Review Article

# Review Article on Floating Drug Delivery System

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**ABSTRACT**
The purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. The recent developments of FDDS including the 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 and in vivo studies to evaluate the performance and application of floating systems, and applications of these systems.

**Keywords:** Floating drug delivery systems, Characterization, Evaluation in vitro and in vivo.

## INTRODUCTION

A drug that is released from a dosage form in a controlled manner in the stomach will empty together with fluids and will have the whole surface area of the small intestine available for absorption[1]. These considerations have lead to the development of oral controlled gastro retentive dosage forms possessing gastric retention capabilities. Thus Gastroretentive dosage forms, i.e. those designed to exhibit a prolonged gastric residence time (GRT), have been a topic of interest in terms of their potential for controlled drug delivery[2,3,4,5]. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs[6,7]. Such retention systems are important for drugs that are degraded in the intestine or for drugs like antacids or certain antibiotics, enzymes that should act locally in the stomach [8]. If drug is poorly soluble in intestine due to alkaline pH and then its retention in gastric region may increase the solubility before they are emptied, resulting in increased bioavailability [9]. Such systems are more advantageous in improving G.I. absorption of drugs with narrow absorption windows as well as for controlled release of the drugs having site-specific absorption limitation. Retention of drug delivery system in stomach prolongs over all G.I. transit time, thereby resulting in improved bioavailability for some drugs[6,10]

## BASIC GASTROINTESTINAL TRACT PHYSIOLOGY

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum [fig 1&2] . 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[11]. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an inter digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours[12]. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington[13] [fig 3].

- 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.

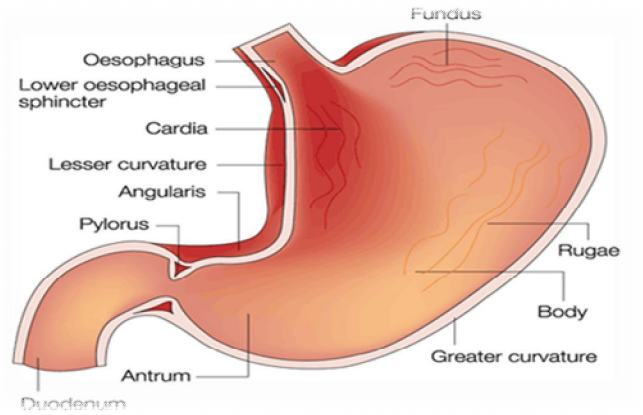



**Fig. 1: Structure of stomach**

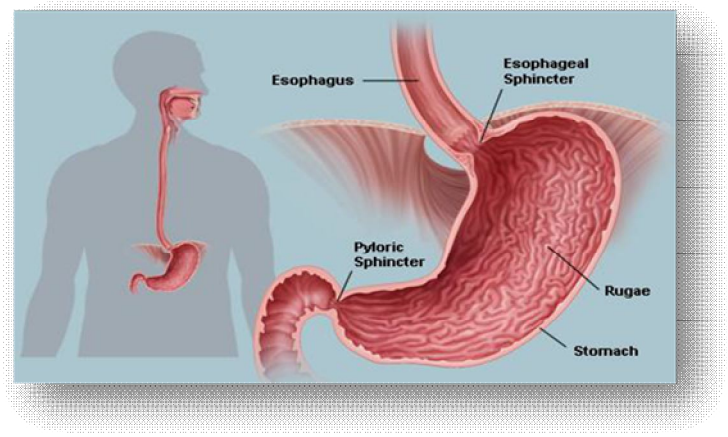



**Fig. 2: Gastro intestinal tract**

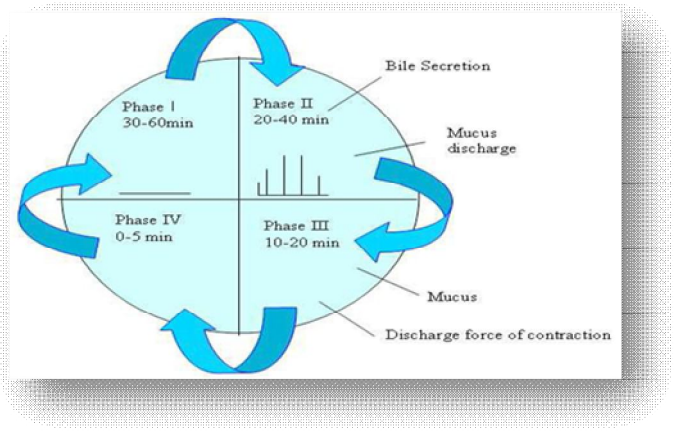



**Fig. 3: Gastrointestinal motility pattern**[14-17]

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.

**ADVANTAGES OF FDDS**

- **Sustained drug delivery:** A floating drug delivery system can remain in the stomach for several hours and the assumed prolongation in the gastric retention is postulated to cause sustained drug release behaviour. [18,19]
- **Site-specific drug delivery:** Targeting of drug to stomach appears to be useful for all substances intended to produce a lasting local action on the gastro duodenal wall.[19]
- **Pharmacokinetic advantage:** In addition, with the total gastrointestinal transit duration is increased, a greater amount of drug may be delivered and thus the relative bioavailability will consequently be increased
- **Targeted therapy for local ailments in the upper GIT:** The prolonged and sustained administration of the drug from gastro retentive dosage form [GRDF] to the stomach may be advantageous for local therapy in the stomach and small intestine. eg. Antibiotic for Helicobacter pylori based ulcer, Antacid.
- **Reduced counter-activity of the body:** Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.
- **Minimized adverse activity at the colon:** Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented.
- **Enhanced bioavailability:** The bioavailability of riboflavin controlled release GRDF [CR-GRDF] is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations.[20,21,22]

**DISADVANTAGES OF FDDS**

- Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat, water.
- The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
- Some drugs present in the floating system causes irritation to gastric mucosa.[23]

**CRITERIA FOR SELECTION OF DRUG CANDIDATE FOR FDDS** [24]

- **Desirable half-life:** If the drug has a short half-life of less than 2 hours, the dosage form may contain a prohibitively large quantity of the drug.
- **High therapeutic index:** Drugs with low therapeutic index are not suitable for incorporation in controlled release formulations. e.g. Digitoxin.
- **Small dose:** The dose of a drug in the conventional dosage form is high, its suitability as a candidate for controlled release is seriously undermined
- **Aqueous solubility:** Drugs with aqueous solubility make good candidates for controlled release dosage form.
- **Stability to wide pH range, GI enzymes and flora:** Stability of the drug in the GI contents is important to ensure a complete and reproducible drug input into the body. Typically the drug must be stable in the pH range of 1 to 8.
- **First pass clearance:** Delivery of the drug to the body in desired concentration is seriously hampered in case of drugs undergoing extensive hepatic first pass metabolism, when administered in controlled release form. Saturable hepatic metabolism may render a drug unsuitable because systemic availability for such drug is highly reduced when the input rate is small.

**DRUG CANDIDATES SUITABLE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEM** [25,26]

• Drugs which act primarily in the stomach. E.g. antacids.
• Drugs that are primarily absorbed from the stomach. E.g. amoxicillin
• Drugs those are poorly soluble at alkaline pH. E.g. verapamil, diazepam, etc.
• Drugs with a narrow window of absorption. E.g. levodopa, cyclosporine,etc.
• Drugs which are rapidly absorbed from the GIT. E.g. tetracycline
• Drugs that degrade in the colon. E.g. ranitidine, metformin, etc.
• Drugs that disturb normal colonic microbes. E.g. Antibiotics against Helicobacter pylori.

**DRUG CANDIDATES UNSUITABLE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEM [25,26]**

- Drugs that have very limited acid solubility E.g. phenytoin etc.
- Drugs that suffer instability in the gastric environment E.g. erythromycin etc.
- Drugs intended for selective release in the colon E.g. 5- amino salicylic acid and corticosteroids etc.

**FACTORS AFFECTING GASTRIC RETENTION [26]**

- **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 (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes
- **Biological factors:** Diabetes and Crohn's disease.
- **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.
- **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 form.

**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 4 (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 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 4(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 intra gastric buoyancy capability variations

$$F = F_{buoyancy} - F_{gravity}$$
$$= (Df - Ds)\, gv$$

Where, F= total vertical force, Df = fluid density,Ds = object density, v = volume and g = acceleration due to gravity[27]

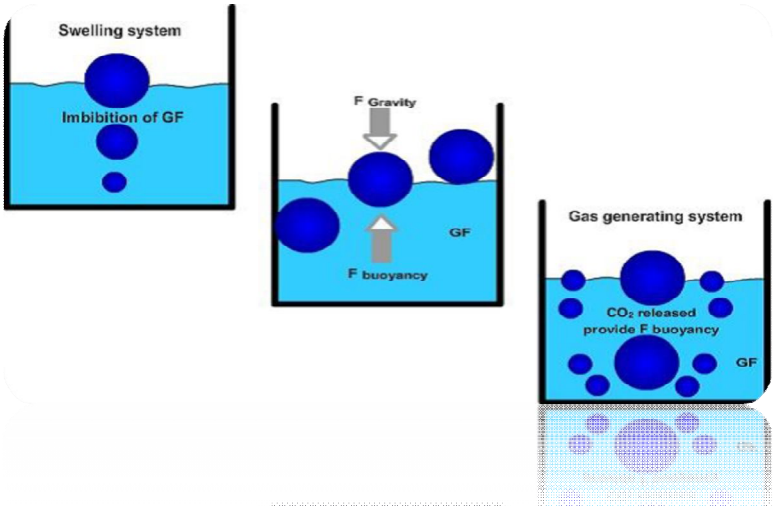



**fig (a) fig ( b) fig (c)**

**Fig. 4: Mechanism of floating systems, GF= Gastric fluid**

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.

**APPROACHES TO ACHIEVE GASTRIC RETENTION**

1. High density (sinking) system or non floating drug delivery system
2. Floating drug delivery systems:
   - A. Non effervescent systems
     - a) Hydro dynamically balanced systems
     - b) Micro balloons/ hollow microspheres
     - c) Alginate beads
     - d) Micro porous compartment systems
   - B. Effervescent gas generating systems
3. Bio adhesive/muco adhesive systems
4. Expandable, un foldable and swelling systems
5. Super porous hydro gel systems
6. Magnetic systems
7. Raft forming systems

**1. High density (sinking) system or non- floating drug delivery system**

This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content (~ 1.004 gm/cm3). These formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulphate, zinc oxide and titanium oxide etc[28]. The materials increase density by up to 1.5- 2.4 gm/cm3. A density close to 2.5 gm/cm3 seems necessary for significant prolongation of gastric residence time[29.] But, effectiveness of this system in human beings was not observed[30] and no system has been marketed.

**2. Floating drug delivery systems**

Floating delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability[31]. This delivery systems is desirable for drugs with an absorption window in the stomach or in the upper small intestine [32]. This have a bulk density less then gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly as a desired rate from the system. After release of drug, the residual system is emptied from the stomach. This result in an increased gastric retention time (GRT) and a better control of the fluctuation in plasma drug concentration. The major requirements for floating drug delivery system are [28]:

• It should release contents slowly to serve as a reservoir.
• It must maintain specific gravity lower than gastric contents (1.004 – 1.01 gm/cm3).
• It must form a cohesive gel barrier.

The inherent low density can be provided by the entrapment of air (e.g. hollow chambers)[33] or by the incorporation of low density materials (e.g. fatty materials or oils, or foam powder)[34,35]. These following approaches have been used for the design of floating dosage forms of single and multiple-unit systems. Recently a single-unit floating system was proposed consisting of polypropylene foam powder, matrix forming polymers, drug and filler[36]. The good floating behaviour of these systems could be successfully combined with accurate control of the resulting drug release patterns. Single-unit dosage forms are associated with problems such as sticking together or being obstructed in the gastrointestinaltract (GIT) which may produce irritation. On the other hand multiple-unit floating systems may be an attractive alternative since they have been shown to reduce the inter- and intra-subject availabilities in drug absorption as well as to lower the possibility of dose dumping[32]. Various multiple-unit floating system like air compartment multiple-unit system , hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method[55] , microparticles based on low density foam powder , beads prepared by emulsion gelatin method[56] etc. can be distributed widely throughout the GIT, providing the possibility of achieving a longer lasting and more reliable release of drugs. Based on the mechanism of buoyancy two distinctly different technologies, i.e. non-effervescent and effervescent systems have been utilized in the development of floating drug delivery system.

**A. Non-effervescent Systems**

Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment [57]. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methylcellulose (HPMC) polyacrylates, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates . This system can be further divided into the sub-types

**a. Hydrodynamically balanced systems**

Sheth and Tossounian[58] first designated these 'hydrodynamically balanced systems'. These systems contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. These are single-unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxypropyl methylcellulose (HPMC), hydroxethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans or alginic acid are commonly used excipients to develop these systems[59,60]. The polymer is mixed with drugs and usually administered in hydrodynamically balanced system capsule. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period. Because, continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form[60]. Incorporation of fatty excipients gives low-density formulations reducing the erosion. Madopar LP®, based on the system was marketed during the 1980's[61]. Effective drug deliveries depend on the balance of drug loading and the effect of polymer on its release profile. Several strategies have been tried and investigated to improve efficiencies of the floating hydrodynamically balanced systems[60,61].

**b. Microballoons / Hollow microspheres**

Microballoons / hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion / evaporation methods[62] (Figure 5) to prolong the gastric retention time (GRT) of the dosage form. Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer polymer ratio and the solvent used for formulation. The microballoons floated continuously over the surface of an acidic dissolution media containing surfactant for >12 hours . At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good floating.

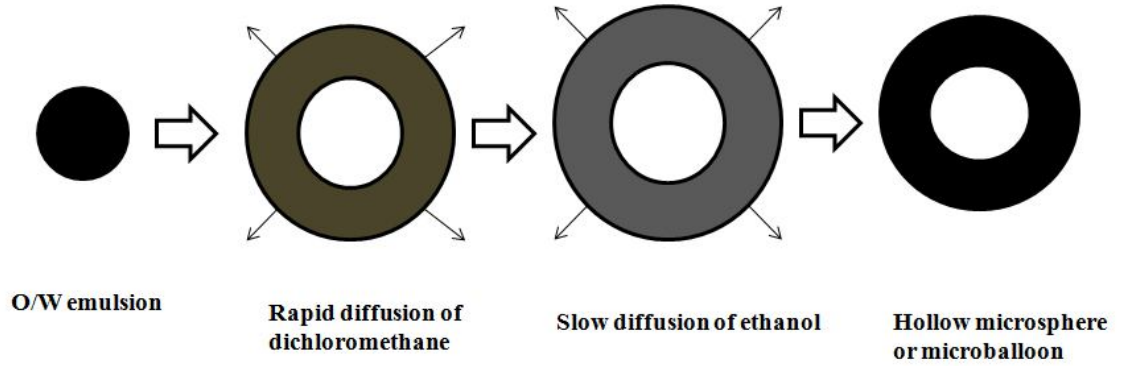



**Fig. 5: Formulation of floating hollow microsphere or microballoon**

**c. Alginate beads**

Talukdar and Fassihi[56] recently developed a multiple-unit floating system based on cross-linked beads. They were made by using Ca2+ and low methoxylated pectin (anionic polysaccharide) or Ca2+ low methoxylated pectin and sodium alginate. In this approach, generally sodium alginate solution is dropped into aqueous solution of calcium chloride and causes the precipitation of calcium alginate. These beads are then separated and dried by air convection and freeze drying, leading to the formulation of a porous system, which can maintain a floating force for over 12 hrs. These beads improve gastric retention time (GRT) more than 5.5 hrs[63].

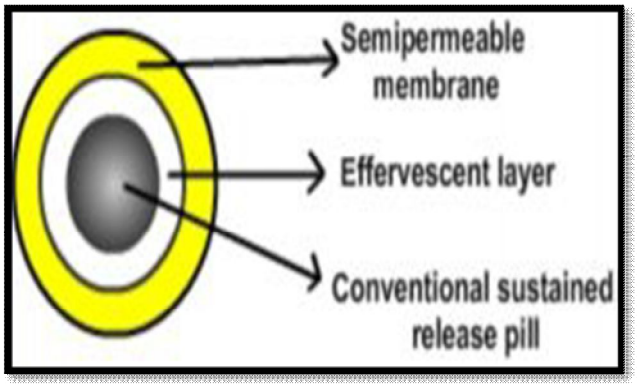
**d. Microporous compartment system:**

This approach is based on the principle of the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls[64]. The peripheral walls of the device were completely sealed to present any direct contact of the gastric surface with the undissolved drug. In the stomach the floatation chamber containing entrapped air causes the delivery system to float in the gastric fluid[28]. Gastric fluid enters through the aperture, dissolves the drug and causes the dissolved drug for continuous transport across the intestine for drug absorption.

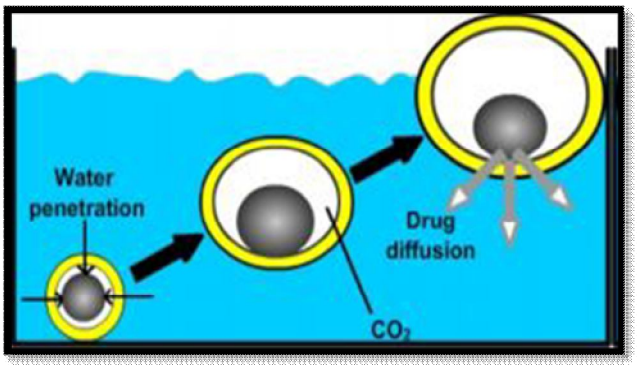
**B. Effervescent (gas generating) systems**

Floatability can be achieved by generation of gas bubbles. These buoyant systems utilize matrices prepared with swellable polymers such as polysaccharides (e.g. chitosan), effervescent components (e.g. sodium bicarbonate, citric acid or tartaric acid)[64]. The optimal stochiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1. In this system carbon dioxide is released and causes the formulation to float in the stomach (Figure 6 : a and b). Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating dosage forms that generate gas (carbon dioxide) when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone (PVP) coated with hydroxypropyl methylcellulose (HPMC), and floating system based on ion exchange resin technology etc . Bilayer or multilayer system has also been designed[65,66].

Drugs and excipients can be formulated independently and the gas generating material can be incorporated in to any of the layers. Further modifications involve coating of the matrix with a polymer which is permeable to water, but not to carbon dioxide. The main difficulty of these formulations is finding a good compromise between elasticity, plasticity and permeability of the polymers.




**[a]**




**[b]**

**Fig. 6: a) Different layers i) Semi-permeable membrane, ii) Effervescent Layer iii) Core pill layer b) Mechanism of floatation via CO2 generation**

### 3. Bioadhesive or Mucoadhesive drug delivery systems

Bioadhesive drug delivery systems are used as a delivery device within the human to enhance drug absorption in a site-specific manner. In this approach, bio adhesive polymers are used and they can adhere to the epithelial surface in the stomach[67]. Thus, they improve the prolongation of gastric retention. The basis of adhesion in that a dosage form can stick to the mucosal surface by different mechanism. These mechanisms[68,69] are:

1) The wetting theory, which is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucous layers.
2) The diffusion theory which proposes physical entanglement of mucin strands the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate.
3) The absorption theory, suggests that bioadhesion is due to secondary forces such as Vander Waal forces and hydrogen bonding.
4) The electron theory, which proposes attractive electrostatic forces between the glycoprotein mucin net work and the bio adhesive material.

Materials commonly used for bioadhesion are poly acrylic acid, chitosan, cholestyramine, sodium alginate, hydroxypropyl methylcellulose (HPMC), sucralfate, tragacanth, dextrin, polyethylene glycol(PEG) and polylactic acids etc. Even though some of these polymers are effective at producing bioadhesive, it is very difficult to maintain it effectively because of the rapid turnover of mucus in the gastrointestinal tract (GIT).

### 4. Expandable, unfoldable and swellable systems

A dosage form in the stomach will withstand gastric transit if it bigger than pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, their configurations[70,71] are required to develop an expandable system to prolong gastric retention time(GRT)

1) a small configuration for oral intake,
2) an expanded gastroretentive form, and
3) a final small form enabling evacuation following drug release from the device.

Thus, gastroretentivity is improved by the combination of substantial dimension with high rigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach. Unfoldable and swellable systems have been investigated and recently tried to develop an effective gastroretentive drug delivery. Unfoldable systems are made of biodegradable polymers. They are available in different geometric forms like tetrahedron, ring or planner membrane (4 - label disc or 4 - limbed cross form) of bioerodible polymer compressed within a capsule which extends in the stomach [72,73]. Swellable systems are also retained in the gastro intestinal tract (GIT) due to their mechanical properties. The swelling is usually results from osmotic absorption of water and the dosage form is small enough to be swallowed by the gastric fluid . Expandable systems have some drawbacks like problematical storage of much easily hydrolysable, biodegradable polymers relatively short-lived mechanical shape memory for the unfolding system most difficult to industrialize and not cost effective. Again, permanent retention of rigid, large single-unit expandable drug delivery dosage forms may cause brief obstruction, intestinal adhesion and gastropathy .

**5. Super porous hydro gel systems**

These swellable systems differ sufficiently from the conventional types to warrant separate classification. In this approach to improve gastric retention time (GRT) super porous hydro gels of average pore size >100 micro meter, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores[75]. They swell to a large size (swelling ratio: 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is advised by co-formulation of hydrophilic particulate material[76].

**6. Magnetic Systems**

This approach to enhance the gastric retention time (GRT) is based on the simple principle that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance[45].

**7. Raft-forming System**

Raft forming system is not only helpful for sustained drug delivery but also convenient for paediatric and geriatric patients. This system is helpful as an alternative of oral solid dosage form with the advantages of liquid dosage form. Sustained and prolonged release of the drug, good stability and bioavailability characteristics make the raft forming system very suitable candidate for gastric retention of the drug. Thus the raft forming system promises to be the potential approach for gastric retention drug delivery system In this gel forming solution (e.g., Sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO2 bubbles on contact with gastric fluid. Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Nowadays Raft Forming Systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders.[37]

**Recent combinational approaches for Gastro retention**

Currently following combination approaches used in GRDDS[38, 39]

1. Swellable and floating.
2. Bio adhesive and floating.
3. Bio adhesion and swelling.
4. Bio adhesion and High density,
5. Floating pulsatile system.

**Methods used for Gastric retention[40]**

1. By reducing particle size and filling it in a capsule.
2. By utilising gel forming hydrocolloids such as hydrophilic gums, gelatine, alginates, cellulose derivatives, etc.
3. By Using low density enteric materials such as meth acrylic polymer, cellulose acetate phthalate.
4. By forming carbon dioxide gas and subsequent entrapment of it in the gel network.
5. By preparing hollow micro-balloons of drug using acrylic polymer and filled in capsules.

**FORMULATION EXCIPIENTS USED IN FDDS [43, 44, 45]**

**1.Polymers**

The following polymers used in preparations of FDDS -HPMC K4 M, Calcium alginate, Eudragit S100, Eudragit RL, Propylene foam, Eudragit RS, ethyl cellulose, poly methyl methacrylate, Methocel K4M, Polyethylene oxide, β Cyclodextrin,HPMC 4000, HPMC 100, CMC, Polyethylene glycol, polycarbonate, PVA, Polycarbonate, Sodium alginate, HPC-L, CP 934P, HPC, Eudragit S, HPMC, Metolose S.M. 100, PVP, HPC-H, HPC-M, HPMC K15, Polyox, HPMC K4, Acrylic polymer, E4 M and Carbopol.

**2.Inert fatty materials (5%-75%)**

Edible, inert fatty material having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. E.g. Beeswax, fatty acids, long chain fatty alcohols, Gelucires 39/01 and 43/01.

**3. Effervescent agents**

Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine).

**4. Release rate accelerants (5%-60%)**

eg. lactose, mannitol.

**5. Release rate retardants (5%-60%)**

eg. Dicalciumphosphate,talc, magnesium stearate.

**6. Buoyancy increasing agents (upto80%)**

eg. Ethyl cellulose.

**7. Low density material**

Polypropylene foam powder (AccurelMP 1000).

**Table 1: commonly used drug in gastro retentive dosage forms[41,42]**

| Dosage forms | Drugs |
|---|---|
| Floating Tablets | Acetaminophen, Acetylsalicylic acid, Ampicillin, Atenolol, Captopril, Cinnerzine, Chlorpheniramine maleate, Ciprofloxacin, Diltiazem, Fluorourac,Isosorbide dinitrate, Isosorbid mononitrate, p- Aminobenzoic acid(PABA), Nimodipine, Sotalol, Theophylline,verapamil |
| Floating Capsules | Chlordiazepoxide HCl, Diazepam,furosemide, L-DOPA and Benserazide,Pepstatin Nicardipine, Misoprostol, Propranolol, |
| Floating microspheres | Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfenadine, Tranilast |
| Floating granules | Diclofenac sodium, Indomethacin, Prednisolone |
| powders | Several basic drugs |
| Films | Cinnerzine |

**EVALUATION OF FLOATING DRUG DELIVERY SYSTEMS**

**1. SIZE AND SHAPE EVALUATION**

The particle size and shape plays a major role in determining solubility rate of the drugs and thus potentially its bioavailability**.** The particle size of the formulation was determined using Sieve analysis (Jayant, Mumbai), Air elutriation (Bahco TM) analysis, Photo analysis, Optical microscope (Olympus (India) pvt.ltd), Electro résistance counting methods (Coulter counter), Sedimentation techniques, Laser diffraction methods, ultrasound attenuation spectroscopy, Air Pollution Emissions Measurements etc[45].

**2. FLOATING PROPERTIES**

Effect of formulation variables on the floating properties of gastric floating drug delivery system was determined by using continuous floating monitoring system and statistical experimental design.[48]

**3. SURFACE TOPOGRAPHY**

The surface topography and structures were determined using scanning electron microscope (SEM, JEOL JSM – 6701 F, Japan) operated with an acceleration voltage of 10k.v, Contact angle meter, Atomic force microscopy (AFM), Contact profiliometer. [49]

## 4. DETERMINATION OF MOISTURE CONTENT

The water content per se is seldom of interest. Rather, it shows whether a product intended for trade and production has standard properties such as

1. Storability
2. Agglomeration in the case of powders
3. Microbiological stability
4. Flow properties, viscosity
5. Dry substance content
6. Concentration or purity
7. Commercial grade (compliance with quality agreements)

Thus moisture content of the prepared formulations was determined by Karl fisher titration, vacuum drying, Thermo gravimetric methods, Air oven method, Moisture Meters, Freeze drying as well as by physical methods .[50]

## 5. SWELLING STUDIES

Swelling studies were performed to calculate molecular parameters of swollen polymers**.** Swelling studies was determined by using Dissolution apparatus, optical microscopy and other sophisticated techniques which include H1NMRimaging, Confocal laser scanning microscopy (CLSM), Cryogenic scanning electron microscopy (Cryo SEM), Light scattering imaging (LSI) etc. The swelling studies by using Dissolution apparatus (USP disso-lution apparatus (usp-24) lab india disso 2000) was calculated as per the following formula .[51]

Swelling ratio = Weight of wet formulation **/** Weight of formulations

## 6. DETERMINATION OF THE DRUG CONTENT

Percentage drug content provides how much amount of the drug that was present in the formulation. It should not exceed the limits acquired by the standard monographs. Drug content was determined by using HPLC, HPTLC methods, Near infrared spectroscopy (NIRS), Micro titrimetric methods, Inductively Coupled Plasma Atomic Emission Spectrometer (ICPAES) and also by using spectroscopy techniques (Elico Limited, Hyderabad) .[52]

## 7. PERCENTAGE ENTRAPMENT EFFICIENCY

Percentage entrapment efficiency was reliable for quantifying the phase distribution of drug in the prepared formulations. Entrapment efficiency was determined by using three methods such as Micro dialysis method, Ultra centrifugation, and pressure Ultra filtration.[53]

## 8. IN-VITRO RELEASE STUDIES

In vitro release studies (USP dissolution apparatus (usp-24) lab india disso 2000) were performed to provide the amount of the drug that is released at a definite time period. Release studies were performed by using Franz diffusion cell system and synthetic membrane as well as different types of dissolution apparatus.[45]

## 9. POWDER X-RAY DIFFRACTION

X-ray powder diffraction (Philips analytical, model-pw1710) is the predominant tool for the study of poly-crystalline materials and is eminently suited for the routine characterization of pharmaceutical solids. Samples were irradiated with α radiation and analyzed between 2 ºC and 60 ºC .The voltage and current used were 30KV and 30mA respectively. [54]

## 10. FOURIER TRANSFORMS INFRARED ANALYSIS

Fourier transform infrared spectroscopy (FT-IR, Shimadzu, Model-RT-IR-8300) is a technique mostly used to identify organic, polymeric, and some inorganic materials as well as for functional group determination. Fourier Transform Infrared Analysis (FT-IR) measurements of pure drug, polymer and drug loaded polymer formulations were obtained on FT-IR. The pellets were prepared on KBr press under hydraulic pressure of 150kg/cm2; the spectra were scanned over the wave number range of 3600 to 400 $cm^{-1}$ at the ambient temperature.[54]

## 11. DIFFERENTIAL SCANNING CALORIMETRY (DSC)

DSC (Shimadzu, Model-DSC-60/DSC-50/ Metler Toldeo) are used to characterize water of hydration of pharmaceuticals .Thermo grams of formulated preparations were obtained using DSC instrument equipped with an intercooler. Indium/Zinc standards were used to calibrate the DSC temperature and enthalpy scale. The sample preparations were hermitically sealed in an aluminium pan and heated at

a constant rate of 10°C/min; over a temperature range of 25° C – 65°C. Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 50ml/min.[54]

## APPLICATION OF FLOATING DRUG DELIVERY SYSTEM [46]

- ✓ 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.B of hypertensive patients.
- ✓ Modapar R 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. CytotechR- containing Misoprostol, 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.

## PHARMACOKINETIC AND PHARMACODYNAMIC ASPECTS OF FDDS [47]

The aim of this section is to delineate these aspects in order to suggest rational selection of drugs for which FDDS would be a beneficial strategy.

## PHARMACOKINETIC ASPECTS

### 1. Absorption window

Validation that the drug is within the category of narrow absorption window agents currently various experimental techniques are available that permit us to verify the absorption properties of the tested molecule, to determine the mechanism of intestinal absorption and to elucidate the permeability at different regions of the GI tract. In the case of absorption by active transporters that are capacity limited, the efficacy of the transport activity may increase following sustained presentation of the drug to the transporting enzymes in comparison to non-control release mode of administration.

### 2. Enhanced bioavailability

Once it has been ascertained that the compound in question is defined as narrow absorption window, the possibility of improving bioavailability by continuous administration of the compound to the specific site should be tested. For example, we have found that certain bisphosphonates, including alendronate, are absorbed directly from the stomach. However, the magnitude of this pathway remains modest even in the case where the prolonged gastric retention of the bisphosphonate in rats is produced by experimental/surgical means. On the other hand, the bioavailability of control release (CR) floating systems of Riboflavin and Levodopa are significantly enhanced in comparison to administration of simple CR polymeric formulations. It may be concluded that several different processes, related to absorption and transit of the drug in the gastrointestinal tract, act concomitantly and influence the magnitude of drug absorption. Therefore, *in vivo* studies are necessary to determine the release profile of the drug from the dosage form that will provide enhanced bioavailability.

### 3. Enhanced first pass biotransformation

In a similar fashion to increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input

### 4. Improved bioavailability due to reduced Pglycoprotein (P-gp) activity in the duodenum

In apparent contrast to the higher density of CYP3A4 at the upper part of the intestine, Pgp mRNA levels increase longitudinally along the intestine such that the highest levels are located in the colon. Therefore, for drugs that are P-gp substrate and do not undergo oxidative metabolism, such as Digoxin, floating systems may elevate absorption compared to the immediate and CR dosage forms.

**5. Reduced frequency of dosing**

For drugs with relatively short biological half life, sustained and slow input from control release floating system may result in a flip flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.

**6. Targeted therapy for local ailments in the upper GIT**

The prolonged and sustained administration of the drug from the floating systems to the stomach may be advantageous for local therapy in the stomach and the small intestine.

**PHARMACO DYNAMIC ASPECTS OF FDDS**

**1. Reduced fluctuations of drug concentration**

Continuous input of the drug following floating system administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index. Improved selectivity in receptor activation: Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations. Reduced counter-activity of the body: In many cases, the pharmacological response, which intervenes with the natural physiologic processes, provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

**2. Minimized adverse activity at the colon**

Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activitiesof the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for floating formulation for betalactam antibiotics that are absorbed only from the small intestine and presence in the colon leads to development of microorganisms

**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 towards commercializing this technique.

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