CODEN (USA): IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com Review Article

A COMPREHENSIVE REVIEW ON GASTRORETENTIVE DRUG DELIVERY SYSTEMS

Rajendra Kumar Jadi[1*] and Krishna Mohan Chinnala[2]

[1]Chaitanya College of Pharmacy Education and Research, Hanamkonda, Warangal,Telangana, India.
[2]School of Pharmacy, Nalla Narasimha Reddy Education Society's Group of Institutions, Hyderabad, Telangana, India.

Abstract:

The purpose of writing this review was to investigate, compile, recent, current and past literatures. In recent years several advancements has been made in research and development of oral drug delivery system. Various drugs, which are unstable in alkaline pH, soluble in acidic pH, having narrow absorption window, site specific to stomach can be developed by using this technique. Gastroretentive drug delivery systems (GRDDS) can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches absorption site. These include floating system, swelling system, expanding system, low density systems, high density system, bioadhesive and mucoadhesive systems etc. In fact the buoyant dosage unit enhances gastric residence time (GRT) without affecting the intrinsic rate of emptying. GRDDS is an approach to prolong gastric residence time, thereby targeting site-specific drug release in upper gastro intestinal tract improving the oral sustained delivery of drug. For minimizing the limitations and achieving better gastric retention various combinational approaches like floating and swelling, floating and bioadhesion, etc., multi-particulate systems, super porous hydrogel etc., have been discussed. The present review addresses briefly about suitable drug candidates, formulation considerations, physiological difficulties and classification, factors effecting gastric retention, merits, demerits and limitations of gastroretentive drug delivery systems.

Keywords: *Gastroretentive drug delivery systems, controlled release systems, gastric residence time, gastric emptying time and absorption window.*

Corresponding author:

Rajendra Kumar Jadi

Department of Pharmaceutics
Chaitanya College of Pharmacy Education and Research,
Hanamkonda, Warangal, Telangana, India.
Email: *rajendra.rajaji@gmail.com*
Mobile: +919866575814

QR code

Please cite this article in press as Rajendra Kumar and Krishna Mohan, ***A Comprehensive Review on Gastroretentive Drug Delivery Systems****, Indo Am. J. Pharm. Sci, 2016; 3(2).*

INTRODUCTION:

Historically, oral drug administration has been the predominant route for drug delivery. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. However, this route has several physiological problems including an unpredictable gastric emptying rate that varies from person to person, a brief gastrointestinal transit time (8 to 12h), and the existence of an absorption window in the upper small intestine for several drugs [1]. Oral drug delivery system is the most convenient, widely utilized route of drug administration among all routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage forms because of their compact nature, better patient compliance, ease of administration, low cost, flexibility in formulation, and also easy to manufacture, pack and transport. However, there are some drawbacks associated with oral drug delivery system like short residence time; unpredictable gastric emptying and sometimes drug may degrade due to the high reactive nature of GI contents. Because of this reason, drugs get absorbed easily from the GIT and are disintegrated quickly from the systemic circulation and shows short half life. So, to achieve the desired therapeutic activity usually frequent dosing is required. The release rate will be controlled depending upon the type and concentration of the polymer that swells, leads to diffusion and erosion of the drug [2, 3].

The problem frequently encountered with extended release dosage forms is the failure to increase the residence time of the dosage form in the stomach and proximal portion of the small intestine. Therefore it would be beneficial to develop extended release formulations which remain at the absorption site for an extensive period of time. One of the possible approaches for achieving delayed and expected drug delivery profile in GIT is to control gastric retention time (GRT) of the formulation. Dosage form with prolonged GRT, i.e. gastroretentive dosage forms (GRDFs) will offer new and important therapeutic options [4].

The real challenge in the development of a gastroretentive drug delivery system is not just extend the drug release but also to prolong the presence of the dosage form in the stomach and due to their inability to restrain and localise the system at targeted areas of the gastrointestinal (GI) tract or the upper part of the GIT until all the drug is completely released [5].

Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Also, longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease. These drugs can be delivered ideally by slow release from the stomach. Many drugs categorised as once-a-day delivery have been demonstrated to have sub-optimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine [6].

GRDDS are beneficial for such drugs by improving their [7]

- Bioavailability
- Therapeutics efficiency
- Possible reduction of the dose.
- Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in the therapeutic levels
- Reduce drug wastage
- Improves solubility of drugs that are less soluble at high pH environment

Anatomy of stomach

The stomach is an expanded section of the digestive tube between the oesophagus and small intestine. The wall of the stomach is structurally similar to the other parts of the digestive tube; with the exception that stomach has an extra, oblique layer of smooth muscle inside the circular layer, which aids in the performance of complex grinding motions [8]. In the empty state, the stomach is contracted and its mucosa and sub-mucosa are thrown up into distinct folds called Rugae; figure 1 illustrates the structure of stomach and GIT:

There are images to four major types of secretary epithelial cells that cover the surface of the stomach and extend down into gastric pits and glands:

1. **Mucous cells:** Secrete alkaline mucus that protects the epithelium against shear stress and acid.
2. **Parietal cells:** Secrete hydrochloric acid.
3. **Chief cells:** Secrete pepsin, a proteolytic enzyme.
4. **G cells:** Secrete the hormone, gastrin.

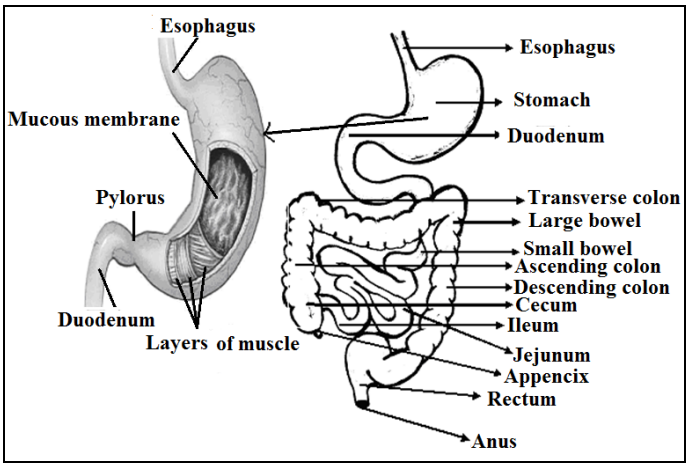

Fig 1: (a) Structure of stomach
(b) Structure of gastrointestinal tract

Gastroretentive dosage form (GRDF)

It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastroretentive dosage form (GRDF).

GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form.

Dosage form with prolonged GRT, i.e. gastroretentive dosage forms (GRDF), will bring about new and important therapeutic options such as [9, 10]:

- This application is especially effective in sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. To override this problem, erodible, gastroretentive dosage forms have been developed that provide continuous, controlled administration of sparingly soluble drugs at the absorption site.
- GRDFs greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentration at the gastric mucosa. (For e.g. Eradicating Helicobacter pylori from the sub-mucosal tissue of stomach) making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis, reduce the risk of gastric carcinoma and administer non-systemic controlled release antacid formulations (calcium carbonate).
- GRDFs can be used as carriers for drugs with so-called absorption windows.

  E.g. Antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillin's, cephalosporin's, amino glycosides, tetracycline's etc.) are taken up only from very specific sites of the GI mucosa.

Absorption window

Drug exhibiting absorption from only a particular portion of GI tract or showing difference in absorption from various regions of GI tract are said to have regional variability in intestinal absorption. Such drugs show absorption window which signifies the regions of GI tract from where absorption primarily occurs. Drug released from the CRDDS after the absorption window has been crossed goes waste with no or negligible absorption occurring is shown below figure 2.

This phenomenon drastically decreases the available drug for absorption, after release of drug from CRDDS.

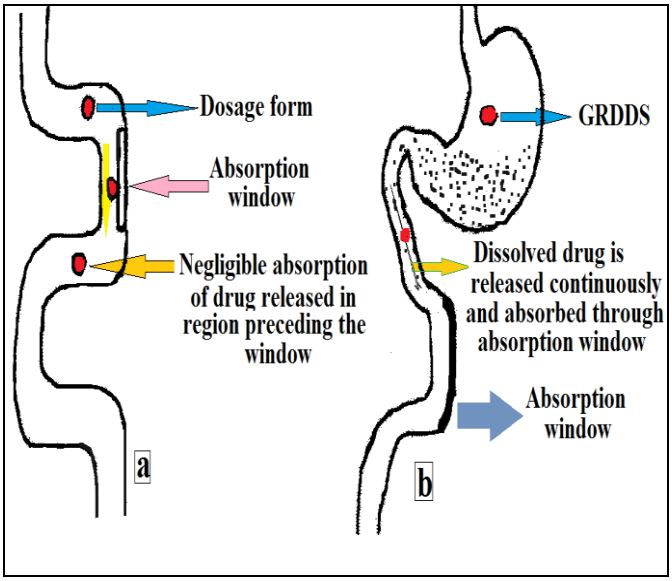

Fig 2: (a) Conventional drug delivery systems
(b) Gastroretentive drug delivery systems

The CRDDS possessing the ability of being retained in the stomach are called GRDDS and they can help in optimizing the oral controlled delivery of drugs having absorption window by continuously releasing drug prior to absorption window, for prolonged period of time thus ensuring optimal bioavailability [11].

Drugs that are required to be formulated into GRDFs include: [12-17]

- ✓ Drugs acting locally in the stomach.
  E.g. Antacids and drugs for H. Pylori viz., misoprostol
- ✓ Drugs that are primarily absorbed in the stomach.
  E.g. Amoxicillin, calcium supplements, chlordiazepoxide and cinnarazine.
- ✓ Drugs that is poorly soluble at alkaline pH
  E.g. Furosemide, diazepam, verapamil etc
- ✓ Drugs with a narrow window of absorption.
  E.g. Cyclosporine, methotrexate, riboflavin, levodopa etc
- ✓ Drugs rapidly absorbed from the GI tract.
  E.g. Metronidazole, tetracycline etc
- ✓ Drugs that degrade in the colon.
  E.g. Ranitidine, metronidazole, metformin HCl etc
- ✓ Drugs that disturb normal colonic microbes.
  E.g. Antibiotics against helicobacter pylori

Gastric motility and transit time

The GI tract is always in a state of continuous motility. There are two modes of motility patterns the digestive mode and inter digestive mode. In case of fasted state inter digestive series of electrical events occurs in cyclic manner both through stomach and small intestine every 2-3 hrs. This electrical activity is termed as inter digestive myoelectric cycle or 'migrating myoelectric complex' (MMC), which is further divided

into four phases. Inter digestive motility pattern shown below in figure 3.

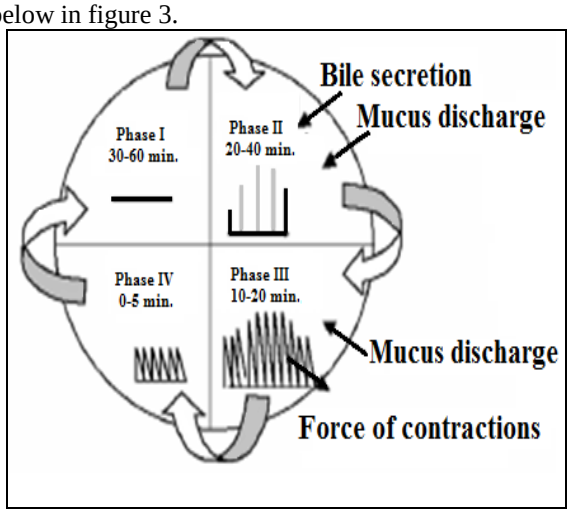

Fig 3: Schematic representation of inter digestive motility pattern, frequency of contraction forces during each phase and average time period for each phase

Phase-I: A quiescent period with no electrical activity and no contractions lasting between 40-60 minutes.
Phase-II: The period of random spike activity or intermittent contractions lasting between 20-40 minutes.
Phase-III: The period of regular spike bursts or regular maximal contraction lasting between 4-6 minutes. These are also called as 'housekeeper waves', since these sweep-undigested materials out of the stomach and down to small intestine.
Phase-IV: The transition period of 0-5 minutes between phase III and phase I.

The pattern and force of the motility vary depending on whether the human is in fed or fasted state. The above-mentioned time period is for fasted state. Thus most dosage forms administered in the fasted state empty in 0-90 minutes. In the fed state, non-disintegrating tablets and capsules stay in the stomach for 2-6 hour and are discharged only at the onset of fasted activity; table 1

Table1: Transit time of different dosage forms across the segments of GIT

Dosage form	Transit time (h)		
	Gastric	Small intestine	Total
Tablets	2.7±1.5	3.1±0.4	5.8
Pellets	1.2±1.3	3.4±1.0	4.6
Capsules	0.8±1.2	3.2±0.8	4.0
Oral solution	0.3±0.07	4.1±0.5	4.4

APPROACHES TO GASTRIC RETENTION

A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts [18]. Schematic representation of different approaches of GRDDS given below in figure 4;

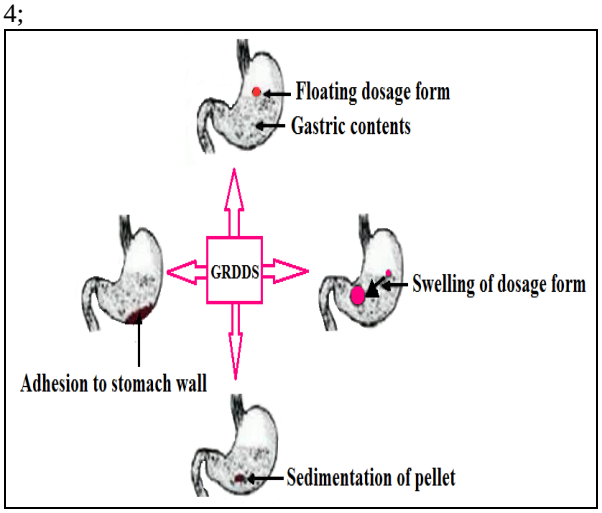

Fig 4: Approaches of gastroretentive drug delivery system

a) Floating systems

Floating drug delivery systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate; figure 5.

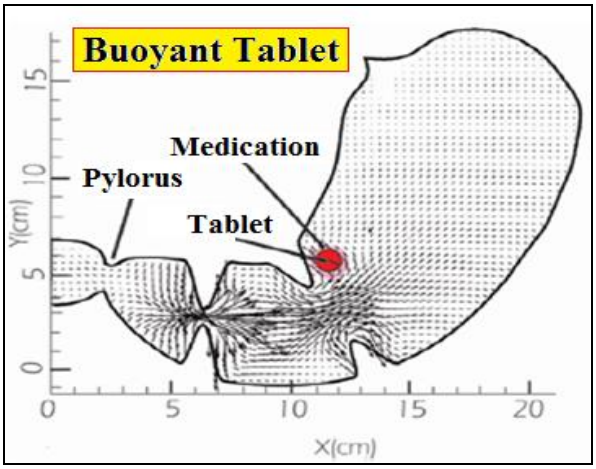

Fig 5: Graphic of buoyant tablet which is less dense than the stomach fluid and therefore remains in the fundus

While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. Floating systems can be classified into two distinct categories, non-effervescent and effervescent systems [19].

b) Bio or mucoadhesive systems

Bio or mucoadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the GRT of drug delivery system (DDS) in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane.

The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS based on bio or mucoadhesive polymers. The ability to provide adhesion of a drug (or a delivery system) to the GI wall provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect.

Binding of polymers to the mucin or epithelial surface can be divided into three broad categories [20].

Hydration mediated adhesion: Certain hydrophilic polymers tend to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties.

Bonding mediated adhesion: The adhesion of polymers to a mucus or epithelial cell surface involves various bonding mechanisms, including physical-mechanical bonding and chemical bonding. Physical-mechanical bonds can result from the insertion of the adhesive material into the folds or crevices of the mucosa. Chemical bonds may be either covalent (primary) or ionic (secondary) in nature. Secondary chemical bonds consist of dispersive interactions (i.e.,vander waals interactions) and stronger specific interactions such as hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl and carboxylic groups.

Receptor mediated adhesion: Certain polymers bind to specific receptor sites on the cell surfaces, thereby enhancing the gastric retention of dosage forms. Various investigators have proposed different mucin polymer interactions, such as:

- Wetting and swelling of the polymer to permit intimate contact with the biological tissue.
- Interpenetration of bioadhesive polymer chains and entanglement of polymer and mucin chains.
- Formation of weak chemical bonds.
- Sufficient polymer mobility to allow spreading.
- Water transport followed by mucosal dehydration.

The bioadhesive coated system when comes in contact with the mucus layer, various non-specific (Vander Waals, hydrogen bonding and/or hydrophobic interactions) or specific interactions occurs between the complimentary structures and these interactions last only until the turnover process of mucin and the drug delivery system should release its drug contents during this limited adhesion time, in order for a bioadhesive system to be successful.

c) Swelling and expanding systems

These are the dosage forms, which after swallowing; swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as "plug type system", since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state; figure 6

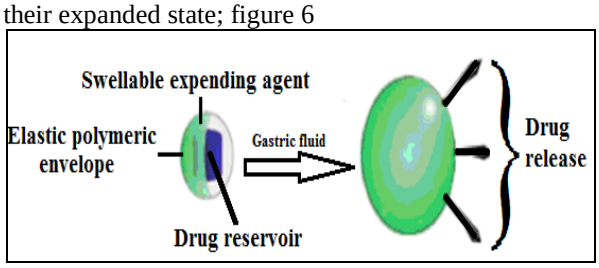

Fig 6: Swelling system

The formulation is designed for gastric retention and controlled delivery of the drug into the gastric cavity. Such polymeric matrices remain in the gastric cavity for several hours even in the fed state

A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system maintaining its physical integrity for prolonged period [13].

d) High density systems

These systems with a density of about 3 g/cm^3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements; figure 7.

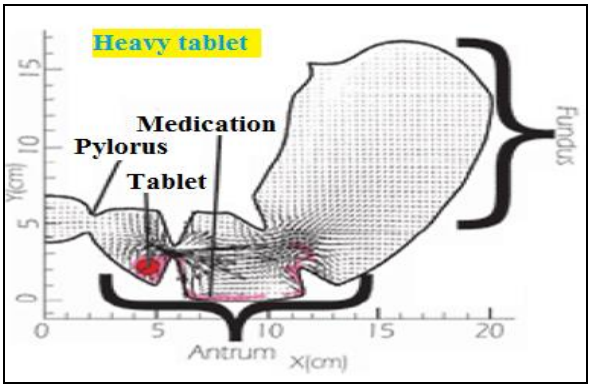

Fig 7: Graphic of heavy tablet which is denser than the stomach fluid and therefore sinks to the antrum

A density of 2.6-2.8 g/cm^3 acts as a threshold value after which such systems can be retained in the lower part of the stomach. High density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc. They are retained in the antrum of stomach [21]

e) Incorporation of passage delaying food agents

Food excipients like fatty acids e.g. salts of myristic acid change and modify the pattern of the stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in the gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C_{10}-C_{14} [22].

f) Ion exchange resins

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable 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 take place. As a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly [23].

g) Osmotic regulated systems

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bio-erodible capsule. In the stomach the capsule quickly disintegrates to release the intra-gastric osmotically controlled drug delivery device. The osmotic controlled drug delivery device consists of two components – drug reservoir compartment and osmotically active compartment [24].

h) Raft forming systems

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. A simple meaning of Raft is a flat structure, typically made of planks, logs, or barrels, that floats on water and is used for transport or as a platform for swimmers. Here also we are considering something that floats on gastric content of stomach. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO_2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense and float on the gastric fluids; figure 8.

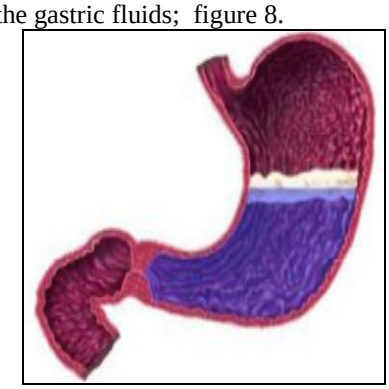

Fig 8: Schematic representation of raft forming system

The system contains a gel forming agent (e.g. alginic acid), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids. The raft thus formed floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the oesophagus by acting as a barrier between the stomach and oesophagus [25].

i) Super porous hydrogels

Conventional hydrogels, with pore size ranging between 10 nm and 10 µm has very slow process of water absorption and require several hours to reach an equilibrium state during which premature evacuation of the dosage form may occur while the super porous hydrogel, having average pore size (>100 µm), swell to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores [26]. Moreover they swell to a large size (swelling ratio 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contractions. This is achieved by a co-formulation of a hydrophilic particulate material, Ac-Di-Sol or CCS (crosscarmellose sodium); figure 9

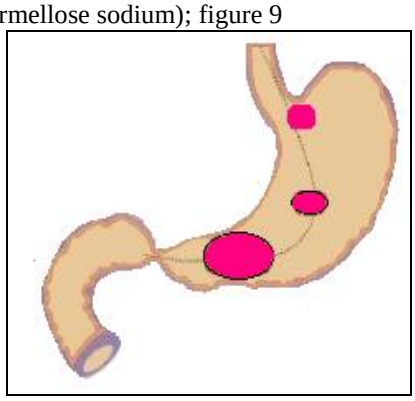

Fig 9: Schematic illustration of the transit of superporous hydrogel

Types of floating drug delivery systems (FDDS)

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

A. Effervescent system

B. Non- effervescent system

A. Effervescent system

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature

These effervescent systems further classified into two types.

I. Gas generating systems
II. Volatile liquid or vacuum containing systems

I. Gas generating Systems

These are formulated by intimately mixing the CO_2 generating agents and the drug within the matrix tablet. These systems are again classified into 3 categories

a. Intra-gastric single layer floating tablets (or) hydrodynamically balanced system (HBS)
b. Intra-gastric bi layer floating tablets
c. Multiunit type floating pills

a. Intra-gastric single layer floating tablets: These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach [27]. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration; figure 10.a.

b. Intra-gastric bi-layer floating tablets: These are also compressed tablet and containing two layers (Mamajek and Moyer, 1980). i.e., immediate release layer and sustained release layer; figure 10.b.

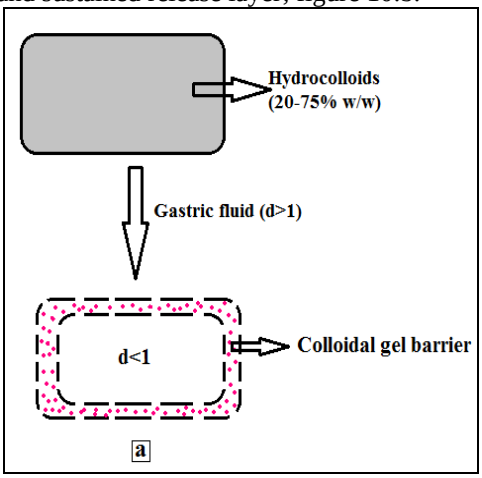

Fig 10: (a) Intra-gastric single layer floating table (b) Intra-gastric bi layer floating tablet

c. Multiple unit type floating pills: These systems consist of consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density [28]. This lower density is due to generation and entrapment of CO_2 within the system; figure 11.

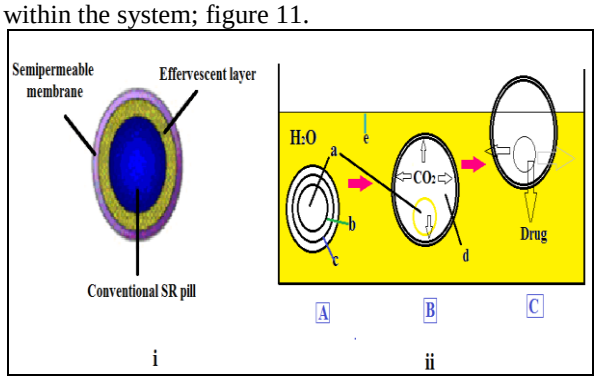

Fig 11: (i) Multi-unit oral floating dosage system (ii) Stages of floating mechanism: (A) Penetration of water (B) Generation of CO_2 and floating (C) Dissolution of drug key. (a) Conventional SR pills; (b) Effervescent layer; (c) Swellable layer; (d) Expanded swellable membrane layer; (e) Surface of water in the beaker

II. Volatile liquid or vacuum Containing Systems

These systems are classified into 3 categories
a. Intra gastric floating drug delivery system
b. Inflatable gastrointestinal delivery systems
c. Intra-gastric osmotically controlled drug delivery system

a. Intra-gastric floating gastrointestinal drug delivery system: These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microprous compartment [29]; figure12.

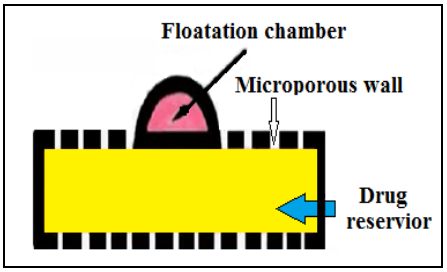

Fig 12: Intra-gastric floating gastrointestinal drug delivery device

b. Inflatable gastrointestinal delivery systems: In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach; figure 13.

These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach.

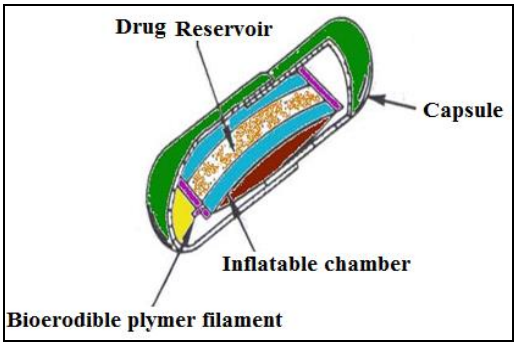

Fig 13: Inflatable gastrointestinal delivery system

The drug continuously released from the reservoir into the gastric fluid [30].

c. Intra-gastric osmotically controlled drug delivery system: It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intra-gastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment [31]. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi-permeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semi-permeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume, activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice; figure 14.

The floating support is also made to contain a bio-erodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.

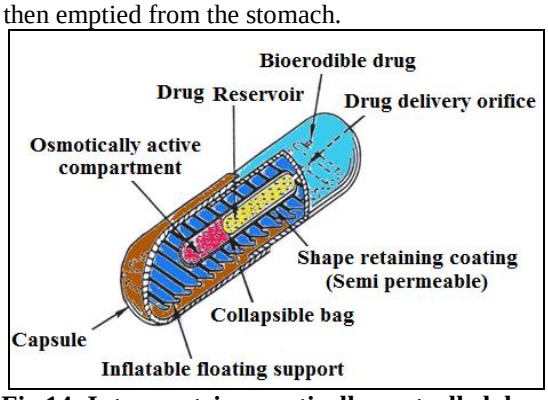

Fig 14: Intra-gastric osmotically controlled drug delivery system

B. Non-effervescent systems

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

The various types of this system are as [32, 33]

i. Single layer floating tablets

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

ii. Bi-layer floating tablets

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

iii. Alginate beads

Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence, time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours [34].

iv. Hollow microspheres

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40^0C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug [35]. The micro-balloons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours; figure 15.

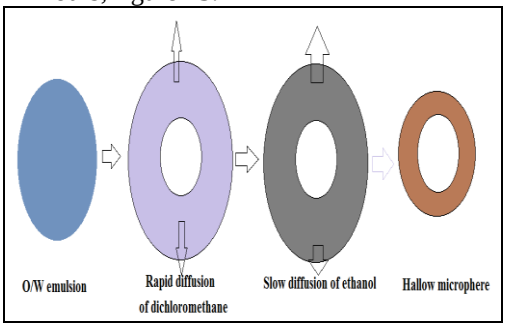

Fig 15: Hallow microspheres

EVALUATION OF GASTRORETENTIVE DOSAGE FORM

Evaluation of a drug product is a tool to ensure:

1. Performance characteristics
2. Control batch to batch quality

Apart from routine tests like general appearance, hardness and friability, drug content, weight variation, uniformity of content, disintegration time, drug release, etc., GRDDS need to be evaluated for gastroretentive performance by carrying out specific tests [36, 37].

I) *IN VITRO* EVALUATION

1) Floating systems

a) Floating lag time: It is determined in order to assess the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test.

b) Floating time: Test for buoyancy is usually performed in SGF Simulated Gastric Fluid maintained at 37^0C.The time for which the dosage form continuously floats on the dissolution media is termed as floating time [29].

c) Specific gravity or density: Density can be determined by the displacement method using Benzene as displacement medium.

d) Resultant weight: Now we know that bulk density and floating time are the main parameters for describing buoyancy. But only single determination of density is not sufficient to describe the buoyancy because density changes with change in resultant weight as a function of time. For example a matrix tablet with bicarbonate and matrixing polymer floats initially by gas generation and entrapment but after some time, some drug is released and simultaneously some outer part of matrixing polymer may erode out leading to change in resultant weight of dosage form [38]. The magnitude and direction of force or resultant weight (up or down) is corresponding to its buoyancy force (F_{buoy}) and gravity force (F_{grav}) acting on dosage form; figure16.

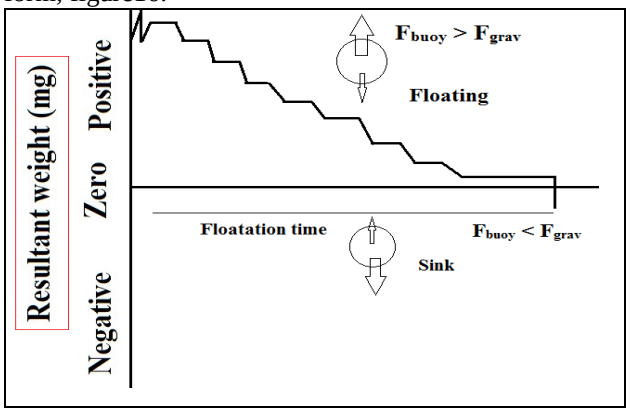

Fig 16: Swelling systems-water uptake

$$F = F_{buoy} - F_{grav}$$
$$F = Df_{\,g}\, V - Ds_{\,g}\, V$$
$$F = (Df - Ds)_{\,g}\, V$$
$$F = (Df - M/V)_{\,g}\, V$$

Where,

F = resultant weight of object
Df = Density of Fluid
DS = Density of Solid object
g = Gravitational force
M = Mass of dosage form
V = Volume of dosage form

So when Ds, density of dosage form is lower, F force is positive gives buoyancy and when it is Ds is higher, F will negative shows sinking.

2) Swelling systems

a) Swelling index: After immersion of swelling dosage form into SGF at 37^0C, dosage form is removed out at regular interval and dimensional changes are measured in terms of increase in tablet thickness or diameter with time.

b) Water uptake: It is an indirect measurement of swelling property of swellable matrix. Here dosage form is removed out at regular interval and weight changes are determined with respect to time.

So it is also termed as Weight Gain.

Water uptake = $W_U = (W_t - W_o) * 100 / W_o$

Where, W_t = Weight of dosage form at time t; W_o = Initial weight of dosage form

II) *IN VITRO* DISSOLUTION TESTS

In vitro dissolution test is generally done by using USP apparatus with paddle and GRDDS is placed normally as for other conventional tablets [39, 40].

i. But sometimes as the vessel is large and paddles are at bottom, there is much lesser paddle force acts on floating dosage form which generally floats on surface. As floating dosage form not rotates may not give proper result and also not reproducible results. Similar problem occur with swellable dosage form, as they are hydrogel may stick to surface of vessel or paddle and gives irreproducible results. In order to prevent such problems, various types of modification in dissolution assembly made are as follows

ii. To prevent sticking at vessel or paddle and to improve movement of dosage form, method suggested is to keep paddle at surface and not too deep inside dissolution medium.

iii. Floating unit can be made fully submerged, by attaching some small, loose, non- reacting material, such as few turns of wire helix, around dosage form. However this method can inhibit three dimensional swelling of some dosage form and also affects drug release. Figure 17 shows *in vitro* dissolution test for different GRDDS.

iv. Other modification is to make floating unit fully submerged under ring or mesh assembly and paddle is just over ring that gives better force for movement of unit.

v. Other method suggests placing dosage form between 2 ring/meshes.

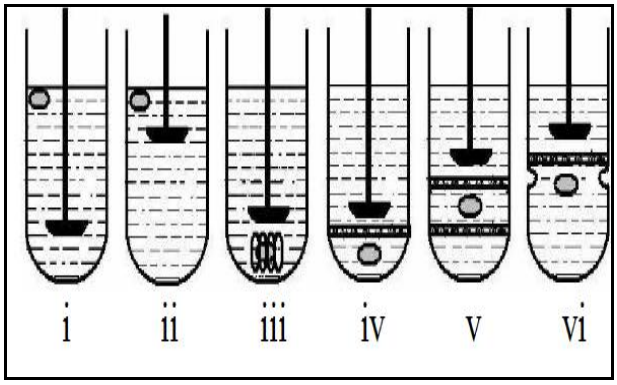

Fig 17: *In vitro* Dissolution tests

vi. In previous methods unit have very small area, which can inhibit 3D swelling of swellable units, another method suggest the change in dissolution vessel that is indented at some above place from bottom and mesh is place on indented protrusions, this gives more area for dosage form.

In-spite of the various modifications done to get the reproducible results, none of them showed correlation with the *in vivo* conditions. So a novel dissolution test apparatus with modification of Rossett-Rice test apparatus was proposed [41].

III) *IN VIVO* EVALUATION

Different tests were included, such as radiology, scintigraphy, gastroscopy, magnetic marker monitoring and ultrasonography etc., [42].

a) Radiology: X-ray is widely used for examination of internal body systems. Barium Sulphate is widely used Radio Opaque Marker. So, $BaSO_4$ is incorporated inside dosage form and X-ray images are taken at various intervals to view gastric residence (GR).

b) Scintigraphy: Similar to X-ray, emitting materials are incorporated into dosage form and then images are taken by scintigraphy. Widely used emitting material is Tc_{99}.

c) Gastroscopy: It is peroral endoscopy used with fiber optics or video systems. Gastroscopy is used to inspect visually the effect of prolongation in stomach. It can also give the detailed evaluation of GRDDS.

d) Magnetic marker monitoring: In this technique, dosage form is magnetically marked with incorporating iron powder inside, and images can be taken by very sensitive bio-magnetic measurement equipment. Advantage of this method is radiation less and so, not hazardous.

e) Ultrasonography: Used sometimes, not used generally because it is not traceable at intestine.

f) 13C Octanoic acid breath test: In stomach due to chemical reaction, octanoic acid liberates CO_2 gas which comes out in breath. The important Carbon atom which will come in CO_2 is replaced with 13C isotope. So time up to which $13CO_2$ gas is observed in breath can be considered as gastric retention time of dosage form. As the dosage form moves to intestine, there is no reaction and no CO_2 release. So this method is cheaper than other.

FACTORS AFFECTING GASTRIC RETENTION TIME OF THE DOSAGE FORM

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

Age: People with age more than 70 have a significant longer GRT.

Density: The density of the dosage form should be less than that of the gastric contents (1.004g/ml)

Size: Dosage form having diameter of more than 7.5mm have more gastric residence time than that of 9.9mm diameter dosage form [43].

Shape of the dosage form: The tetrahedron resided in the stomach for longer period than other devices of similar size.

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

Fed or unfed state: Under fasting conditions, the GI motility is characterized by periods of strong motar activity that occur every 1.5 to 2 hrs. The MMC sweeps undigested material from the stomach and if the timing of the formulation coincides with that of MMC, the GRT of the unit can be very short, however in fast state MMC is delayed and GRT is longer [44].

Nature of meal: Feeding of indigestible polymers or fatty acids can change the motility pattern of the stomach to a fed state, thus decreasing gastric emptying rate and prolonging drug release [45].

Caloric content: GRT can be increased by 4-10 with a meal that is high in protein and fat.

Frequency of feed: The GRT can be increasing over 400 min. when successive meals given are compared with the single meal due to low frequency of MMC.

Gender: Mean ambulatory GRT in male (3.4hrs) is less compared with the age and race matched female counter parts (4.6hrs) regardless of height, weight and body surface [46].

Concomitant drug administration: Anti-cholinergic like atropine and propetheline, opiates like codeine can prolong GRT.

MERITS

GRDDS have following advantages [47, 48]:

- ✓ Delivery of drugs with narrow absorption window in the small intestine region.
- ✓ Longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease.
- ✓ Improved bioavailability is expected for drugs that are absorbed readily upon release in the GIT such as cyclosporine, ciprofloxacin, ranitidine, amoxycillin, captopril, etc.
- ✓ Patient compliance by making a once a day therapy.

- ✓ Improved therapeutic efficacy.
- ✓ Improved bioavailability due to reduced P-glycoprotein activity in the duodenum.
- ✓ Reduces frequency of dosing.
- ✓ Targeted therapy for local ailments in the upper GIT.

DEMERITS

GRDDS have some disadvantages given below [49]

- × Unsuitable for drugs with limited acid solubility.
  E.g. Phenytoin
- × Unsuitable for drugs those are unstable in acidic environment.
  E.g. Erythromycin
- × Drugs that irritates or causes gastric lesions on slow release.
  E.g. Aspirin and other NSAID's
- × Drugs that absorb selectively in colon.
  E.g. Corticosteroid
- × Drugs that absorb equally well through GIT.
  E.g. Isosorbide dinitrate, nifidipine

LIMITATIONS

GRDDS have potential in improving bioavailability of drugs exhibiting 'absorption window'. However they have certain limitations

- ❖ They require high levels of fluids in stomach for the delivery system to float and work efficiently. So more water intake is prescribed with such dosage form.
- ❖ In supine posture (like sleeping), floating dosage form may swept away (if not of larger size) by contractile waves. So patient should not take floating dosage form just before going to bed.
- ❖ Drugs having stability problem in high acidic environment, having very low solubility in acidic environment and drugs causing irritation to gastric mucosa cannot be incorporated into GRDDS.
- ❖ Bio or mucoadhesives systems have problem of high turnover rate of mucus layer, thick mucus layer and soluble mucus related limitations.
- ❖ Swellable dosage form must be capable to swell fast before its exit from stomach and achieve size larger than pylorus aperture. It must be capable to resist the housekeeper waves of Phase III of MMC.

Table 2: List of various drugs commonly used in GRDDS

Dosage Forms	Drugs
Floating Tablets	Aceclofenac [50], ambroxol [51], Amoxycillin trihydrate [52], Atenolol [53], Captopril [54], cephalexin [55], Cinnerazine [56], Bergenin and Cetirizine dihydrochloride [57], Ciprofloxacin [58], Diclofenac sodium [59], Diltiazem hydrochloride [60], Fluorouracil [61], Glipizide [62], Ibruprofen [63], Ketoprofen [64], Pioglitazone [65], Nimodipine [66], Ranitidine hydrochloride [67], Theophylline [68, 69], Tizanidine hydrochloride [70], Venlafaxine hydrochloride [71], Verapamil hydrochloride [72] etc.
Floating Granules	Diclofenac sodium [73], Indomethacin [74] etc.
Floating Capsules	Furosemide [75], Nicardipine [76], Misoprostol [77], Propranolol hydrochloride [78], Cephalosporin [79] etc.
Floating Microspheres	Atenolol [80], Griseofulvin [81], Famotidine[82], Ibuprofen [83], Terfenadine [84], Tranilast Cinnarizine [85] etc.

Table 3: List of various polymers and other ingredients used in GRDDS

Category	Materials
Polymers	**Cellulose polymers:** HPMC K4 M, HPMC K15, HPMC K100 and HPMC 4000 etc. **Eudragits:** Eudragit S100, eudragit RL, eudragit RS, eudragit S etc. **Alginates:** Calcium alginate, sodium alginate etc. **Others:** PEO, PVA, PVP, PEG, carbopol, polycarbonate, acrylic polymer etc.
Effervescent agents	Citric acid, citroglycine, di-sodium glycine carbonate, sodium bicarbonate, tartaric acid etc.
Low density material	Glyceryl palmitostearate, glyceryl behenate, polypropylene foam powder etc.
Buoyancy increasing agents (up to 80%)	Ethyl cellulose
Inert fatty materials (5%-75%)	Beeswax, fatty acids, long chain fatty alcohols, gelucires® 39/01 and 43/01 etc.
Release rate retardants (5% - 60%)	Di-calcium phosphate, talc, magnesium stearate etc.
Release rate accelerants (5% - 60%)	Lactose, mannitol etc.

Table 4: List of various gastroretentive marketed formulations

Sl. No.	Brand name	Drug	Manufacturer	Country
1	Liquid Gaviscon	Al. Hydroxide and Mg. Carbonate	Glaxosmithkline	India
2	Conviron	Ferrous sulphate	Ranbaxy	India
3	Cifran OD	Ciprofloxacin	Ranbaxy	India
4	Oflin OD	Ofloxacin	Ranbaxy	India
5	Madopar	Levodopa and Benserazide	Roche	USA
6	Cytotec	Misoprostol	Pharmacia	USA
7	Valrelease	Diazepam	Roche	USA
8	Topalkan	Al-Mg antacid	Pierre fabre	France

CONCLUSION:

To derive maximum therapeutic benefits from certain drug substances, it is desirable to prolong their gastric residence time. It provides several advantages including greater flexibility and adaptability gives clinicians and those engaged in product development powerful new tools to optimize therapy. The increasing sophistication of delivery technology will ensure the development of increasing number of gastroretentive drug delivery systems to optimize the delivery of molecules that exhibit narrow absorption window, low bioavailability and extensive first pass metabolism. The control of gastro intestinal transit could be the focus of the next decade and may result in new therapeutic possibilities with substantial benefits for patient.

FUTURE PROSPECTS:

In the future, it can be easily assumed that GRDDS will become more popular in delivering drugs to the systemic circulation with improving efficiency of various types of pharmacotherapies.

REFERENCES:

1.Rouge N, Buri P, Doelker E. Drug absorption sites in the gastrointestinal tract and dosage forms for Site specific delivery. Int J Pharma, 1996; 136:117-139.

2.Brahmankar DM, Jaiswal SB. 1995. Biopharmaceutics and pharmacokinetics - a Treatise. Vallabh Prakashan.

3.Lachman L, Lieberman HA, Joseph KL. 1996. The theory and practice of industrial pharmacy: 2nd ed. Bombay: Varghese Publishing House, 171-196.

4.Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery system, Exp Opin Drug Del, 2006; 3: 217-233.

5.Lee TW, Robinson JR. 2000. Controlled release drug delivery systems: In Gennaro, A.R. (ed.) Remington Pharmaceutical Sciences, 20th ed. Lippincott Williams and Willkins, Philadelphia. 903-929.

6.Chien YW. 1992. Concepts and system design for rate controlled drug delivery in novel drug delivery system, 2nd ed. New York: Marcel Dekker Inc.

7.Ali J, Arora S, Khar R K. Floating drug delivery system - A review. AAPS Pharm Sci Tech, 2005; 6: E372-E390.

8.Madhusudan Rao Y, Jithan AV. 2011. Advances in drug delivery. Hyderabad: Pharm Med Press.

9.Mayavanshi AV, Gajjar SS. Floating drug delivery systems to increase gastric retention of drugs - A review, Research J Pharm Tech, 2008; 1: 1-4.

10.Robinson JR, Vincent HL. 2009. Controlled drug delivery. Fundamentals and applications, 2nd en. New York: Marcel Dekker Inc.

11.Klausner EA, Eyal S, Lavy E, Friedman M, Hoffman A. Novel levodopa gastroretentive dosage form: *In vivo* evaluation in dogs. J Contr Rel, 2003; 88:117– 126.

12.Thaherabanu S, Sundaram AM, Umasankar K. Review on gastroretentive drug delivery system. Int J Res Pharm and Nano Sci, 2014; 3: 177 - 185.

13.Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled release system for gastric retention. Pharm Res, 1997; 14: 815-819

14.Davis SS, Stockwell AF, Taylor MJ, Hardy JG, Whalley DR, Wilson CG, Bechgard H, Christensen FN. The effect of density on the gastric emptying of single and multiple unit dosage forms. Pharm Res, 1986; 3: 208-213.

15.Lehr CM. Bioadhesive technologies for the delivery of peptide and protein drugs to the gastrointestinal tract. Crit Rev Ther Drug Car Syst, 1994; 11: 119-160.

16.Groning R, Heun G. Oral dosage forms with controlled gastrointestinal transit. Drug Dev Ind Pharm, 1984; 10: 527-539.

17.Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage forms. J Contr Rel, 2003; 90: 143-162.

18.Bhowmik D, Chiranjib B, Chandira M, Jayakar B, Sampath Kumar P. Floating Drug Delivery System - A review. Der Pharm Let, 2009; 1: 199-218.

19.Banker GS, Rhodes CT. 2007. Modern pharmaceutics, Revised and expanded, 4th ed. New York: Marcel Dekker Inc.

20.Sanjay G, Sharma S. 2003. Gastroretentive drug delivery systems. In: Business briefing, Pharmatech. 5th ed. 160 – 66.

21.Bechgaard H, Ladefoged K. Distribution of pellets in gastrointestinal tract. The influence on transit time exerted by the density or diameter of pellets. J Pharm Pharmac, 1978; 30: 690-692.

22.Chitnis VS, Malshe VS, Lalla JK. Bioadhesive polymers synthesis, evaluation and application in controlled release tablets. Drug Dev Ind Pharm, 1991; 17: 879-92.

23.Hejazi R, Amiji M. Stomach-specific anti-H. Pylori therapy: II. Gastric residence studies of tetracycline - loaded chitosan microspheres in gerbils, Pharm Dev Tech, 2003; 8: 253–262.

24.Urquhart J, Theeuwes F. Drug delivery system comprising a reservoir containing a plurality of tiny pills, US Patent 4, 434; 153: 1984.

25.Vinod K, Santhosh V, Anbuazaghan S, David B, Padmasri A, Sandhya S. Approaches for gastroretentive drug delivery systems. Int J App Bio Pharm Tech, 2010; 1: 589-601.

26.Punitha S, Sabitha G, Vishal K, Rajasekar S. Floating drug delivery system: Chronotherapeutic Approach. Int Res J Phar, 2011; 2: 38-45.
27.Mamajek RC, Moyer ES. Drug - dispensing device and method. US Patent 4, 207; 890: 1980.
28.Rednick AB, Tucker SJ. Sustained release bolus for animal husbandry. US Patent 3, 507; 952: 1970.
29.Singh BN, Kim KH. Floating drug delivery systems: An approach to oral controlled drug delivery via gastric retention. J Contrl Rel, 2000; 63: 235-259.
30.Ritschel WA. Targeting in the gastrointestinal tract: New approaches, methods find. Exp Cl Phar 1991; 13:313-336.
31.Ozdemir N, Ordu S, Ozkan Y. Studies of floating dosage forms of furosemide: *In vitro* and *in vivo* evaluation of bilayer tablet formulations. Drug Dev Ind Pharm, 2000; 26: 857-66.
32.Fassihi R, Yang L, Eshraghi J. A new intra-gastric delivery system for the treatment of H. pylori associated gastric ulcer: *In vitro* evaluation. J Contr Rel, 1999; 57: 215-22.
33.Clarke GM, Newton JM, Short MB. Comparative gastrointestinal transit of pellet system of varying density. Int J Pharm, 1995; 114: 1-11.
34.Whitehead L, Fell JT, Collett JH. Development of a gastroretentive dosage form. Eur J Pharm Sci, 1996; 4:182.
35.Goyal M, Prajapati R, Purohit KK, Mehta S. Floating drug delivery system. J Cur Pharm Res, 2011; 5: 7- 18.
36. Sunil K, Faraz J, Meenu R, Saurabh S. Gastroretentive drug delivery system: Features and facts. Int J Res Pharma Bio Sci, 2012; 3: 125-136.
37.Arora S, Ali J, Ahuja A, Khar R.K, Baboota S. Floating drug delivery systems: A review, AAPS Pharm Sci Tech, 2005; 6: E372-390.
38.Sangekar S, Vadino WA, Chaudry I, Parr A, Beihn R, Digenis G. Evaluation of effect of food and specific gravity of tablets on gastric retention time. Int J Pharm, 1987; 35: 187-191.
39.Rajeev KM, Satyanarayana B, Nagakanyaka DP, Kondavamsi N, Muddasar S, Irfan PS, Spandana V, Deepthi P. A comprehensive review on gastroretentive drug delivery system. Acta Chim Pharm Ind, 2013; 3: 149-164.
40.Nath B, Nath LK, Mazumdar B, Sharma NK, Sarkar MK. Preparation and *in vitro* Evaluation of Gastric Floating Microcapsules of Metformin HCl. Ind J Pharm Edu Res, 2009;43: 177-186.
41.Burns SJ, Corness D, Hay G. Development and validation of an *in vitro* dissolution method for a floating dosage form with biphasic release characteristics. Int J Pharm, 1998; 121:213.
42.Asane GS. 2007. Mucoadhesive Gastrointestinal drug delivery system: An overview. 5 (6): Available at www.pharmainfo.net.
43.Devkant S, Anjali S. Gastroretentive drug delivery system – A mini review. Asian Pac J Heal Sci, 2014; 1: 80-89.
44.Robinson JR, Lee R. 1987. Controlled drug delivery, 2nd en. New York: Marcel Dekker, Inc. 418.
45.Bardonnet PL, Faivre V, Pugh WJ, Piffaretti JC, Falson F. Gastroretentive dosage forms: overview and special case of Helicobacter pylori. J Contl Rel, 2006; 111: 1-18.
46.Patel GM, Nagesh C, Chandrashekhar S, Patel HR, Jani D. Floating drug delivery system: An innovative acceptable approach in gastroretentive drug delivery. Asi J Pharm Res, 2012; 2: 07-18.
47.Wilson CG, Washington N. 1989. The stomach: Its role in oral drug delivery. In: Rubinstein, MH ed. Physiological pharmaceutical: biological barriers to drug absorption. Ellis Harwood, Chichester: 47-70.
48.Garg R, Gupta GD. Progress in controlled gastroretentive delivery. Trop J Phar Res, 2008; 7: 1055-1066.
49.Amit Kumar N, Ruma M, Biswarup D. Gastroretentive drug delivery system: A review. Amer J Adv Drug Del, 2010; 3: 2-10.
50.Brahma Reddy A, Samyuktha RB, Eswar TD, Raja SD, Sindhura L, Sarath Kumar N. Aceclofenac floating tablets – A promising sustained release dosage form. Int J Drug Dev Res, 2011; 3: 290-300.
51.Preeti M, Devadasu VR, Vemula SK, Venisetty RK, Saritha CH. Formulation and evaluation of floating drug delivery system of Ambroxol tablets. Int J pharm sci let, 2013; 4: 333-338.
52.Radhakrishna M, Parthiban KG, Ramarao N, Santhoshi DN, Abhishek P. Formulation and evaluation of floating drug delivery system of amoxicillin trihydrate. Int Res J pharm, 2012; 3: 233-237.
53.Ashok PH, Pooja RG, Rachana VD,Pooja RJ, Pushpita PR. Development and evaluation of gastroretentive floating tablets of an antihypertensive drug using hydrogenated cottonseed oil. ISRN Pharm, Hindawi Publishing Corporation. 2013; 2013: 1-9.
54.Sameer S, Kalpana P, Pathak AK, Mishra A . Formulation and evaluation of floating tablet of captopril. Int J Phar Res, 2011; 3: 333-341.
55.Anil Kumar JS, Arun NW, Manoj BP, Harinath NM. Formulation and *in vitro* evaluation of sustained release floating tablet of cephalexin using hydrophilic polymers, Int J Pharmacy Pharm Sci, 2010; 2:58-65.
56.Dhaval KV, Pujara N, Kanzariya V, Doshi S. Formulation and evaluation of cinnarizine floating tablet for improved absorption. Inventi Rapid: NDDS, 2013; 4: 1-5.
57.He S, Li F, Zhou D, Du J, Huang Y. Formulation and evaluation of novel coated floating tablets of bergenin and cetirizine dihydrochloride for gastric delivery. Drug Dev Ind Pharm, 2012; 38:1280-8.
58.Upendarrao G, Bharath KN, Rasagny T, Praveen KG, Sandeep KV. Formulation and *in vitro* evaluation of gastroretentive drug delivery system of ciprofloxacin hydrochloride. Der Pharmacia Sinica, 2011; 2:33-39.
59.Garepally P, Vemula SK, Bontha VK, Chilukala S. Formulation and evaluation of oral gastroretentive tablets of diclofenac sodium using natural resin mangifera indica. Inv Rap: Pharm Tech, 2010; 1: 1-6.
60.Patel H, Manish J. Formulation development and evaluation of diltiazem hydrochloride gastro retentive floating tablets. J Drug Del Ther, 2013; 3: 48-55.
61.Wei ZP, Huang L, Han J, Li Y. Preparation of the 5-Fu floating sustained release tablet for gastric retention. Beijing Da Xue Xue Bao, 2004; 36: 439-42.
62.Nirav P, Nagesh C, Jinal P, Chandrashekhar S, Jani D. Formulation and evaluation of floating tablet containing glipizide. Asian J. Pharm. Tech, 2012; 2: 135-140.
63.Chandrasekhara Rao B, Vidyadhara S, Raghavendra Rao KV, Vanitha PK, Umashankar B. Formulation and evaluation of ibruprofen floating tablets. Int J Pharma Chem Bio Sci, 2012; 2: 472-481.
64.Manjula B, Ishaq MB, Hari Kumar C, Usha RG. Formulation and evaluation of gastroretentive floating drug delivery system of ketoprofen. Der Pharmacia Lettre, 2010; 2: 197-208.
65.Seth M, Goswami DS, Dhaliwal H, Uppal N, Kashyap S, Sharma KD. Design and characterization of floating tablets of anti-diabetic drug. Int J Res Pharm Chem, 2013; 3: 605-611.

66.Ajaykumar P, Shaik M, Gulam I. Floating tablets of nimodipine and its inclusion complex with β-cyclodextrin for controlled release. Int J Pharm Res, 2011; 3: 619-625.
67.Gharti KP, Thapa P, Budhathoki U, Bhargava A. Formulation and *in vitro* evaluation of floating tablets of hydroxypropyl methylcellulose and polyethylene oxide using ranitidine hydrochloride as a model drug. J Young Pharm, 2012; 4: 201–208.
68.Bijumol C, Helen W, Jose K, Thomas K. Formulation and evaluation of floating tablets of theophylline. Hygeia. J D Med, 2013; 5: 23-31.
69.Khan F, Razzak ISM, Khan ZR, Azad MA, Chowdhury JA, Reza S. Theophylline loaded gastroretentive floating tablets based on hydrophilic polymers: preparation and *in vitro* evaluation. Pak J Pharm Sci, 2009; 22: 155-61.
70.Vishwateja B, Vemula SK, Garepally P, Bontha VK. Formulation and evaluation of gastroretentive floating tablets of tizanidine hydrochloride. Inst J pharm sci, 2012; 2: 36-49.
71.Ashok PH, Rachana D. Development and evaluation of gastroretentive floating tablets of an antidepressant drug by thermoplastic granulation technique. Beni-Suef Univer J Basic App Sci, 2014; 3:122–132.
72.Dawange SR, Khadabadi SS, Saboo SS. Formulation and evaluation of floating tablets of verapamil hydrochloride by using gastroretentive technology. Int. J. Pharm. Sci. Rev. Res, 2015; 34: 263-269.
73.Zadeh MBS, Jamei T, Rahim F, Abbaspur M. Multiple unite sustained released floating of sodium diclofenac: Formulation and evaluation using factorial design. Int J Drug Del, 2010; 2: 344-351.
74.Jitendra J, Bhavna HM, Mittal RP, Mandev P. Formulation and evaluation of indomethacin bilayer sustained release tablets. Int J Pharm Res, 2011; 3: 1132-1138.
75.Vishal GK, Manish AS, Ritesh R. Formulation and evaluation of floating tablets of furosemide. Int J Pharma Res Dev, 2010; 1: 1-9.
76.Moursy NM, Afifi NN, Ghorab DM, El-Saharty Y. Formulation and evaluation of sustained release floating capsules of nicardipine hydrochloride. Pharmazie, 2003; 58: 38-43.
77.Neelima G, Mukul T, Pathak AK. Formulation, optimization and *in vitro* evaluation of floating tablet of misoprostol. World J Pharm Res, 2014; 3: 649-659.
78.Koteswara Rao GSN, Ramana Murthy KV, Aayisha B, Roja Rani B, Ragha Naveen CH, Raj Kumar B, Uma Devi P. Formulation and evaluation of floating drug delivery systems of propranolol HCl using modified pulsincap technique. Int J Phar Res Rev, 2014; 3:15-22.
79.Darshan P, Shivakumar S. Formulation and evaluation of floating capsules of 3rd generation cephalosporin. Int J Pharm Res, 2012; 4; 986-993.
80.Ashok T, Harish C, Mukesh P, Arvind D, Chatterjee D. P. Formulation and evaluation of floating microspheres of atenolol. Pan J Pharm Pharma Sci, 2015; 4: 654-679.
81.Vojnovic D, Rubessa F, Bogataj M, Mrhar A. Formulation and evaluation of vinylpyrrolidone or vinylacetate copolymer microspheres with griseofulvin. J Microencapsul. 1993; 10: 89-99.
82.Rishikesh G, Prajapati SK, Snigdha P, Apoorva G, Sapna M. Performance and evaluation of floating microspheres of famotidine and comparison of their physical properties. Int J Pharm Pharma Sci, 2012; 4: 376-382.
83.Burcu D, Kandemir C. Preparation and evaluation of modified release ibuprofen microspheres with acrylic polymers (eudragit®) by quasiemulsion solvent diffusion method: effect of variables. Acta Polon Pharma Drug Res, 2006; 63: 521-534.
84.Jayanthi G, Jayaswal SB, Srivastava AK. Formulation and evaluation of terfenadine microballoons for oral controlled release. Pharmazie, 1995; 50:769-70.
85.Arabinda P, Shubhrajit M. Formulation and evaluation of gastroretensive floating microsphere of cinnarizine. Asian J Pharm Cli Res, 2012; 5: 100-109.