It could be concluded that although excretion of riboflavin following administration of floating microballoons was not sustained in fasted state, it was significantly sustained in comparison to riboflavin powder and nonfloating microspheres in the fed state. This could be due to the reason that the nonfloating formulation passes through the proximal small intestine at once from where riboflavin is mostly absorbed, while the floating microballoons gradually sank in the stomach and then arrived in the proximal small intestine in a sustained manner. Total urinary excretion (%) of riboflavin from the floating microballoons was lower than that of riboflavin powder. This was attributed to incomplete release of riboflavin from microballoons at the site of absorption. Shimpi et al studied the application of hydrophobic lipid, Gelucire 43/01 for the design of multi-unit floating systems of a highly water-soluble drug, diltiazem HCl. Diltiazem HCl-Gelucire 43/01 granules were prepared by the melt granulation technique. The granules were evaluated for in vitro and in vivo floating ability, surface topography, and in vitro drug release. In vivo floating ability was studied by γ-scintigraphy in 6 healthy human volunteers and the results showed that the formulation remained in the stomach for 6 hours. It could be concluded that Gelucire 43/01 can be considered as an effective carrier for design of a multi-unit FDDS of highly water-soluble drugs such as diltiazem HCl.

A gastroretentive drug delivery system of ranitidine hydrochloride was designed using guar gum, xanthan gum, and hydroxy propyl methyl cellulose. Sodium bicarbonate was incorporated as a gas-generating agent. The effect of citric acid and stearic acid on drug release profile and floating properties was investigated. The addition of stearic acid reduces the drug dissolution due to its hydrophobic nature. A 3^2 full factorial design was applied to systemically optimize the drug release profile and the results showed that a low amount of citric acid and a high amount of stearic acid favor sustained release of ranitidine hydrochloride from a gastroretentive formulation. Hence, it could be concluded that a proper balance between a release rate enhancer and a release rate retardant could produce a drug dissolution profile similar to a theoretical dissolution profile of ranitidine hydrochloride. In a recent work by Sriamornsak et al, a new emulsion-gelation method was used to prepare oil-entrapped calcium pectinate gel (CaPG) beads as a carrier for intragastric floating drug delivery. The gel beads containing edible oil were prepared by gently mixing or homogenizing an oil phase and a water phase containing pectin, and then extruded into calcium chloride solution with gentle agitation at room temperature. The oil-entrapped calcium pectinate gel beads floated if a sufficient amount of oil was used. Scanning electron photomicrographs demonstrated very small pores, ranging between 5 and 40 µm, dispersed all over the beads. The type and percentage of oil played

an important role in controlling the floating of oil-entrapped CaPG beads. The oil-entrapped CaPG beads were a good choice as a carrier for intragastric floating drug delivery. Reddy and Murthy have discussed advantages and various disadvantages of single- and multiple-unit hydrodynamic systems. Floating drug delivery is associated with certain limitations. Drugs that irritate the mucosa, those that have multiple absorption sites in the gastrointestinal tract, and those that are not stable at gastric pH are not suitable candidates to be formulated as floating dosage forms. Floatation as a retention mechanism requires the presence of liquid on which the dosage form can float on the gastric contents. To overcome this limitation, a bioadhesive polymer can be used to coat the dosage so that it adheres to gastric mucosa, or the dosage form can be administered with a full glass of water to provide the initial fluid for buoyancy. Also single unit floating capsules or tablets are associated with an "all or none concept," but this can be overcome by formulating multiple unit systems like floating microspheres or microballoons.

Dosage Form	Drugs Available
Tablets	Chlorpheniraminemaleate[22]
	Theophylline[12]
	Furosemide[28]
	Ciprofolxacin[23]
	Pentoxyfillin[7]
	Captopril[11]
	Acetylsalicylicacid[24]
	Nimodipine[25]
	Amoxycillintrihydrate[19]
	VerapamilHCl[23]
	Isosorbidedinitrate[24]
	Sotalol[27]
	Atenolol[42]
	Isosorbidemononitrate[54]
	Acetaminophen[26,27]
	Ampicillin[28]
	Cinnarazine[29]
	Diltiazem[30]
	Florouracil[31]
	Piretanide[32]
	Prednisolone[33]
	Riboflavin- 5′ Phosphate[34]
Capsules	Nicardipine[37]
	L-Dopaandbenserazide[35]
	hlordiazepoxideHCl[35]
	Furosemide[34]
	Misoprostal[39]
	Diazepam[36]
	Propranlol[37]
	Urodeoxycholic acid[38]
Microspheres	Verapamil[39]
	Ketoprofen[9]
	Aspirin, griseofulvin, and p-nitroaniline[14]
	Tranilast[26]
	Iboprufen[40]
	Terfenadine[41]
Granules	Indomathacin[19]
	Diclofenac sodium[41]

	Prednisolone[10]
Films	Cinnarizine[64]
	Drug delivery device[42]
Powders	Several basic drugs[43]

Table 2: List of Drugs Formulated as Single and Multiple Unit Forms of Floating Drug Delivery Systems.

The use of large single-unit dosage forms sometimes poses a problem of permanent retention of rigid large-sized single-unit forms especially in patients with bowel obstruction, intestinal adhesion, gastropathy, or a narrow pyloric opening (mean resting pyloric diameter 12.8 ± 7.0 mm). Floating dosage form should not be given to a patient just before going to bed as the gastric emptying of such a dosage form occurs randomly when the subject is in supine posture. One drawback of hydrodynamically balanced systems is that this system, being a matrix formulation, consists of a blend of drug and low-density polymers. The release kinetics of drug cannot be changed without changing the floating properties of the dosage form and vice versa.

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. FDDS promises to be a potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique.

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