FLOATING DRUG DELIVERY SYSTEM: INNOVATIVE APPROACH OF GASTRORETENTION

Hetangi Rathod*, Vishnu Patel, Moin Modasia
A.P.M.C. college of Pharmaceutical Education and Research, Motipura, Himatnagar - 383001, Gujarat state, INDIA
***Email:** het_pharma277@yahoo.co.in

ABSTRACT

Controlled release (CR) dosage forms have been extensively used to improve therapy with several important drugs. Incorporation of the drug in a controlled release gastroretentive dosage forms (CR-GRDF) which can remain in the gastric region for several hours would significantly prolong the gastric residence time of drugs and improve bioavailability, reduce drug waste, and enhance the solubility of drugs that are less soluble in high pH environment. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bioadhesive systems, high-density systems, modified-shape systems and other delayed gastric emptying devices. In this review, current & recent developments of Stomach Specific FDDS are discussed that helps to overcome physiological adversities like short gastric residence times and unpredictable gastric emptying times.

Keywords: Floating drug delivery systems, single unit, multiple units, evaluation - in vitro and in vivo, gastric residence time, effervescent, noneffervescent.

INTRODUCTION

The high level of patient compliance in taking oral dosage forms is due to the ease of administration, patient compliance, flexibility in formulation and handling of these forms. Although tremendous advances have been seen in oral controlled drug delivery system during last two decades. This system has been of limited success. This approach is bedilled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility. Furthermore, the relatively brief gastric emptying time in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose.[1]

Normal gastric residence times usually range between 5 minutes and 2 hours. Migrating myoelectric complex (MMC) is characterized by four phases: Phase I–Period of no contraction (40-60 minutes), phase II –Period of intermittent contractions (20-40 minutes), phase III–Period of regular contractions at the maximal frequency that travel distally also known as housekeeper wave. (10-20 minutes) and phase IV Period of transition between phase III and phase I (0-5 minutes).[2] (Figure 1)

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients also increase gastric retention of dug.[3] these efforts resulted in GRDFs that were designed, in large part, based on the following approaches. (Figure 2)

- Low density form of the DF that causes buoyancy in gastric fluid.[4,5]
- High density DF that is retained in the bottom of the stomach.[6, 7]
- Bioadhesion to stomach mucosa[8]
- Expansion by swelling or unfolding to a large size which limits passage of dosage form through the pyloric sphincter[9]

Figure 1: Schematic representation of interdigestive motility

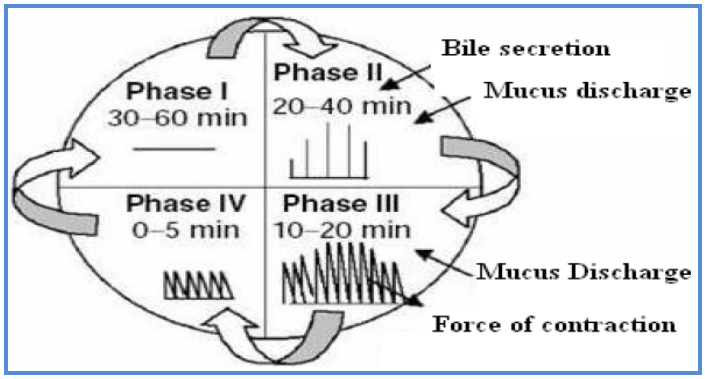


Figure 2: Different approaches of gastric retention

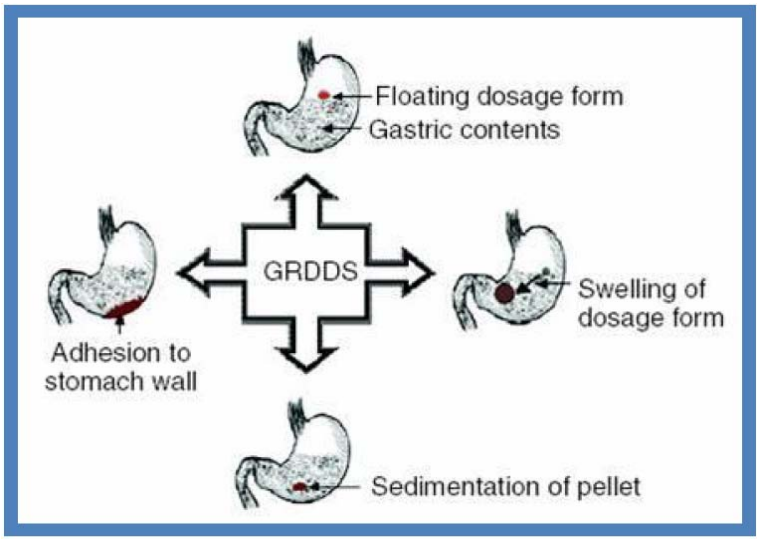
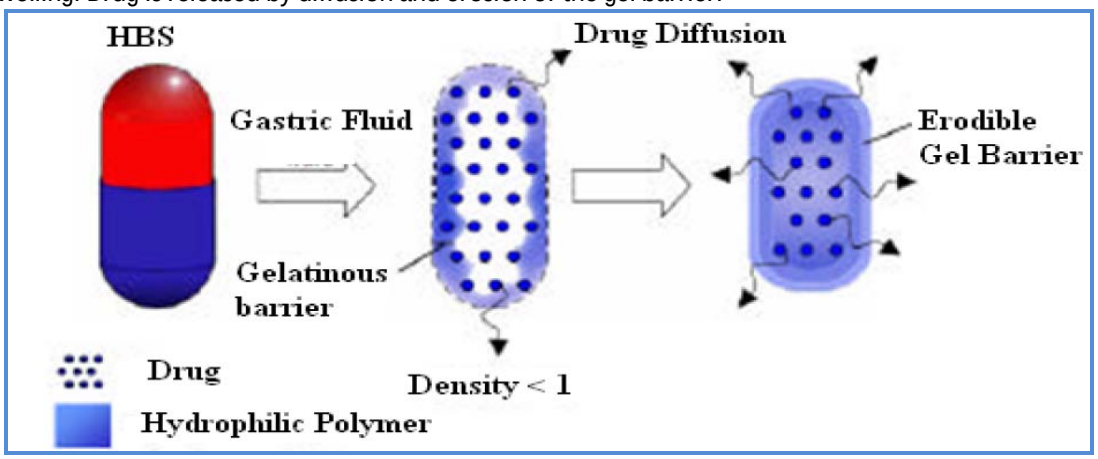


Figure 4: Hydrodynamically balanced system (HBS). The gelatinous polymer barrier formation results from hydrophilic polymer swelling. Drug is released by diffusion and erosion of the gel barrier.



FLOATING DRUG DELIVERY SYSTEM

Floating Oral Drug Delivery System (FDDS) are retained in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids. Floating drug delivery system (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. [10] While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system (Figure 3). After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentration.

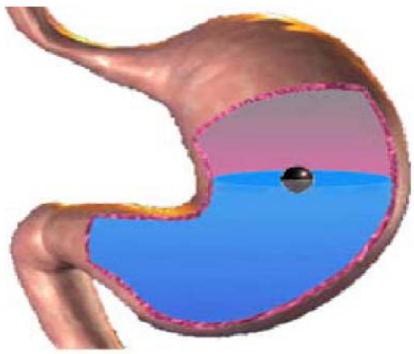
A. Single unit floating system

a) Noneffervescent system

Hydrodyanamic balanced systems

Sheth and Tossounian first designated this 'hydrodynamically balanced system'. Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption (Figure 4). This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g., hydroxypropylcellulose, hydoxyethyl cellulose, hydroxypropyl methyl cellulose (HPMC), polysacharides and matrix-forming polymer such as polycarbophil, polyacrylate and polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface. [11]

Figure 3: Intragastric residence positions of floating unit.



Yang et al[12] developed a swellable asymmetric triple-layer tablet with floating ability to prolong the gastric residence time of triple drug regimen (tetracycline, metronidazole, and clarithromycin) in Helicobacter pylori–associated peptic ulcers using hydroxy propyl methyl cellulose (HPMC) and poly (ethylene oxide) (PEO) as the rate-controlling polymeric membrane excipients. Bismuth salt was included in one of the outer layers for instant release. The floatation was accomplished by incorporating a gas-generating layer consisting of sodium bicarbonate: calcium carbonate (1:2 ratios) along with the polymers.

Figure 5: Schematic presentation of working of a triple-layer system. (A) Initial configuration of triple-layer tablet. (B) On contact with the dissolution medium the bismuth layer rapidly dissolves and matrix starts swelling. (C) Tablet swells and erodes. (D) and (E) Tablet erodes completely.

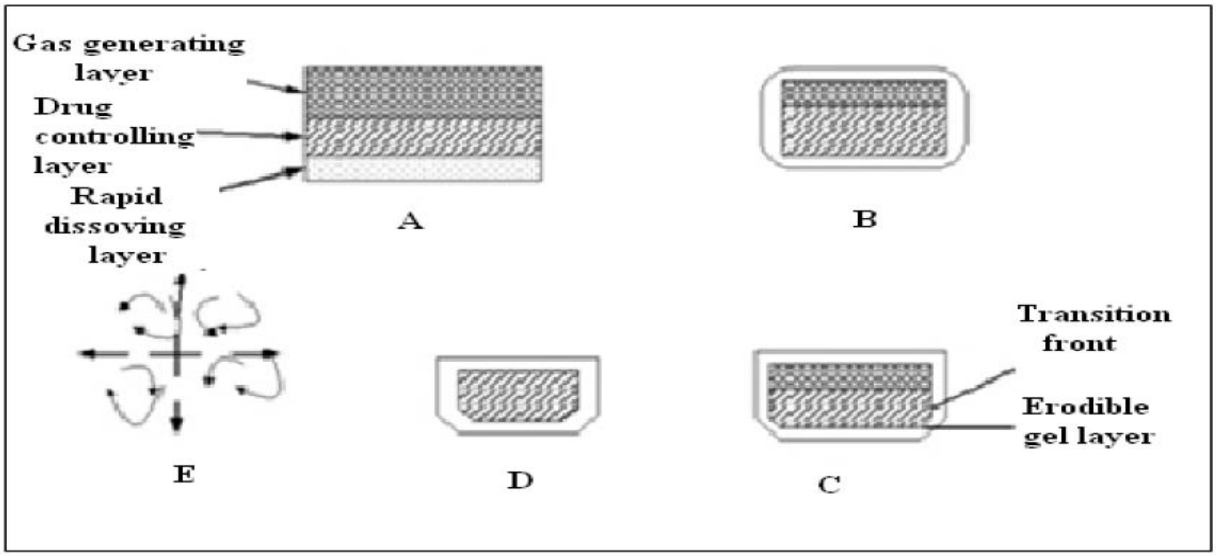
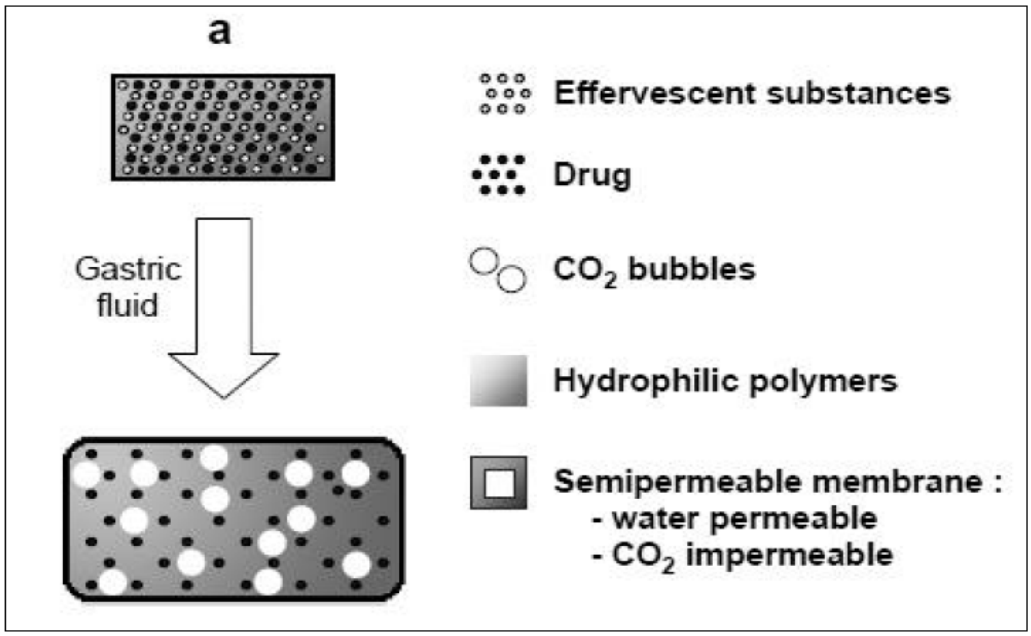


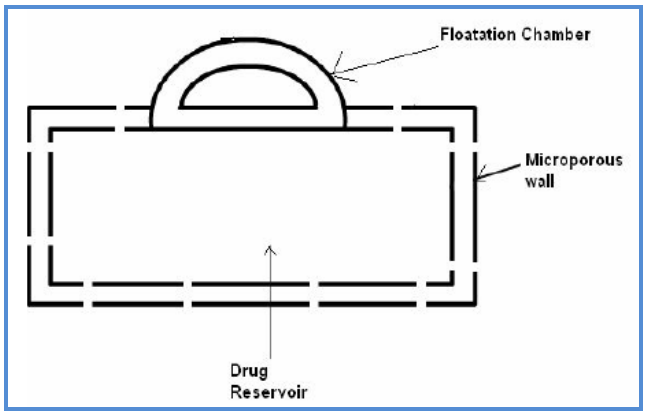
Figure 7: Gas generating system: schematic monolayer drug delivery system



Floating chamber

Fluid- filled floating chamber[13] which includes incorporation of a gas-filled floatation chamber into a microporous component that houses a drug reservoir. Apertures or openings are present along the top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. The fluid present could be air, under partial vacuum or any other suitable gas, liquid, or solid having an appropriate specific gravity and an inert behaviour. The device is of swallowable size, remains afloat within the stomach for a prolonged time, and after the complete release the shell disintegrates, passes off to the intestine, and is eliminated. (Figure 6)

Figure 6: Gas filled floatation chamber



Tablets with Hollow Cylinder

A new floating device consists of two drug-loaded HPMC matrix tablets, placed within an open impermeable, hollow polypropylene cylinder. Each matrix tablet closes one of the ends of the cylinder so that an air-filled space is created between them, which in turn provided a low, overall density of the system. The device should remain floating until at least one of the tablets has dissolved.[14]

Multilayer Flexible Film

This device is multilayered, flexible, sheet like medicament device that was buoyant in the gastric juice of the stomach and had sustained release characteristics. The device consisted of self supporting carrier film(s) made up of a water insoluble polymer matrix with the drug dispersed there in, and a barrier film overlaying the carrier film. The barrier film consisted of a water insoluble and a water and drug permeable polymer or copolymer. Both films were sealed together along their periphery, in such a way as to entrap a plurality of small air pockets, which imparted the laminated films their buoyancy. The time for buoyancy and the rate of drug release can be modulated by the appropriate selection of the polymer matrix.[15]

b) Effervescent Floating Dosage Forms Gas Generating Systems:

Floating systems containing effervescent components

These are matrix type of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, co_2 is liberated and gets entrapped in swollen hydrocolloids, which provide buoyancy to the dosage forms. In vitro, the lag time before the unit floats is <1 min and the buoyancy is prolonged for 8 to 10 h (Figure 7). In vivo experiments in fasted dogs showed a mean gastric residence time increased up to 4 h. compressing the gas generating components in a hydrocolloid containing layer and the drug in another layer formulated for a sustained release effect, thereby producing a bilayered tablet.[16]

Floating System Based On Ion Exchange Resin

The resin beads were loaded with bicarbonate and theophylline which were bound to the resin. The loaded resin beads were coated with a semipermeable membrane to overcome rapid loss of CO2. After exposure to gastric media, exchange of bicarbonate and chloride ions took place and lead to the formation of CO2, which was trapped within the membrane, causing the particles to float. Gastric residence time was substantially prolonged, compared with a control, when the system was given after a light, mainly liquid meal. Furthermore, the system was capable of sustaining the drug release.

Floating system with infalatable chamber

An alternative mechanism of gas generation can be developed as an osmotically controlled floating device, where gases with a boiling point < 37°C (e.g., cyclopentane, diethyl ether) can be incorporated in solidified or liquefied form into the systems. At physiological temperatures, the gases evaporate enabling the drug containing device to float. To enable the unit to exit from the stomach, the device contained a bioerodible plug that allowed the vapor to escape.[17]

Programmable drug delivery

A programmable, controlled release drug delivery system has been developed in the form of a non-digestible oral capsule (containing drug in a slowly eroding matrix for controlled release) was designed to utilize an automatically operated geometric obstruction that keeps the device floating in the stomach and prevents it from passing through the remainder of the GIT. Different viscosity grades of hydroxypropyl-methyl-cellulose were employed as model eroding matrices. The duration during which the device could maintain its geometric obstruction (caused by a built-in triggering ballooning system) was dependent on the erosion rates of the incorporated polymers (the capsule in-hosed core matrix). After complete core matrix erosion, the ballooning system is automatically flattened off so that the device retains its normal capsule size to be eliminated by passing through the GIT.[18]

B. Multiple unit floating system

a) Non-effervescent Systems:

Alginate beads

Alginates have received much attention in the development of multiple unit systems. Alginates are non-toxic, biodegradable linear copolymers composed of L-glucuronic and L-mannuronic acid residues. 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 in to 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,

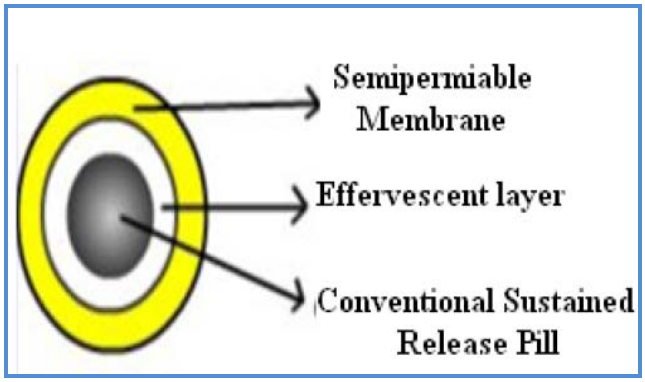
leading to the formation of porous system, which can maintain a floating force over 12 hours. [19, 20] A multiple unit system can be developed comprising of calcium alginate core and calcium alginate/PVA membrane, both separated by an air compartment. Air compartment provides byoncy to beads. In presence of water, the PVA leaches out and increases the membrane permeability, maintaining the integrity of the air compartment. Increase in molecular weight and concentration of PVA, resulted in enhancement of the floating properties of the system.[21]

b) Effervescent systems:

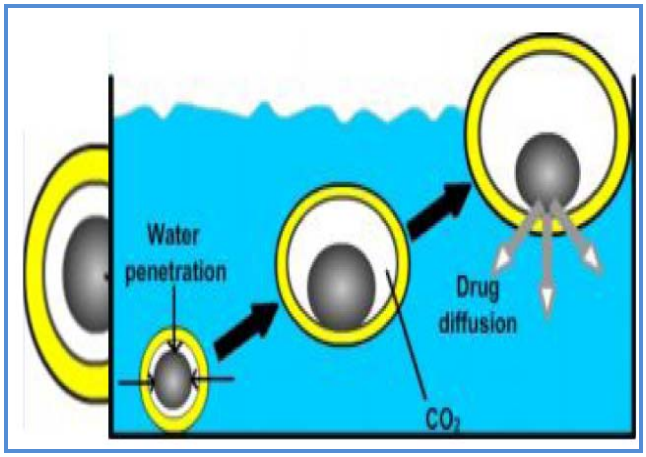
Floating pills

Ichikawa et al developed a new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sublayers to avoid direct contact between the 2 agents. This is surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37ºC, produce swollen pills (like balloons) with a density less than 1.0 g/mL due to incorporation of co_2. [22] (Figure 8)

Figure 8: (A) Multiple-unit oral floating drug delivery system. (B) Working principle of effervescent floating drug delivery system.



(A)

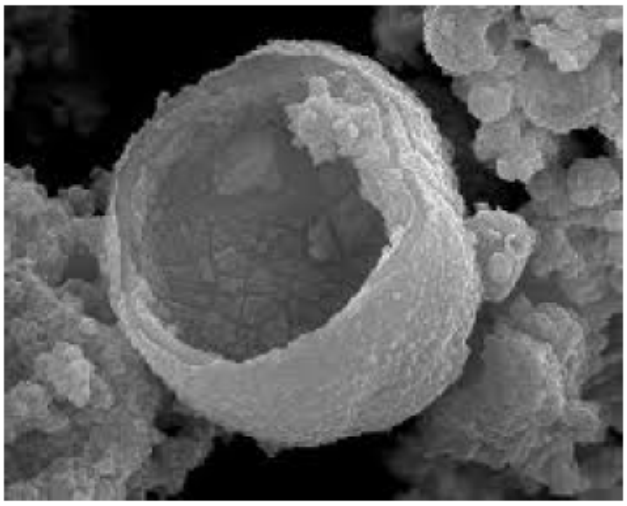


(B)

C) **Hollow Microspheres:**

Hollow microspheres are considered as one of the most promising buoyant systems , as they possess the unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microsphere(Figure 9). The general techniques involved in their preparation include simple solvent evaporation, and solvent diffusion and evaporation. Polycarbonate, Eudragit S, cellulose acetate, calcium alginate, agar and low methoxylated pectin are commonly used as polymers in preparation of hollow microsphere. Buoyancy and drug release are dependent on quantity of polymer, the plasticizer–polymer ratio and the solvent used.[5, 23, 24]

Figure 9: Micro balloons

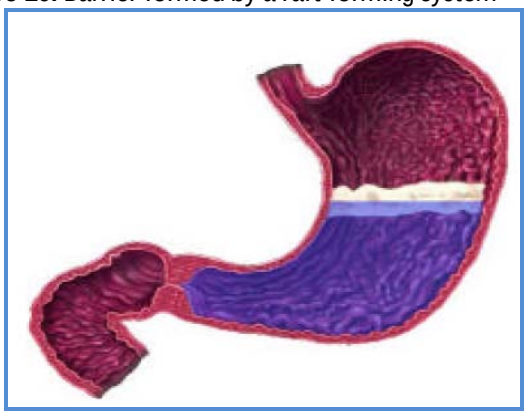


D. Raft forming system

Raft-forming systems[25]

On contact with Gastric fluid A gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO2 bubbles. Which forms Raft layer on top of gastric fluid which releases drug slowly in stomach. Such formulation typically contain antiacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. They are often used for gastro esophageal reflux treatment as with Liquid Gaviscon (GlaxoSmithkline) (Figure 10).

Figure 10: Barrier formed by a raft-forming system



FACTORS AFFECTING THE FLOATING AND FLOATING TIME

1. Density: - Floating is a function of dosage form buoyancy that is dependent on the density.
2. 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. [26]
3. Concomitant drug administration: - Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride; can affect floating time.
4. 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. [27]
5. 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. [26]
6. 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.
7. Age: - Elderly people, especially those over 70, have a significantly longer; floating. [28]. Disease condition such as diabetes and crohn's disease etc also affect drug delivery.
8. Posture: - Floating can vary between supine and upright ambulatory states of the patient.[29]

ADVANTAGES OF FLOATING ORAL DRUG DELIVERY SYSTEM [4, 30]

1. The principle of floating drug delivery system can be used for any particular medicament or class of medicament.
2. The Floating drug delivery system are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.
4. The efficacy of the medicaments can be increased utilizing the sustained release.
5. When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected under such circumstances it may be advantage drug in floating condition in stomach to get a relatively better response.
6. Floating DDS provides advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.
7. The Floating drug delivery formulations are not restricted to medicaments, which are principally absorbed from the stomach. Since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine e.g. Chlorpheniramine maleate.
8. Certain types of drugs can benefit from using FODDS. These include:

   a) Drugs acting locally in the stomach.

   b) Drugs those are primarily absorbed in the stomach.

   c) Drugs those are poorly soluble at an alkaline pH.

   d) Drugs with a narrow window of absorption.

   e) Drugs absorbed rapidly from the GI tract.

   f) Drugs those degrade in the colon

DISADVANTAGES OF FDDS[31]

1. There are certain situations where gastric retention is not desirable. Aspirin and non steroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted.
2. Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems.
3. 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.
4. It requires sufficient high level of fluids in the stomach for the drug delivery to float.
5. The dosage form should be administered with a full glass of water (200-250 ml).[4]

Drugs Used In the Formulations of Stomach Specific

Floating Dosage Forms

· Floating microspheres – Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Ketoprofen[32], Piroxicam, Verapamil HCl, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol, Tranilast[33] and Terfinadine[34]

· Floating granules - Diclofenac sodium, Indomethacin and Prednisolone

· Films[35] – Cinnarizine, Albendazole

· Floating tablets and Pills - Isosorbide mononitrate[23], Diltiazem[36], Acetylsalicylic acid[37], Piretanide[38],

Sotalol[39], carbamazepine, Furosamide[40], Floating Capsules -Diazepam[55], Ursodeoxycholic acid[46], Pentoxyphylline[46], captopril[41], Nimodipine[42]. Verapamil HCl[47], Nicardipine[48], Furosemide[49], Acetaminophen[43], Amoxycillin trihydrate[44], Misoprostal[50] Diazepam[45]

Table-1: Commercial gastroretentive floating formulations

Name	Type and Drug	Remarks	Company name
Madopar®HBS (PropalHBS)	Floating capsule, Levodopa and benserazide	Floating CR capsules	Roche Products, USA
Valrelease®	Floating capsule, Diazepam	Floating Capsules	Hoffmann-LaRoche, USA
Topalkan®	Floating Antacid, aluminum and magnesium mixture	Effervescent floating liquid alginate preparation	Pierre Fabre Drug, France
Conviron®	Ferrous sulphate	Colloidal gel forming FDDS	Ranbaxy, India
Cifran OD®	Ciprofloxacine (1 gm)	Gas generating floating form	Ranbaxy, India

EVALUATION OF FLOATING DRUG DELIVERY SYSTEMS

Various parameters[30] that need to be evaluated in gastroretentive 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.

A. In Vitro Methods

1) Floating lag time and floating time:

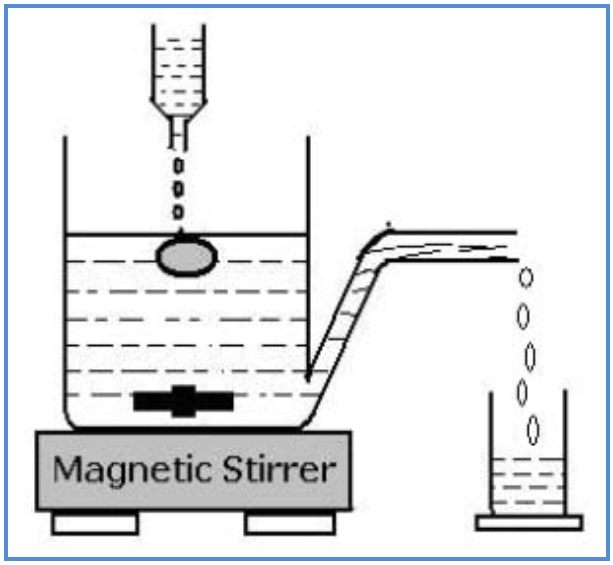
The test for floating time measurement is usually performed in stimulated gastric fluid or 0.1 mole.lit^{-1} HCl maintained at 37^{0}C. It is determined by using USP dissolution apparatus containing 900 ml of 0.1 mole.lit- 1 HCl as a dissolution medium at 37^{0}C. The time taken by the dosage form to float is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time.[22]

The system to check continuous floating behavior contains a stainless steel basket connected to a metal string and suspended from a sartorius electronic balance. The floating object is immersed at affixed depth into a water bath, which is covered to prevent water evaporation. The upward floating force could be measured by the balance and the data transmitted to an online PC through RS232 interphase using a sarto wedge program. A lotus- spread sheet could automatically pick up the reading on the balances. Test medium used in floating kinetics measurements was 900 ml simulated gastric fluid (pH 1.2) maintained at 37°C, data was collected at 30 sec interval; baseline was recorded and subtracted from each measurement. Dissolution basket had a holder at the bottom to measure the downward force.

2) Dissolution study

Gohel et al[51] proposed a more relevant in vitro dissolution method to evaluate a floating drug delivery system (for tablet dosage form). A 100-mL glass beaker was modified by adding a side arm at the bottom of the beaker so that the beaker can hold 70 ml of 0.1 mole.lit-1 HCl dissolution medium and allow collection of samples. A burette was mounted above the beaker to deliver the dissolution medium at a flow rate of 2 ml/min to mimic gastric acid secretion rate. The performance of the modified dissolution apparatus was compared with USP dissolution Apparatus 2 (Paddle). The problem of adherence of the tablet to the shaft of the paddle was observed with the USP dissolution apparatus[52]. The tablet did not stick to the agitating device in the proposed dissolution method. The drug release followed zero-order kinetics in the proposed method. The proposed test may show good in vitro-in vivo correlation since an attempt is made to mimic the in vivo conditions such as gastric volume, gastric emptying, and gastric acid secretion rate. [66]

Figure 13: In vitro dissolution method



3) Resultant weight test:

An in vitro measuring apparatus has been conceived to determine the real floating capabilities of buoyant dosage forms as a function of time. It operates by measuring the force equivalent to the force F required to keep the object totally submerged in the fluid[53]

This force determines the resultant weight of the object when immersed and may be used to quantify its floating or nonfloating capabilities. The magnitude and direction of the force and the resultant weight corresponds to the vectorial sum of buoyancy (F bouy) and gravity (F grav) forces acting on the object as shown in the equation

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

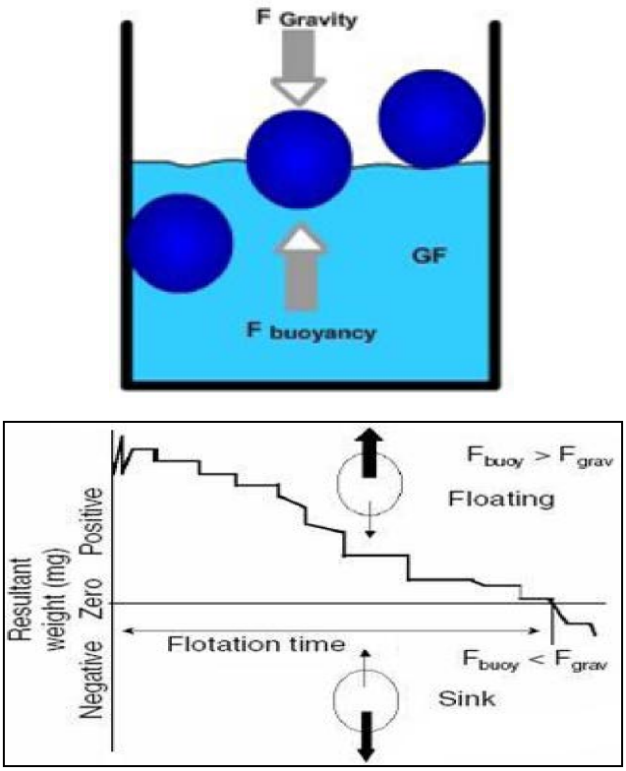
$F = d_f gV - d_s gV = (d_f - d_s) gV$

$F = (d_f - M / V) gV$

in which F is the total vertical force (resultant weight of the object), g is acceleration due to gravity, d_f is the fluid density, d_s is the object density, M is the object mass, and V is the volume of the object .

By convention, a positive resultant weight signifies that the force F is exerted upward and that the object is able to float, whereas a negative resultant weight means that the force F acts downward and that the object sinks

Figure 14: Effect of various forces on floating system



B. In vivo method

1) X-Ray method

X-Ray is a very popular evaluation parameter for floating dosage form now a day.[54] It helps to locate dosage form in the g.i.t. and by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Here the inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays.

2) gamma-Scintigraphy

Gamma -Emitting radioisotopes compounded into CR-DFs has become the state-of-art for evaluation of gastroretentive formulation in healthy volunteers. A small amount of a stable isotope e.g. Sm, is compounded into DF during its preparation. The main drawbacks of gamma - scintigraphy are the associated ionizing radiation for the patient, the limited topographic information, low resolution inherent to the technique and the complicated and expensive preparation of radiopharmaceuticals.[55]

3) Gastroscopy

It comprises of peroral endoscopy, used with a fibereoptic and video systems. It is suggested that gastroscopy may be used to inspect visually the effect of prolonged stay in stomach milieu on the FDDS. Alternatively, FDDS may be drawn out of the stomach for more detailed evaluation.[56]

4) Ultrasonography

Ultrasonic waves reflected substantially different acoustic impedances across interface enable the imaging of some abdominal organs[57]. Most DFs do not have sharp acoustic mismatches across their interface with the physiological milieu. Therefore, Ultrasonography is not routinely used for the evaluation of FDDS. The characterization included assessment of intragastric location of the hydrogels, solvent penetration into the gel and interactions between gastric wall and FDDS during peristalsis.

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. Dosage forms with a prolonged GRT will bring about new and important therapeutic options. The currently available polymer-mediated Noneffervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be a very much effective approach to the modulation of controlled oral drug delivery. Number of commercial products and patents issued in this field are the evidence of it. The FDDS become an additional advantage for drugs that are absorbed primarily in the upper part of GI tract, i.e., the stomach, duodenum, and jejunum. Some of the unresolved, critical issues like the quantitative efficiency of floating delivery systems in the fasted and fed states, role of buoyancy in enhancing GRT of FDDS and more than that formulation of an ideal dosage form to be given locally to eradicate H.Pylori, responsible for gastric ulcers worldwide. Due to the complexity of pharmacokinetic and pharmacodynamic parameters, in vivo studies are required to establish the optimal dosage form for a specific drug. For a certain drug, interplay of its

pharmacokinetic and pharmacodynamic parameters will determine the effectiveness and benefits of the CRGRDF compared to the other dosage forms.

REFERENCES

1. Rouge N, Buri P, Doelker E. Drug absorption sites in the gastrointestinal tract and dosage forms for site specific delivery. Int J Pharm. 1996; 136:117-139.
2. Wilson C.G, Washington N., Physiological Pharmaceutics: Biological Barriers to Drug Absorption, Horwood Ellis, Chichester, 1989; 47-70.
3. Groning R, Heun G. Oral dosage forms with controlled gastrointestinal transit. Drug Dev Ind Pharm. 1984; 10: 527-539.
4. Deshpande A.A., Shah N.H., Rhodes C.T., Malick W., Development of a novel controlled release system for gastric retention, Pharm. Res. 1997; 14: 815-819.
5. Kawashinia Y, Niwa T. Takcuchi H. Hino T, Itoh Y. Hallow microspheres for use as a floating controlled drug delivery system in the stomach. J.Pharm. Sci.1992; 81(2): 135-140.
6. Bechgaard H., Ladefoged K. Distribution of pellets in the gastrointestinal tract: The influence on transit time exerted by density or diameter of pellets. J.Pharm. Pharmacol. 1978; 30:690-692.
7. Davis S.S, Stockwell S.F, Taylor M.J, Hardy J.G, Whelley D.R, The effect on density on the gastric emptying of Single and multiple-unit dosage form. Pharm.Res.1986; 3:208-213.
8. Ponchel G., Irache J.M. Specific and nonspecific bioadhesive particulate system for Oral delivery to the gastrointestinal tract. Adv.Drug.Del.Rev.1998;34:191-219
9. Klausner EA, Lavy E, Friedman M, Hoffman A.Expandable gastroretentive dosage forms. J Control Release. 2003; 90:143-162.
10. Singh B.N., Kim K.H., Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Rel 2000; 63:235-9.
11. Seth P.R., Tossounian J. The hydrodynamically balanced system, a novel drug delivery system for oral use. Drug Dev. Ind Pharm. 1984; 10: 313-339.
12. Yang L., Esharghi J., Fassihi R. A new intra gastric delivery system for the treatment of helicobacter pylori associated gastric ulcers: in vitro evaluation. J. Cont. Rel. 1999; 57:215- 222.
13. Joseph N.H. Laxmi S., Jayakrishnan A. A floating type oral dosage from for piroxicam based on hollow microspheres: in vitro and in vivo evaluation in rabbits. J. Cont. Rel. 2002; 79:71-79.
14. Krögel, I., Bodmeier, R., 1999b. Floating or pulsatile drug delivery systems based on coated effervescent cores. Int. J. Pharm. 187, 175-184.
15. (Mitra, S.B.W., MN), 1984. Sustained release oral medicinal delivery device. Minnesota Mining and Manufacturing Company (St. Paul, MN), United States.
16. Ingani, H.M., Timmermans, J., Moës, A.J., Conception and in vivo investigation of peroral sustained release floating dosage forms with enhanced gastrointestinal transit. Int. J. Pharm. 1987; 35: 157-164.
17. Atyabi F.,Sharma H.L., Mohammad H. AH. and Fell J. T., Controlled drug release from coated floating ion exchange resin beads. Journal of Controlled Release.1996;42: 25-28.
18. Bashaw, J.D.P.A., CA), Zaffaroni, Alejandro (Atherton, CA), Michaels, Alan S. (Atherton, CA), 1976. Self-monitored device for releasing agent at functional rate. ALZA Corporation (Palo Alto, CA), United States.
19. Sakr F.M., A programmable drug delivery system for oral administration. International Journal of Pharmaceutics,Volume, 1999: 184(1):131-139.
20. Vyas S.P and Khar R.K. Targetted and controlled Drug Delivery Novel carrier system1st Ed., CBS Publishers and distributors, New Delhi, 2002; 196-217.
21. Jain N.K., Progress in Controlled and Novel Drug Delivery Systems, 1st Ed. CBS Publishers and Distributors, New Delhi, 2004; 84-85.
22. Iannuccelli V., Coppi G., Bernabei M.T. and Cameroni R., Air compartment multiple-unit system for prolonged gastric residence. Part I. Formulation study, Int.J.Pharm. 1998; 174: 47- 54.
23. Ichikawa M, Watanabe S, Miyake Y. A new multiple unit oral floating dosage system. I: Prepration and in vitro evaluation of floating and sustained-release kinetics. J Pharm Sci. 1991; 80:1062-1066.
24. Sato Y., Kawashima Y., Takeuchi H. and Yamamoto H., In vivo evaluation of riboflavincontaining microballoons for floating controlled drug delivery system in healthy human volunteers, J. Cont. Rel. 2003; 93: 39- 47.
25. Washington N., Investigation into the barrier action of an alginate gastric reflux suppressant, Liquid Gaviscon, Drug Investig. 1987; 2:23-30.
26. Fabrcgas J.L, Cucala C.G., Pous J., Sites R.A. In vitro testing of an antacid formulation with prolonged gastric residence time. Drug Dev. Ind. Pharm. 1994;20:1199-1212
27. Chawla G., Gupta P., Koradia V. and Bansal A.K., Gastroretention: A Means to Address Regional Variability in intestinal drug Absorption, Pharmaceutical technology. 2003; 27(2) 50-68.
28. Talukder R. and Fissihi R., Gastroretentive Delivery Systems: A Mini review, Drug Dev.and Ind. Pharm, vol-30, No.10, 2004, 1019-1028.

29. Mojaverian P., Vlasses P.H., Kellner P.E. and Rocci M.L.Effects of gender, posture, and age on gastric residence time of an indigestible solid: pharmaceutical considerations. Pharm. Res.1988; 10: 639–64.
30. Whitehead H, Fell J.T. and Collett J.H.,Development of a Gastroretentive Dosage Form", European Journal of Pharmaceutical Sciences.1996; 4 (1): 182-186.
31. Shivkumar H.G., Vishakante D.,Kumar T.M.P., Floating Controlled Drug Delivery Systems For Prolong Gastric Residence, Indian.J.Pharm.Educ. 2004;38 (4):172-179
32. El-Kamel A.H., Sokar M.S, Algamal S.S, Naggar V.F. Preparation and evaluation of ketoprofen floating oral drug delivery system. Int. J. Pharm. 2001; 220:13-21
33. Kawashima Y., Niwa T., Takeuchi H., Hino T., ItoY. Preparation of multiple unit hollow microspheres (microballoons) with acrylic resins containing tranilast and their drugrelease characteristics (in vivo). J. Cont. Rel. 1991; 16:279-290.
34. Jayanthi G., Jayaswal S.B., Srivastava A.K. Formulation and evaluation of terfenadine microballoons for oral controlled release. Pharmazie. 1995; 50:769-770.
35. Harrigan B.M., Drug delivery device for preventing contact of undissolved drug with the stomach lining. US patent 4055178. October 25, 1977.
36. Gu T.H. Pharmacokinetics and pharmacodynamics of diltiazem floating tablets. Chung Kao Yao Li Hsuesh Pao. 1992; 13:527-531
37. Sheth P.R., Tossounian J.L., Novel sustained release tablet formulations. U.S.patent 4167558. September 11, 1979.
38. Rouge N., Cole E.T., Doelker E., Buri P. Buoyancy and drug release patterns of floating mini tablets containing piretanide and atenolol as model drugs. Pharm. Dev. Technol. 1998; 3:73-84.
39. Cheuh H.R., Zia H., Rhodes C.T. Optimization of Sotalol floating and bioadhesive extended release tablet formulation. Drug Dev. Ind. Pharm. 1995; 21:1725-1747.
40. Ozdemir N, Ordu S, Ozkan Y. Studies of floating dosage forms of furosemide: in vitro and in vivo evaluation of bilayer tablet formulation.Drug Dev Ind Pharm. 2000; 26(8):857-866.
41. Nur A.O., Zhang J.S.. Captopril floating and/or bioadhesive tablets: design and release kinetics. Drug Dev Ind Pharm. 2000; 26:965-969.
42. Wu W, Zhou Q, Zhang H.B., Ma G.D., Fu C.D., Studies on nimodipine sustained release tablet capable of floating on gastric fluids with prolonged gastric resident time. Yao Xue Xue Bao. 1997; 32:786-790.
43. Phuapradit W. Influence of Tablet Buoyancy on Oral Absorption of Sustained Release Acetaminophen Matrix Tablets [dissertation]. 1989, Jamaica, NY, St John's University.
44. Hilton A.K., Deasy P.B., In vitro and in vivo evaluation of an oral sustained release floating dosage form of amoxycillin trihydrate. Int J Pharm. 1992; 86:79-88.
45. Gustafson J.H., Weissman L., Weinfeld R.T. Clinical bioavailability evaluation of a controlled release formulation of diazepam. J. Pharmacokinet. Biopharm. 1981; 9:679-691.
46. Simoni P., Cerre C., Cipolla A., et al. Bioavailabilty study of a new sinking, enteric coated ursodeoxycholic acid formulation. Pharmacol. Res. 1995;31:115-119.
47. Chen G.L., Hao W.H., In vitro performance of floating sustained release capsules of verapamil. Drug Dev Ind Pharm.1998; 24:1067-1072.
48. Moursy N.M., Afifi N.N., Ghorab D.M., El-Saharty Y. Formulation and evaluation of sustained release floating capsules of Nicardipine hydrochloride. Pharmazie. 2003; 58:38-43.
49. Menon A, Ritschel W.A., Sakr A. Development and evaluation of a monolithic floating dosage form for furosemide. J Pharm Sci. 1994;83:239-245.
50. Oth M, Franz M, Timmermans J, Moes A. The bilayer floating capsule: a stomach directed drug delivery system for misoprostal. Pharm Res. 1992; 9:298-302.
51. Gohel M.C., Mehta P.R.., Dissolutiontech. 2004, 11(4),22-25.
52. Karande A.D., Yeole P.G. Comparative Assessment of Different Dissolution Apparatus for Floating Drug Delivery Systems. Dissolutiontech.2006; 13(1):20-23.
53. Timmermanns J. and Moes A. (1990). How well do floating dosage forms float? Int.J.Pharm.1987; 62(3): 207 – 216.
54. Fell J., Digenis C.G. Imaging and behavior of solid oral dosage forms in vivo. Int.J.Pharm.1984; 22(1):1-15.
55. Gansbeke, B.V., Timmermans J., Schoutens A and Moes A.J. Intragastric positioning of two concurrently ingested pharmaceutical matrix dosage forms, Nucl Med Biol.1991;18:711-718.
56. Jao, F., Edgren, D E. and Wong, P S. (2000). Gastric retention dosage form havin multiple layers. Int Application WO0038650.July, 2006
57. Hendee, W. R. In Textbook of Diagnostic Imaging II, 2nd Ed., W B Saunders, Philadelphia, 1999; 1:1-6.

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