

**GASTRORETENTIVE DRUG DELIVERY SYSTEMS: A  
COMPREHENSIVE OVERVIEW**

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Article Received on  
27 March 2015,

Revised on 20 April 2015,  
Accepted on 14 May 2015

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**ABSTRACT**

Recent technologies and scientific research has been devoted to the development of suitable dosage form keeping in mind maximum utilization of drug, minimizing wastage and avoiding side effect of drug to be administered. In the same way to formulate dosage form to be administered orally and make drug available in stomach or upper part of GI tract, gastroretentive drug delivery system can be a good approach. Differences in gastric physiology such as gastric pH and motility exhibit both intra and inter subject variability demonstrating significant impact on gastric residence time and drug delivery behaviour. This triggered an increased interest towards formulation of novel delivery systems which retained in the stomach for prolonged and predictable period of time. Several approaches such as floating drug delivery systems (FDDS), swelling and expanding systems, bioadhesive systems, modified shape systems, high density systems or

other delayed gastric emptying devices have been discovered till now. FDDS are of particular interest for drugs that are locally active and have narrow absorption window in stomach or upper small intestine, unstable in the intestinal or colonic environment, and exhibit low solubility at high pH values. This article highlights all the key points related to gastroretentive drug delivery system, approaches available, factors affecting gastric retention,

advantages and disadvantages of gastroretentive drug delivery system its evaluation test and applicability.

**KEYWORDS:** Floating drug delivery systems, Gastric residence time, Swelling index, Buoyancy.

## INTRODUCTION

The design of oral control drug delivery systems should be primarily aimed to achieve more predictable and increased bioavailability.<sup>[1]</sup> Overall of the drug available in the market are administered orally and these systems have more advantages due to patients acceptance and ease of administration. Nowadays most of the pharmaceutical scientist is involved in developing the ideal drug delivery system. This ideal system should have advantage of single dose for the whole duration of treatment and it should deliver the active drug directly at the specific site. Scientists have succeeded to develop a system and it encourages the scientists to develop control release systems. Control release implies the predictability and reproducibility to control the drug release, drug concentration in target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose.<sup>[2][3]</sup> Under certain circumstances prolonging the gastric retention of a delivery system is desirable for achieving greater therapeutic benefit of the drug substances. For example, drugs that are absorbed in the proximal part of the gastrointestinal tract<sup>[4]</sup>, and the drugs that are less soluble or are degraded by the alkaline pH may benefit from the prolonging gastric retention.<sup>[5][6]</sup> In addition, for local and sustained drug delivery to the stomach and the proximal small intestine to treat certain conditions, prolonging gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailability, therapeutic efficacy and possible reduction of the dose size.<sup>[7][8]</sup> It has been suggested that prolong local availability of antibacterial agents may augment their effectiveness in treating H.Pylori related peptic ulcers. Gastroretentive Drug delivery systems (GRDDS)<sup>[9-14]</sup>, however are not suitable for drugs that may cause gastric lesions, e.g., Non-steroidal anti-inflammatory agents.

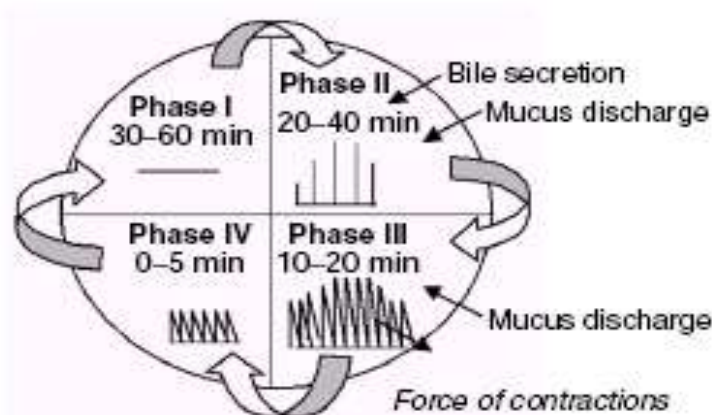
## BASIC PHYSIOLOGY OF THE GASTROINTESTINAL TRACT

The complex anatomy and physiology of the GIT, including variations in acidity, bile salts, enzyme content, and the mucosal absorptive surface, significantly influence the release, dissolution, and absorption of orally administered dosage forms. Two distinct patterns of gastrointestinal (GI) motility and secretion exist, corresponding to the fasted and fed states.

As a result, the BA of orally administered drugs will vary depending on the state of feeding. The fasted state is associated with various cyclic events, commonly referred to as the migrating motor complex (MMC), which regulates GI motility patterns. The MMC is organized into alternating cycles of activity and quiescence and can be subdivided into basal (Phase I), preburst (Phase II), and burst (Phase III) intervals (Fig1).<sup>[1]</sup> Phase I, the quiescent period, lasts from 30 to 60 min and is characterized by a lack of secretory, electrical, and contractile activity. Phase II exhibits intermittent action for 20–40 min during which contractile motions increase in frequency and size. Bile enters the duodenum during this phase, whereas gastric mucus discharge occurs during the latter part of Phase II and throughout Phase III. Phase III is characterized by intense, large, and regular contractions, termed housekeeper waves, that sweep off undigested food and last 10–20 min. Phase IV is the transition period of 0–5 min between Phases III and I. This series of electrical events originates in the foregut and continues to the terminal ileum in the fasted state, repeating every 2–3 hrs. Feeding sets off a continuous pattern of spike potentials and contractions called postprandial motility. The particular phase during which a dosage form is administered influences the performance of peroral CRDDS and GRDDS. When CRDDS are administered in the fasted state, the MMC may be in any of its phases, which can significantly influence the total gastric residence time (GRT) and transit time in the GIT. This assumes even more significance for drugs that have an absorption window because it will affect the amount of time the dosage form spends in the region preceding and around the window. The less time spent in that region, the lower the degree of absorption. Therefore, the design of GRDDS should take into consideration the resistance of the dosage form to gastric emptying during Phase III of the MMC in the fasted state and also to continuous gastric emptying through the pyloric sphincter in the fed state. This means that GRDDS must be functional quickly after administration and able to resist the onslaught of physiological events for the required period of time.

**Table 1: Summary of Stomach and Intestine pH and Absorption pathway**

Section	Transit Time	pH	Absorbing Surface area (m <sup>2</sup> )	Absorption Pathway
Stomach	Variable	1-4	0.1	Passive, Active, Aqueous Channel transport
Small Intestine	3±1	5-7.5	120-200	Passive, Active, Aqueous Channel transport, Facilitated transport, Ion pair transport, Enterocytosis, Carrier mediated transport.



**Fig 1: Motility patterns of the GIT in fasted state**

### GASTRIC EMPTYING AND PROBLEMS

It is well recognized that the stomach may be used as a depot for Sustained release dosage forms, both in human and veterinary applications, stomach is anatomically divided in to three parts: Fundus, body and pylorus.<sup>[15]</sup> The proximal stomach made up of the fundus and body region serves as a reservoir for ingested materials, while the distal region (antrum) is the major site for the mixing motion, acting as a pump to accomplish gastric emptying. The process of the gastric emptying occurs both during fasting and fed stages. Scintigraphy study involving measurement of gastric emptying rates in healthy human subject have revealed that an orally administered Controlled release dosage form is mainly subjected to two physiological adversities.<sup>[15]</sup>

- a) The short GRT (Gastric Residence Time)
- b) Variable (unpredictable) GET (Gastric Emptying Time)

Yet another major adversity encountered through the oral route is the first pass effect, which leads to reduce systematic availability of a large number of a drug. These problems can be exacerbated by alteration in the gastric emptying that occur due to factors such as age, race, sex and disease states, as they may seriously affect the release of a drug from drug delivery system. It is therefore desirable to have a Controlled release product that exhibits an extended, GI residence and a drug release profile independent of patients' related variables.

### Potential Drug Candidates for Stomach Specific Drug Delivery Systems

1. Drugs those are locally active in the stomach e.g. misoprostol, antacids etc.
2. Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. l-dopa, paraaminobenzoic acid, furosemide, riboflavin etc.

3. Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.
4. Drugs that disturb normal colonic microbes e.g. antibiotics against *Helicobacter pylori*.
5. Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide, verapamil HCl.

#### **Drugs those are Unsuitable for Stomach Specific Drug Delivery Systems**

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

#### **APPROACHES TO GASTRIC RETENTION/ STOMACH SPECIFIC DELIVERY**

Various approaches have been paused to increase the duration of oral dosage form in the stomach, including floating systems, swelling and expanding system, modified shape system, high density systems and other delayed gastric emptying devices. (Magnetic systems, super porous –biodegradable hydrogel systems).

##### **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 ( $\sim 1.004 \text{ gm/cm}^3$ ). 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. The materials increase density by up to 1.5- 2.4  $\text{gm/cm}^3$ . A density close to 2.5  $\text{gm/cm}^3$  seems necessary for significant prolongation of gastric residence time. But, Effectiveness of this system in human beings was not observed and no system has been marketed. <sup>[16]</sup>

##### **2 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. 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 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 network 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).

**3 Expandable, Unfoldable and Swellable Systems**

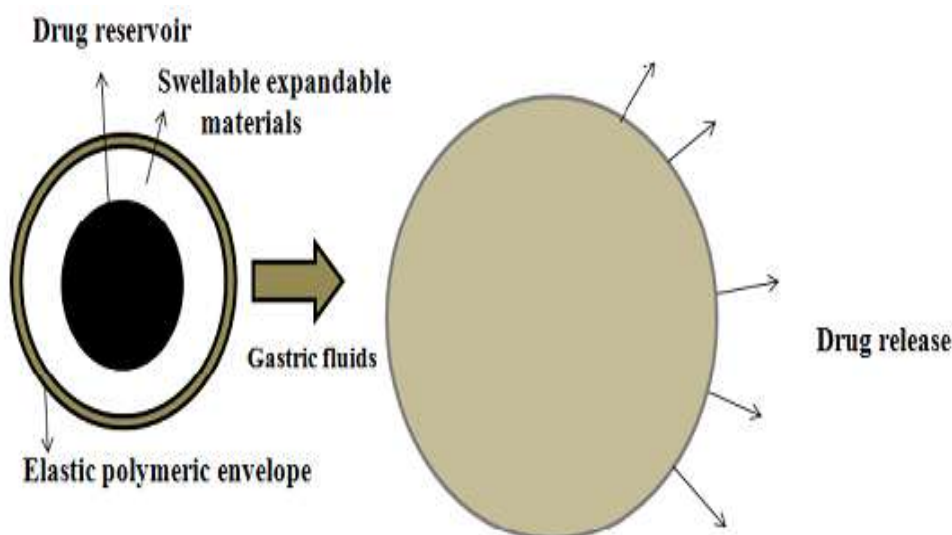
A dosage form in the stomach will withstand gastric transit if it bigger than pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, their configurations are required to develop an expandable system 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. Swellable systems are also retained in the gastrointestinal 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 (Figure 2). 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.<sup>[17]</sup>



**Figure 2: Drug release from swellable systems**

#### **4 Super Porous Hydrogel 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 hydrogels 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. 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 coformulation of hydrophilic particulate material.<sup>[17]</sup>

#### **5 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.

## 6 Ion Exchange Resins

Ion exchange resins are loaded with bicarbonate, and a negatively charged drug is bound to the resin. Resultant beads are then encapsulated in a semipermeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions takes place. As a result of this reaction, carbon dioxide is released and trapped in the membrane thereby carrying beads towards the top of the gastric contents and producing a floating layer of resin beads – in contrast to uncoated beads, which sink quickly.

## 7 Raft Systems

Raft systems incorporate alginate gel solution (e.g. sodium alginate solution containing carbonates or bicarbonates) that upon reaction with gastric fluid, swell and form a viscous cohesive gel containing entrapped carbon dioxide bubbles, enabling floatation of the drug delivery system. Because raft-forming systems produce a layer on the top of the gastric fluids, they are often used for gastroesophageal reflux treatment, as with Liquid Gaviscon (GlaxoSmithKline).

Other delayed gastric emptying approaches of interest include sham feeding of digestible polymers or fatty acid salts that charges the motility pattern, of the stomach to a fed stage thereby decreasing the gastric emptying rate and permitting considerable prolongation of the drug release. But some of this has certain drawbacks, which could limit their uses described in the following Table 2. <sup>[19]</sup>

**Table 2: Drawback associated with different types of GRDDS<sup>[19]</sup>**

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

## FLOATING DRUG DELIVERY SYSTEMS

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 prolong period. This results in an



increase in the GRT and a better control of fluctuations in the plasma drug concentrations. Floating system can be effervescent or Non effervescent in nature.

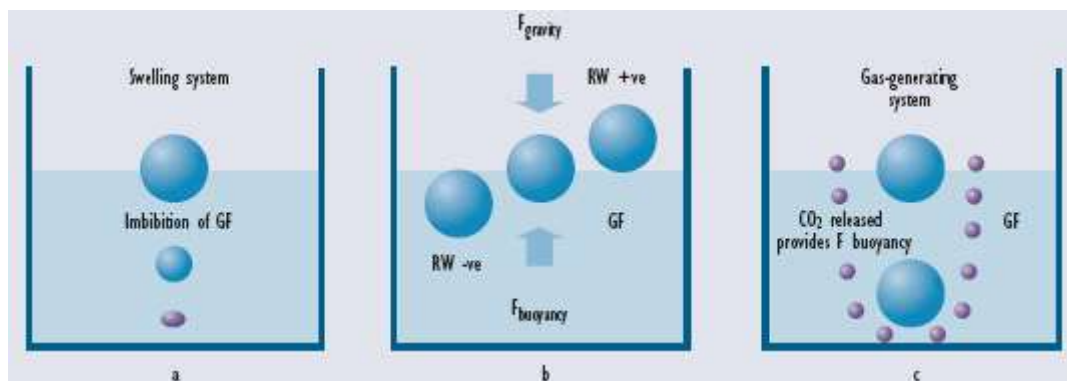
## EFFERVESCENT SYSTEM

### 1 Volatile Liquid Containing Systems

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of PVA, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.<sup>[20]</sup>

### 2 Gas-Generating Systems

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO<sub>2</sub>, which gets entrapped in the jellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme.<sup>[1][18]</sup> How the dosage form float is shown in the following figure (Figure 3).<sup>[21]</sup>



**Fig 3: The mechanism of floating systems**

## 2 NON-EFFERVESCENT SYSTEMS

### 1 Colloidal Gel Barrier Systems

Hydrodynamically balance system (HBSTM) was first design by Sheth and Tossounian in 1975. Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids. e.g. HEC, HPMC, NaCMC, Polysaccharides and matrix forming polymer such as polycarbophil, polyacrylates and polystyrene, incorporated

either in tablets or in capsule. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to these dosage forms.<sup>[22]</sup>

## 2 Microporous Compartment System

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

## 3 Alginate Beads

Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping a sodium alginate solution into aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated, snap and frozen in liquid nitrogen and freeze dried at -40°C for 24 hrs., leading to the formation of porous system, which can maintain a floating force over 12 hours.<sup>[22]</sup>

## 4 Hollow Microspheres

Hollow microspheres (microballoons), loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol : dichloromethane solution of the drug and enteric acrylic polymers was poured into an agitated aqueous solution of PVA that was thermally controlled at 40°C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microspheres of the polymer with drug. The microballoons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 hrs. *in-vitro*.<sup>[22]</sup>

## FACTORS AFFECTING GASTRIC RETENTION

### 1 Density

Density of the dosage form should be less than the gastric contents (1.004gm/mL).

## 2 Size and shape

Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT compared to those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devices with a flexural modulus of 48 and 22.5 kilopond per square inch (KSI) are reported to have better GIT @ 90 to 100 % retention at 24 hrs. compared with other shapes 1,23.

## 3 Fed or unfed state

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (MMC) that occurs every 1.5 to 2 hrs.. 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.<sup>[18]</sup>

## 4 Nature of the meal

Feeding of indigestible polymers of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release.<sup>[14]</sup>

## 5 Caloric content

GRT can be increased between 4 to 10 hrs. with a meal that is high in proteins and fats.

## 6 Frequency of feed

The GRT can increase by over 400 min when successive meals are given compared with a single meal due to the low frequency of MMC.<sup>[22]</sup>

## 7 Gender

Mean ambulatory GRT in meals ( $3.4 \pm 0.4$  hrs.) is less compared with their age and race-matched female counterparts ( $4.6 \pm 1.2$  hrs.), regardless of the weight, height and body surface.

## 8 Age

Elderly people, especially those over 70 years have a significantly longer GRT.<sup>[23]</sup>

## 9 Posture

GRT can vary between supine and upright ambulatory states of the patients.<sup>[24]</sup>

## 10 Concomitant drug administration

Anticholinergic like atropine and propantheline opiates like codeine and prokinetic agents like metoclopramide and cisapride.

## FORMULATION OF STOMACH SPECIFIC DOSAGE FORM

Following types of the ingredients can be incorporated in to HBS dosage form in addition to drugs.<sup>[23] [25]</sup>

- **Hydrocolloids**
- **Inert Fatty Materials**
- **Release Rate Accelerants**
- **Release Rate Retardant**
- **Buoyancy Increasing Agents**
- **Miscellaneous**

### 1 Hydrocolloids

Suitable hydrocolloids are synthetics, anionic or non ionic like hydrophilic gums, modified cellulose derivatives. E.g. accasia, pectin, agar, alginates, gelatin, casein, bentonite, veegum, MC, HPC, HEC, and Na CMC can be used. The hydrocolloids must hydrate in acidic medium i.e. gastric fluid is having pH 1.2. Although the bulk density of the formulation may initially be more than one, but when gastric fluid is enter in the system, it should be hydrodynamically balanced to have a bulk density of less than one to assure buoyancy.

### 2 Inert Fatty Materials

Edible, pharmaceutical inert fatty material, having a specific gravity less than one can be added to the formulation to decrease the hydrophilic property of formulation and hence increases the buoyancy. Example: Purified grades of beeswax, fatty acids, long chain alcohols, glycerides, and mineral oils can be used. Such materials may be present from about 5-75 % by weight.

### 3 Release Rate Accelerant

The release rate of the medicament from the formulation can be modified by including excipient like lactose and/or mannitol. These may be present from about 5-60% by weight.

#### 4 Release Rate Retardant

Insoluble substances such as dicalcium phosphate, talc, magnesium stearate decreased the solubility and hence retard the release of medicaments. Such, materials may be present about 5-60 % by weight.

#### 5 Buoyancy Increasing Agents

Materials like ethyl cellulose, which has bulk density less than one, can be used for enhancing the buoyancy of the formulation. It may be added up to 80 % by weight.

#### 6 Miscellaneous

Pharmaceutically acceptable adjuvant like preservatives, stabilizers, and lubricants can be incorporated in the dosage forms as per the requirements. They do not adversely affect the hydrodynamic balance of the systems.

### EVALUATION OF STOMACH SPECIFIC SYSTEMS

#### 1. Thickness and diameter

Control of physical dimensions of the tablets such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness of tablet is measured in mm using micrometer screw gauge and diameter defined by die used in the preparation of tablets.

#### 2. Hardness

The Monsanto hardness tester, Pfizer, Erweka hardness tester is used to determine the tablet hardness (crushing strength). The tablet is held between affixed and moving jaw. Scale is adjusted to zero; load is applied until the tablet fractured. The value of the applied load at that point gives the measure of the hardness of the tablet which is expressed in kg/cm<sup>2</sup>.

#### 3. Friability (Tumbling test)

Tablet strength is tested by Roche friabilator. Pre weighted tablets are allowed for 100 revolutions in 4 min and dedusted. The percentage weight loss was calculated by reweighing the tablets.

The % Friability is then calculated by,

$$\% \text{ Friability} = \frac{(W_{\text{initial}}) - (W_{\text{final}})}{(W_{\text{initial}})} \times 100$$

#### 4. Weight variation:

Randomly selected 20 tablets are weighted individually and together in a single pan balance. The average weight is noted and standard deviation is calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double percentage limit.

#### 5. Bio/Mucoadhesive systems

##### Bioadhesive strength

Bioadhesive strength of a polymer can be determined by measuring the force required to separate a polymer specimen sandwiched between layers of either an artificial (e.g. cellophane) or a biological (e.g. rabbit stomach tissue) membrane. This force can be measured by using a modified precision balance or an auto mated texture analyzer.

#### 6. Swelling and expanding systems

##### Water uptake study

The swelling of the polymers can be measured by their ability to absorb water and swell. Water uptake studies of the formulation (tablet or granules) are performed using USP dissolution apparatus II. The medium used is usually distilled water or 0.1 N HCl (900 mL) rotated at 50 rpm, and maintained at  $37 \pm 0.5^\circ\text{C}$  through-out the study. After a selected time interval, the formulation is withdrawn, blotted to remove excess water, and weighed. Swelling characteristics of the tablets expressed in terms of water uptake (WU) are calculated as (equation 1).

$$\% \text{ of hydration} = (W_2 - W_1) \times 100 / W_1$$

Where

$W_1$  = initial weight of disc,  $W_2$  = weight of disc after specified time interval.

In-vitro dissolution studies in swelling and expanding systems are usually carried out by a modified dissolution method, as in the case of FDDS.

#### 7. Floating drug delivery systems

##### In-vitro floating time determination

Floating time is determined by using the USP disintegration apparatus containing 900mL of 0.1 N HCl solution as a testing medium maintained at  $37 \pm 0.5^\circ\text{C}$ . The time required to float

different dosage forms is noted as floating (or buoyancy) lag time, and floating duration of the dosage form is determined by visual observation.

## **TYPES OF FLOATING DOSAGE FORMS**

- 1. New Floating Bilayer Compressed Matrices**
- 2. New Multiple Unit Oral Floating Dosage Form**
- 3. Sustained Release Intra gastric Floating Granules**

### **1 New Floating Bilayer Compressed Matrices<sup>[27]</sup>**

One of the tablet layers mainly contains the carbon dioxide generating blend and a hydrodynamic polymer. The carbon dioxide being entrapped in the gasified hydrocolloid as liberated by the action of the gastric medium produces the upward motion of the tablet and maintains its buoyancy. The outer layer is hydrophilic matrix and contained the drug which is release in the prolonged and controlled way.

#### **Advantages**

- Double layer matrix tablet shows a more homogenous behaviour with regard to erosion and is less sensitive to the GI peristalsis and the formulation of the matrix dosage form with two distinct layers allows the separate regulation of the floating capabilities and the drug release kinetics.
- Consequently this type of sustained release matrix could be advantageously used for conveying drugs which are sufficiently stable and soluble in acidic media, better reabsorbed in the proximal or middle portion of the GI tract, requiring a sustained release period to improve the bioavailability of poorly soluble products in non acid media or aiming to produce a local and specific effect in the stomach.

### **2 New Multiple Unit Oral Floating Dosage Forms<sup>[28]</sup>**

The Gastric Emptying Time in the humans is in fed state from 1-6 hrs. has been reported. Accordingly when a sustained release dosage form was administered orally, sufficient bioavailability and prolongation of the effective plasma level occasionally could not be obtained especially for drug having a limited absorption site in the intestinal tract. Recently some studies have been reported prolongation of GET (Gastric Emptying Time) of certain preparations, such as the floating dosage systems and bioadhesive systems.



However, as most of the floating dosage systems were single unit preparations, it was possible that a single unit type might be transited in to the small intestine in a short time, irrespective floating ability. A Multiple type of oral floating dosage systems has been prepared in order to prolong the GET of the preparation. The system was composed of the sustained release pills containing the drug and the double layer surrounding the pills. Inner layer was an effervescent layer containing both sodium bicarbonate and the outer layer was swellable membrane was divided in to two sub layers to avoid direct contact between sodium bicarbonate and tartaric acid in the outer one.

### **Advantages**

- Preparation process of the floating dosage systems is easy and simple.

Moreover, conventional sustained release pills, such as matrix type or barrier membrane type, can be used as the central seeds of the system.

- The floating dosage system is compact before immersion in water, the system has higher density compared with other floating systems and is easy to handle.

### **3 Sustained Release Floating Granules<sup>[29]</sup>**

Drug granules, which remain in the stomach, comprise core- pharmaceutically effective ingredients coated with expansive films. Drug used was Dextromethorphan HCl (20%). Granules are developed based on chitosan of different buoyancy, both in acidic and neutral fluids, and gave the sustained release of prednisolone. The release rate of indomethacine from chitosan granules was compared with that of conventional commercial indomethacine capsules. Furthermore, enhancing the mixing ratio of drug and chitosan can control the release rate. In case of conventional capsule, the plasma concentration reach the maximum level one-hour after administration, while in case of granules with a 1:2 mixing of drug and chitosan, the chitosan produced a sustained plateau level of the drug.

### **ADVANTAGES OF STOMACH SPECIFIC DRUG DELIVERY SYSTEMS<sup>[23][34]</sup>**

1. The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT by this gastroretentive drug delivery approach in comparison to the administration of non-gastroretentive drug delivery. There are several different factors related to absorption and transit of the drug in the gastrointestinal tract (GIT) that act concomitantly to influence the magnitude of drug absorption.

2. For drugs with relatively short half life, sustained release may result in a flip-flop pharmacokinetics and also enable reduced frequency of dosing with improved patient compliance.
3. They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric fluids.
4. Gastroretentive drug delivery can produce prolong and sustain release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.
5. The controlled, slow delivery of drug from gastroretentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable effects or side effects.
6. Gastroretentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drug with a narrow therapeutic index.
7. Gastroretentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency.
8. Reduction of fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.
9. The sustained mode of drug release from Gastroretentive dosage form enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes.

#### **LIMITATIONS/DISADVANTAGES**

1. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat, water.
2. Not suitable for drugs that have solubility or stability problem in GIT.
3. Drugs such as nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.
4. Drugs which are irritant to Gastric mucosa is also not desirable or suitable.

5. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.<sup>[1]</sup>
6. The dosage form should be administered with a full glass of water (200-250 mL).<sup>[3]</sup>
7. These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract.

### APPLICATION OF FLOATING DRUG DELIVERY SYSTEM<sup>[5]</sup>

- Recent study indicated that the administration of Diltiazem floating tablets twice a day might be more effective compared to normal tablets in controlling the Blood pressure of hypertensive patients.
- Developing HBS dosage form for tacrin provide better delivery systems and reduced its GI side effects.
- Treatment of gastric and duodenal ulcer.

### MARKETED PRODUCTS

**Table 3: Marketed Products**<sup>[36-38]</sup>

Sr. no	Brand Names	Drug (Dose)	Company, Country	Remark
1	Madopar ®	Levodopa (100 mg)	Roche Product USA	Floating CR Capsule
2	Valrelease ®	Diazepam (15 mg)	Hoffmann-LaRoche, USA	Floating capsule
3	Cytotec ®	Misoprostol (100 mcg)	Pharmacia, USA	Bilayer floating Tablets
4	Cifran OD ®	Ciprofloxacin (1 gm)	Ranbaxy, India	Gas generating Floating system
5	Convion	Ferrous Sulphate	Ranbaxy, India	Colloidal gel forming FDDS

### FUTURE POTENTIAL

1. Floating dosage form offers various future potential as evident from several recent publications. The reduced fluctuations in the plasma level of drug results from delayed gastric emptying.
2. Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailability.
3. Buoyant delivery system considered as a beneficial strategy for the treatment of gastric and duodenal cancers.

4. The floating concept can also be utilized in the development of various anti-reflux formulations.
5. Developing a controlled release system for the drugs, which are potential to treat the Parkinson's disease.
6. To explore the eradication of H-pylori by using the narrow spectrum antibodies.

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