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GASTRO RETENTIVE DRUG DELIVERY SYSTEM: A COMPREHENSIVE REVIEW

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ABSTRACT

In recent years several advancements has been made in research and development of oral drug delivery system. Gastro retentive drug delivery system is one such novel approach in which the delivery system retains in the stomach for a prolonged period and hence availability of the drug for its absorption is increased. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. Purpose of this review is to compile the recent literature with special focus on various gastro retentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery. This article gives an overview on approaches, rational, advantages & disadvantages of gastro retentive drug delivery systems. This review also includes few recent trends and marketed formulations of gastro retentive drug delivery.

Key Words: Gastro retention, Floating Systems, Raft Forming System, Gastric retention time

INTRODUCTION

Drug delivery refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect. Conventional oral dosage forms provide specific drug concentration in systemic circulation without offering any control over drug delivery [1].Unlike the majority of parenteral dosage forms, it allows ease of administration by the patient and it's the natural, and therefore a highly convenient way for substances to be introduced into the human body. Oral drug delivery systems (DDS) are divided into immediate release and modified release systems. Immediate release DDS are intended to disintegrate rapidly, and exhibit instant drug release [2]. Modified release systems, on the other hand, have been developed to improve the pharmacokinetic profiles of active pharmaceutical ingredients (APIs) and patient compliance, as well as reducing side effects. Oral modified release delivery systems are most commonly used for Delayed release (e.g., by using an enteric coating),

Extended release (e.g., zero-order, first-order, biphasic release, etc.), Programmed release (e.g., pulsatile, triggered, etc.) and Site specific or timed release.

Oral and sustained drug delivery systems has several physiological problems as drug delivery is usually incomplete, highly dependent on patient compliance, increased drug- drug, and drug- food interactions and drugs are also exposed to first pass effect. These drug delivery system also have two main drawback first is short gastric retention time (GRT) and second unpredictable have short gastric emptying time, which can result in incomplete drug release from the dosage form in the absorption zone (Stomach or upper part of small intestine) leading to diminished efficacy of administered dose. Gastric emptying of dosage form is extremely variable process and ability to prolong and control the emptying time is valuable asset for dosage forms, which reside in the stomach for a long period of time than conventional dosage forms [3, 4].

These difficulties have prompted researchers to design a drug delivery system which can stay in the stomach for prolonged and predictable period. To formulate a site-specific orally administered controlled release dosage form it is desirable to achieve prolong gastric residence time by the drug delivery. Prolonged gastric retention time in the stomach is useful for local action [3]. One novel approach in this area is GRDDSs (gastro retentive drug delivery system). GRDFs greatly improves the pharmacotherapy of stomach by releasing the drug locally and thus results into high concentration of drug at the gastric mucosa which can be sustained over a longer duration[4].

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment.GRDDS are designed on the basis of delayed gastric emptying and are intended to restrain and localize the drug delivery device in the stomach or within the upper parts of the small intestine until all the drug is released [4, 5].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 its absorption site [5].

Anatomy of the Gastrointestinal Tract

The gastrointestinal tract can be divided into three main regions namely

1. Stomach
2. Small intestine- Duodenum, Jejunum and Ileum
3. Large intestine

The organization of the GIT, from stomach to large intestine, is shown in Fig.1. The stomach is a J-shaped enlargement of the GIT which can be divided into four anatomical regions: cardia, fundus, body and antrum. When empty, the stomach occupies a volume of about 50 ml, but this may increase to as much as 1 litre when full [6].

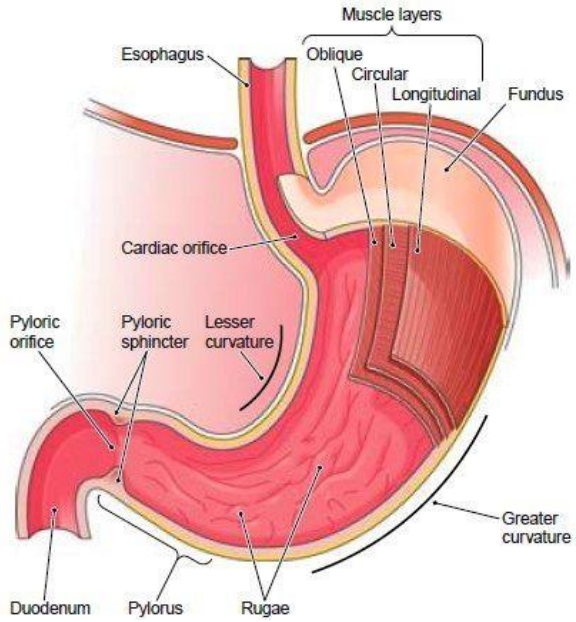


Fig: 1 Anatomy of the gastrointestinal tract

The walls of the GIT, from stomach to large intestine, have the same basic arrangement of tissues, the different layers, from outside to inside, comprising serosa, longitudinal muscle, intermuscular plane, circular muscle, submucosa, muscularis mucosae, lamina propria and epithelium. In addition to longitudinal and circular muscle, the stomach has a third muscle layer known as the "oblique muscle layer", which is situated in the proximal stomach, branching over the fundus and higher regions of the gastric body. The different smooth muscle layers are responsible for performing the motor functions of the GIT, i.e. gastric emptying and intestinal transit [7].

Anatomy and Physiology of Stomach

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. Pyloric antrum is separated from duodenum by the narrow and tubular pyloric canal. The mucosa of empty stomach contains longitudinal folds known as gastric rugae. The stomach is supplied by sympathetic nerves derived from T_6-T_{10} segments of the spinal cord, and parasympathetic nerves derived from vagi. Stimulation of parasympathetic nerves results in increased motility of stomach and secretion of gastric juice containing HCl and pepsin[6]. The physiological behavior of stomach varies, when it is empty or contains food. The nature of the GI motor functions is determined mainly by the stimulating effects of food in the GIT. When food enters the stomach, due to vagovagal reflex the muscular tone of the body wall of stomach reduces enabling it to expand outward and accommodating more quantities of food [8].

Weak peristaltic constrictor waves initiated by the basic electrical rhythm begin in the mid portion of the stomach wall and move towards the antrum at every 15-20s. These constrictor waves intensify as they proceed towards antrum, providing powerful constrictor rings which force the antral contents towards the pylorus at a high pressure. Because of these stomach contractions, the partially digested food is discharged into the small intestine and the undigested food is retropelled into the main part of the stomach for further digestion. At the end of digestion process, the stomach enters fasting state and begins a cycle called the Interdigestive Myoelectric Complex (IMMC). It causes the peristaltic waves to sweep slowly and rhythmically downward along the stomach and

small intestine approximately every 2 hr, sweeping the excess digestive secretions into the colon and preventing accumulation downward along the stomach secretions into the colon and preventing their accumulation in the upper GIT [8-11].

The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states [8].

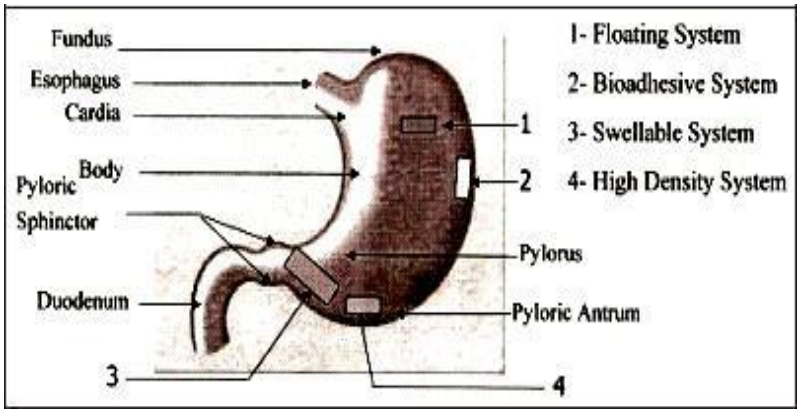


Fig. 2: Site Specific Physiology of stomach

During the fasting state an interdigestive series of electrical events take place, which cycle through both stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases

The various phases are as below- (Figure 3)

Phase I (basal phase)-Period of no contraction (40-60 minutes).

Phase II (preburst phase)- It consists of intermittent contractions that gradually increase in intensity as the phase progresses, and it lasts about 20 to 40 minutes. Gastric discharge of fluid and very small particles begins later in this phase.

Phase III (burst phase)-Period of regular contractions at the maximal frequency that travel distally also known as housekeeper wave; includes intense and regular contractions for short period. It is due to this wave that all the un-digested material is swept out of the stomach down to the small intestine (10-20 minutes).

Phase IV- This is a short transitory period of about 0 to5 minutes, and the contractions dissipate between the last part of phase III and quiescence of phase I [9,10,11].

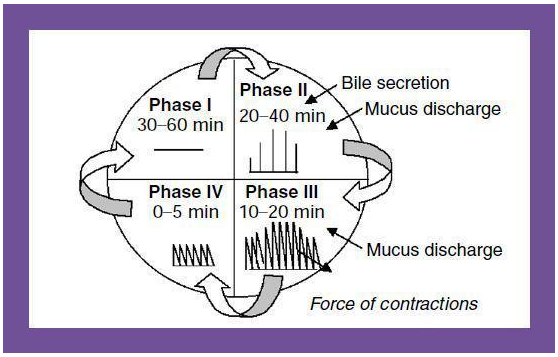


Fig: 3 Phases of gastric cycle

Need or Rationale of GRDDS

The idea of enhancing drug absorption pioneered the idea of development of Gastro retentive

drug delivery system (GRDDS). On the basis of the mechanism of mucoadhesion, floatation, sedimentation or by the simultaneous administration of pharmacological agents, the controlled gastric retention of solid dosage forms may be achieved, which delay gastric emptying. [5].

The needs are

1) The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT.

2) For drugs with relatively short half life, sustained release may result in a flip- flop pharmacokinetics.

3) Gastro retentive drug delivery can produce prolongs 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 .

4) The controlled, slow delivery of drug form gastro retentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs [10].

5) Gastro retentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for drug with a narrow therapeutic index.

6) Gastro retentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency.

7) Reduction of fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.

8) Drugs that act locally in the stomach e.g. antacids and Misoprostol show batter effect by GRDDS which are particularly useful for the treatment of peptic ulcers caused by H Pylori Infections [12].

9) Drugs that are less soluble or are degrade by alkaline pH they encounter at lower part of GIT.

10) The sustained mode of drug release from Gastro retentive doses form enables extension of the time over a critical concentration [13].

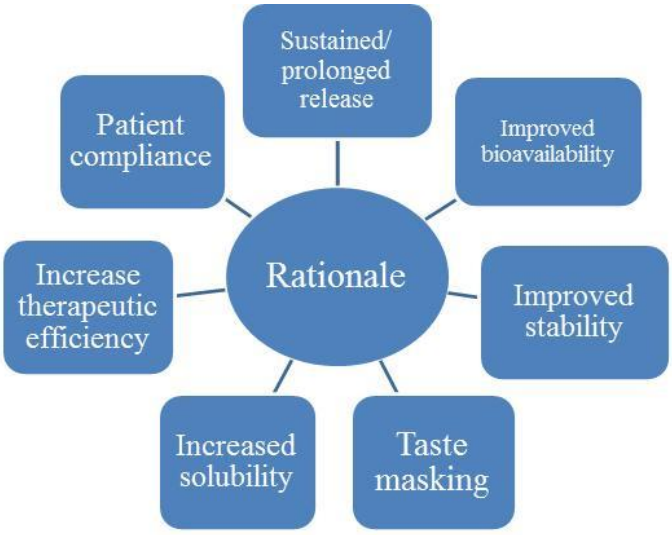


Fig: 4 Need for the use of GRDDS

In recent year, oral dosage forms for gastric retention have drown more and more attention for their therapeutic advantage in permitting command over the time and site of drug release. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in small intestine

Drugs suitable for Gastro Retentive Drug Delivery System [5, 14, 15]

1) Drugs acting locally in the stomach; misoprostol, 5-fluorouracil, antacids and antireflux preparations, anti Helicobacter pylori agents, and certain enzymes.
2) Drugs that are primarily absorbed in the stomach. Amoxicillin
3) Drugs that disturb normal colonic microbes e.g. antibiotics against Helicobacter pylori.
4) Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.
5) Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. L-dopa, para amino benzoic acid, furosemide, riboflavin etc.
6) Drugs that are poorly soluble at an alkaline pH; (Drugs insoluble in intestinal fluids /(acid soluble basic drugs)):- chlordiazepoxide, chlorpheniramine, cinnarizine, diazepam, diltiazem, metoprolol, propranolol, quinidine, salbutamol, and verapamil.
7) Drugs absorbed rapidly from GI tract. Metronidazole, tetracycline
8) Drugs that degrades in colon and unstable in lower part of GI tract: captopril.
9) Drugs exhibiting site-specific absorption in the stomach or upper parts of the small intestine: atenolol, furosemide, levodopa, p-aminobenzoic acid, piretanide, riboflavin-50-phosphate, salbutamol (albuterol), sotalol, sulpiride, and thiamine.
10) Drugs with variable bioavailability: sotalol hydrochloride and levodopa.

Drugs those are unsuitable for Gastro Retentive Drug Delivery System [7]

a) Drugs that have very limited acid solubility e.g. phenytoin etc.
b) Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
c) Drugs intended for selective release in the colon e.g. 5- amino salicylic acid, corticosteroids etc.

Factors Controlling the Gastric Retention of the Dosage Forms: [9, 16-19]

1) **Density:** Density of the dosage form should be less than the gastric contents (1.004gm/ml). It should be in the range of 1g/cm3 to 2.5g/cm3 [16,17].
2) **pH of Stomach:** According to pH partition theory, only unionized form of the drug has passive absorption throughout the GIT. So, acidic drugs or weak acidic drugs are remained unionized in acidic pH only, and as gastric fluid has acidic pH, acidic drugs are more absorbed from stomach then intestine [9].
3) **Microbial degradation:** The human colon contains around 400 different species of bacteria and has up to 10^{10} Bacteria per gram content. Some drugs are degraded by these bacteria show poor absorption in colon. E.g. Ranitidine, Metformin.
4) **Size:** Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm [18].
5) **Nature of drug:** Drugs with impact on gastro intestinal transit time e.g.Codeine and pharmacokinetic agents e.g.metclopramide, cisapride increases GRT [18].
6) **Shape:** The dosage form with a shape tetrahedron and ring shape devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT, 90 to 100% retention at 24 hours compared with other shapes [18]
7) **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 hours. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit

can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer [16,17]

8) **Single or multiple unit formulation:** Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms [18].
9) **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.
10) **Caloric Content:** GRT can be increased between 4 to 10 hours with a meal that is high in proteins and fats [16,17].
11) **Frequency of feed:** The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
12) **Gender**: Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down [19].
13) **Age:** Elderly people, especially those over 70 years have a significantly longer GRT [19].
14) **Posture:** GRT can vary between supine and upright ambulatory states of the patients.
15) **Effect of buoyancy--**On comparison of floating and non floating dosage units, it was concluded that regardless of their sizes the floating dosage units remained buoyant on the gastric contents throughout their residence in the gastrointestinal tract, while the non-floating dosage units sank and remained in the lower part of the stomach [16, 17].
16) **Diseased state of the individual:** biological factors also affect the gastric retention e.g. Crohn's disease, gastrointestinal diseases and diabetes.
17) **Concomitant drug administration:** Anti-cholinergics like atropine and propentheline opiates like codeine and prokinetic agents like metoclopramide and cisapride.
18) Enzymatic degradation: Some drugs are acting as substrates for some enzymes (Intestinal metabolic enzymes, Cytochrome p450-CYP3A, which are present in a particular region of GIT, can lead to degradation of drug at that site and make absorptive window [18, 19].
19) Other factors Diseased states of the individual (chronic disease, diabetes etc.) Body mass index Physical activity Molecular weight and lipophilicity of the drug depending on its ionization state.

Advantages compared to conventional DDS including [5, 10, 16, 20]

1) Avoiding drug level fluctuations by maintenance of optimal therapeutic plasma and tissue concentrations over prolonged time periods.
2) Improves Bioavailability: The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations
3) Reducing the administered dose while achieving comparable effects.
4) Reduced frequency of administration leading to improved patients' compliance and subsequently improved efficacy of the therapy and cost effectiveness.
5) Targeting or timing of the drug action. Hence, it is highly desirable to develop sustained DDS releasing the drug at predetermined rates to achieve optimal drug levels at the site of action.

6) Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs.
7) Prolonged gastric retention reduces drug wastage, and improves solubility for drugs that are less soluble in a high pH environment.
8) Enhanced first-pass biotransformation: When the drug is presented to the metabolic enzymes (cytochrome P-450, in particular CYP-3A4) in a sustained manner, the presystemic metabolism of the tested compound may be considerably increased rather than by a bolus input.
9) Local Action: Helps in achieving local delivery of drug to the stomach and proximal small intestine.
10) Reduced frequency of dosing**:** For drugs with relatively short biological half life, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.
11) It gives improved selectivity in receptor activation. Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.
12) Improved receptor activation selectivity: FDDS reduces the drug concentration fluctuation that makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.
13) Reduced counter-activity of the body: In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.
14) Extended time over critical (effective) concentration: For certain drugs that have non-concentration dependent pharmacodynamics, such as Betalactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration.
15) Minimizes the adverse activity at colon: Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented.

Disadvantages [5, 9 ,10]

1. These systems require a high level of fluid in the stomach for drug delivery tom float and work efficiently-coat, water.
2. 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.
3. 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 [9].
4. Unsuitable for drugs that are unstable in acidic environment or not suitable for drugs that have solubility or stability problem in GIT. E.g. Erythromycin, Phenytoin

5. Drugs such as Nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.
6. Bio/mucoadhesives systems have problem of high turnover rate of mucus layer, thick mucus layer & soluble mucus related limitations.
7. Drugs which are irritant to Gastric mucosa are also not desirable or suitable. E.g. Aspirin & NSAID's
8. Drugs that absorb selectively in colon. E.g. Corticosteroid
9. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
10. The dosage form should be administered with a full glass of water (200-250 ml).
    These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract [10].

Applications of GRDDS [5]

Sustained drug delivery

Floating system remains in the stomach for longer period and release the drug over a prolong period of time. This system has bulk density less than 1 so it may float on the gastric content.

Ex. Floating granules of Indomethacin are superior to the conventional Indomethacin containing dosage form for maintaining desired plasma level of drugs.

Site specific drug delivery

This system is particularly advantageous for the drugs which are absorbed from the stomach or proximal part of the small intestine.

Absorption enhancement

Drugs having a poor bioavailability are potential candidate for formulating as a floating system to enhance its absorption. Also reduces side effect. Ex. Tacrine, in the form of FDDS, provide better drug delivery system with reduced GI side effects in Alzheimer's patients.

Maintenance of constant blood flow

This system provides an easy way for maintaining constant blood flow with relatively ease of administration.

Mechanistic Approaches of Gastric Retentive Drug Delivery System [9]

A number of systems have been used to increase the GRT of dosage forms by employing a variety of concepts. These systems have been classified according to the basic principles of gastric retention. Classification of gastro retentive drug delivery system shown in Fig.5

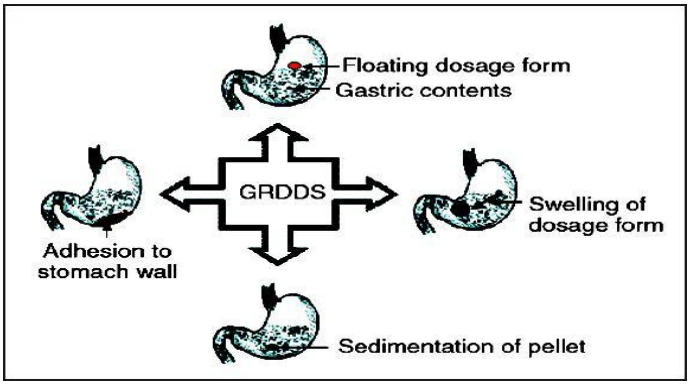
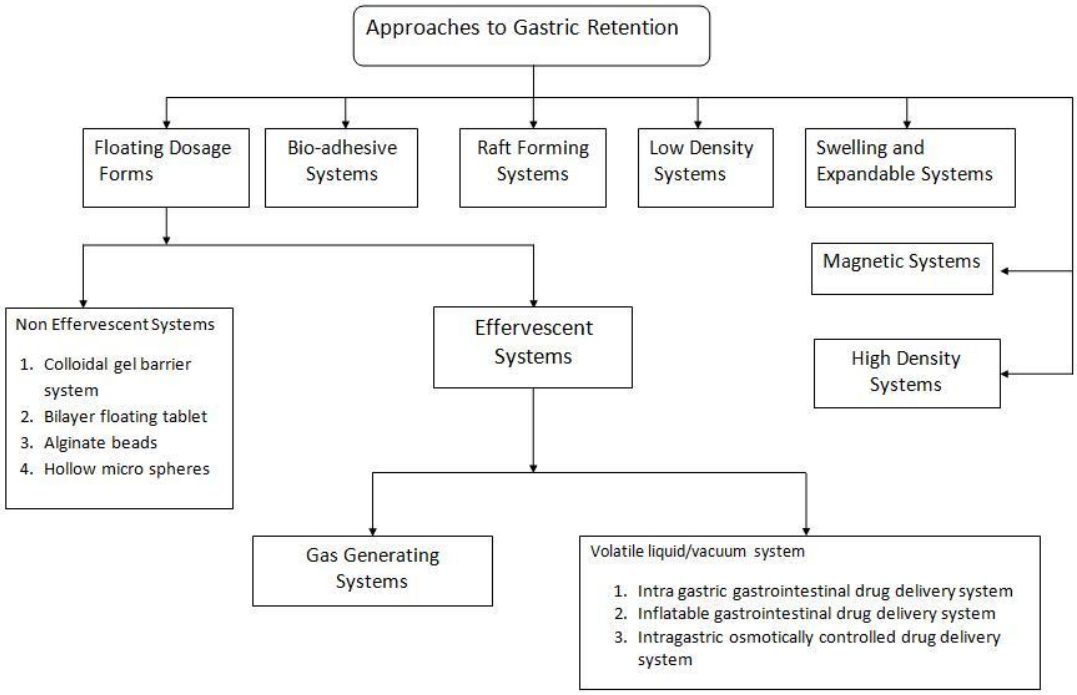


Fig: 5 Classification of Gastroretentive Drug Delivery System



DIFFERENT APPROACHES OF GRDDS

Floating System (Low Density System):

Floating drug delivery systems (FDDS) or hydro dynamically balanced systems have a bulk density less than gastric fluids so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric content, the drug released slowly at a desired rate from system, which results in increase in gastric retention time and better control in fluctuation of plasma drug concentration. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. FDDS can be divided into non-effervescent and effervescent system [9,21-24].

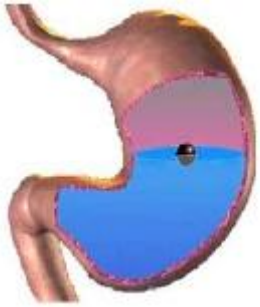


Fig: 6 Floating System

Classification of FDDS

Based on the mechanism of buoyancy, floating systems can be classified into two distinct categories *viz* non-effervescent and effervescent systems.

1) Non-Effervescent systems

(i) Colloidal gel barrier systems: Hydrodynamically balanced system (HBS) of this type contains drug with gel forming or swellable cellulose type hydrocolloids, polysaccharides and matrix

forming polymers. They help prolonging the GI residence time and maximize drug reaching its absorption site in the solution form ready for absorption. These systems incorporate high levels (20 to 75 % w/w) of one or more gel forming highly swellable cellulose type hydrocolloids e.g. hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC) hydroxypropyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (NaCMC) incorporated either in tablets or capsules (Fig. 7) [9, 22-24].

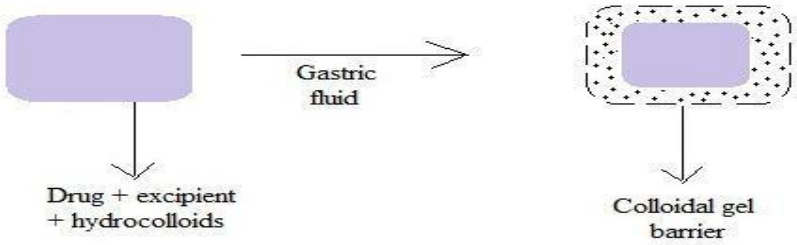


Fig. 7: Figure showing formation of colloidal gel barrier

(ii) Micro-Porous Compartment System: This technology is comprised of encapsulation of a drug reservoir inside a micro porous compartment with pores along its top and bottom surfaces. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric mucosal surface with 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 pores, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption (Fig. 8) [9, 23].

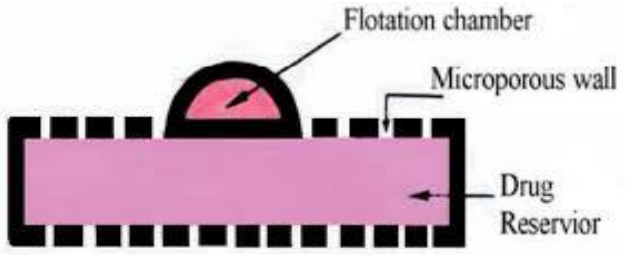


Fig: 8 Floating drug delivery device with microporous membrane and floatation chamber

(iii) Alginate Beads: Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter were prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing a precipitation of calcium alginate. These beads were then separated; snap frozen in liquid nitrogen and freeze-dried at – 40ºC for 24 hrs. leading to formation of porous system that maintained floating force for over 12 hrs [24].

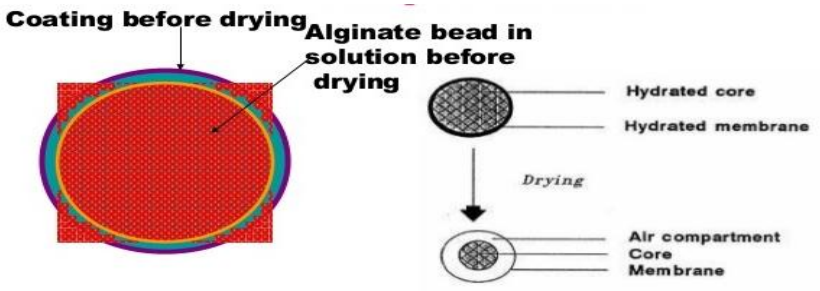


Fig: 9 Floating drug delivery system with Calcium beads

(iv) Hollow Microspheres (Microballoons): Hollow microspheres, loaded with drug in their outer polymer shells were prepared by novel emulsion solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer were poured into an agitated aqueous solution of PVA that was thermally controlled at 400 C. The gas phase was generated in dispersed polymer droplet by evaporation of dichloromethane and formed an internal cavity in microsphere of polymer with drug [9, 23]

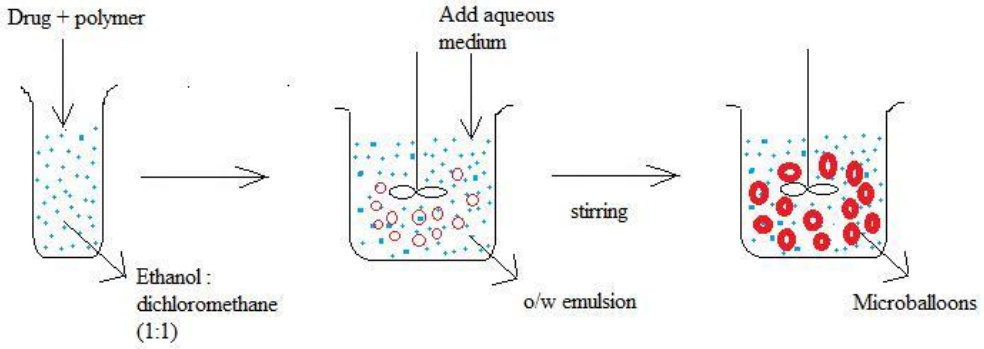


Fig: 10 Flowchart showing steps involved in preparation of microballoons

2) Effervescent systems

A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas. The gas in floating chamber can be introduced either by volatilization of an organic solvent or by effervescent reaction between organic acids and bicarbonate salts. These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). The system is so prepared that upon arrival in the stomach, carbon dioxide is released, causing the formulation to float in the stomach [22].

Volatile Liquid Containing Systems/ Osmotic regulated systems [9, 16, 23]

These devices are osmotically controlled floating systems containing a hollow deformable unit that can be converted from a collapsed to an expanded position and returned to collapse position after an extended period.

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric 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 controlled drug delivery device consists of two components – drug reservoir compartment and osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. The osmotic pressure thus created acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate drug release through the delivery orifice. (Fig. 11) [16, 23].

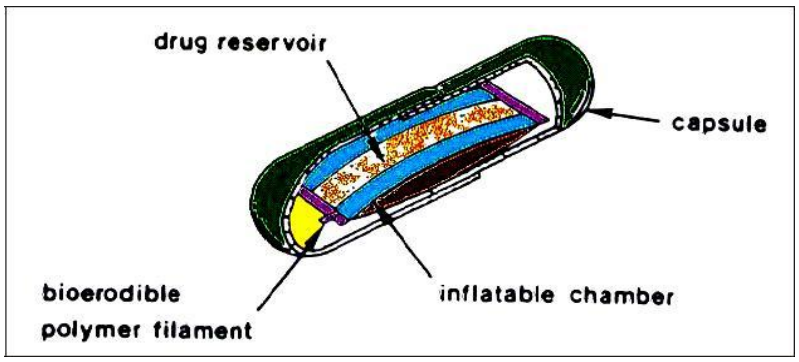


Fig. 11: Volatile Liquid Containing Systems

Gas generating systems

These buoyant delivery systems utilize effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2 which gets entrapped in the jellified hydrochloride layer of the system, thus decreasing its specific gravity and making it float over chime [20, 23]. These tablets may be either single layered wherein the CO_2 generating components are intimately mixed within the tablet matrix or they may be bilayer in which the gas generating components are compressed in one hydrocolloid containing layer, and the drug in outer layer for sustained release effect. Multiple unit type of floating pills that generates CO_2 have also been developed. These kinds of systems float completely within 10 minutes and remain floating over an extended period of 5-6 hrs. (Fig. 11) [25, 26].

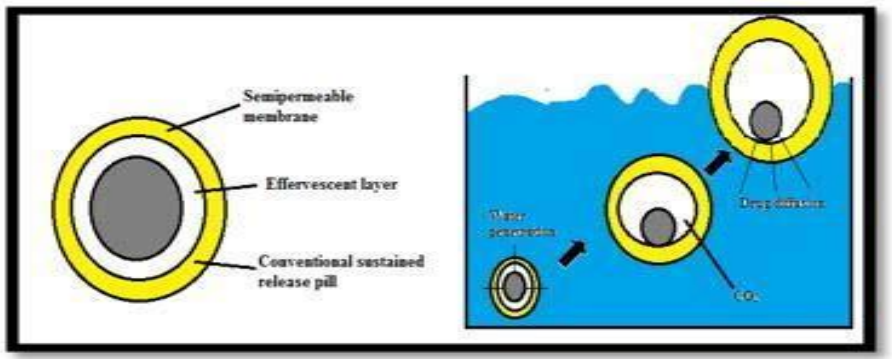


Fig: 12 Gas Generating Systems

High Density Sinking System

These systems possess density greater than the gastric fluids due to which the system sinks to the bottom and remains in the stomach. These are formulated by coating drug on heavy inert materials like zinc oxide, titanium dioxide, iron powder, etc It is shown in Figure.13[27].

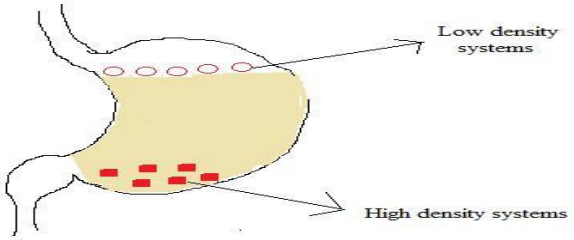


Fig. 13 Figure showing the high density system

Bioadhesive/Mucoadhesive System

Mucoadhesion means attachment of the drug to the mucus coat. This approach helps to increase the gastric residence time of the dosage form by binding them to the gastric mucosa. The adhesion is favored by rapid hydration. This mucoadhesive system is not that much feasible as the bond formation for mucoadhesion is prevented by the acidic environment and presence of thick mucus in the stomach[16]. Polymers used for this purpose may include polycarbophil, carbopol, CMC, chitosan, lectin etc.[27] . Binding of polymers to the mucin/epithelial surface can be divided into three categories.

A. Hydration-mediated adhesion:

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

B. Bonding-mediated adhesion:

The adhesion of polymers to a mucus/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.

C. 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.

Swelling System

These are the dosage forms, which after swallowing, swells to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a longer period of time. These systems may be named as ‘plug type systems’, since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18mm in their expanded state. The 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 [5, 7]

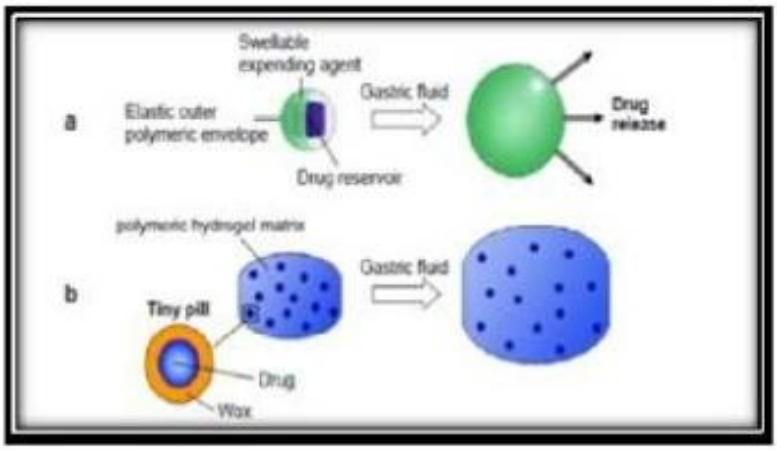


Fig: 14 GRDDS by Swelling System

Super Porous Hydrogel System:

These swellable systems differ significantly from the conventional types to hold a separate classification. In this approach to improve the GRT super porous hydrogels of average pore size > 100 micrometer, swell to equilibrium size within a minute due to the rapid water uptake by capillary wetting through numerous interconnected open pores. They swell to large size (swelling ratio: 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is advised by co-formulation of hydrophilic particulate material, Ac-DiSol [5] .

Raft Forming System:

This system focus more for delivery of antacid and delivery of drugs used to treat gastrointestinal infection and disorders. The basic mechanism involves formation of viscous cohesive gel when the system comes in contact with gastric fluid. In this each portion of liquid swells and forms a continuous layer of gel known as raft. The raft floats because of buoyancy created by formation of CO_2. This raft acts as a physical barrier to prevent the reflex of gastric content into the esophagus. This system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for making the system less dense than the gastric fluid and to float on the gastric fluid. Figure 15 represents raft forming system's mechanism [18, 28].

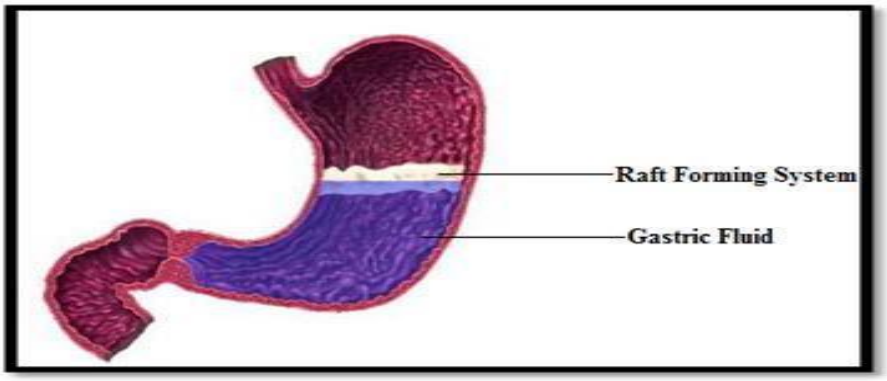


Figure 15: Raft Forming System

Magnetic System:

This approach of increased gastric retention time is base on the principle that dosage form contains a small internal magnet. A magnet is placed in abdomen over the position of stomach that retains dosage form in the gastric region.

Marketed Products of FDDS

S. No.	Brand name	Drug	Company, Country	Remarks
1	Madopar	Levodopa (100 mg), Benserazide (25 mg)	Roche products, USA	Floating CR capsule
2	Valrelease	Diazepam (15 mg)	Hoffman-Laroche, USA	Floating capsule
3	Liquid gaviscon	Al. Hydroxide (95 mg), Mg. Carbonate (358 mg)	Glaxo smith kline, India	Effervescent floating liquid alginate preparation
4	Topalkan	Al-Mg antacid	Pierre fabre drug, France	Floating liquid alginate Preparation
5	Conviron	Ferrous sulphate	Ranbaxy, India	Colloidal gel forming FDDS
6	Cifran OD	Ciprofloxacin (1 g)	Ranbaxy, India	Gas-generating ® floating tablet
7	Cytotec	Misoprostol (100 mcg/200 mcg)	Pharmacia, USA	Bilayer floating capsule
8	Oflin OD	Ofloxacin (400 mg)	Ranbaxy, India	Gas generating floating tablet

Evaluation of GRDDS

(A) *In vitro* evaluation

(i) Floating systems

(a) Buoyancy lag time:

It is determined in order to assess the time takenby 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 370 C. The time for which the dosage form continuously floats on the dissolution media is termed as floating time.

(c) Specific gravity/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 [29] .

(ii) 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/diameter with time.

(b) Continuous monitoring of water uptake:

Although previous method has advantage of un-disturbance of swollen tablet, but for measuring water uptake one has to remove whole assembly out of beaker, so process in not continuous.

Continuous monitoring of water uptake is possible by following apparatus.

In this apparatus, swelling tablet is placed on glass filter as support in one hallow cylinder with smooth surface inside, and one light weight punch is placed on it to prevent floating.

This cylinder is placed pre-heated in dissolution medium.

Another dissolution medium reservoir beaker is placed on digital balance and both are connected with media filled U tube as shown in figure and medium level is kept equal.

As swelling of tablet started, it absorbs water and water level in outer part of cylinder is goes down. The decrease in water level is maintained by importing extra medium via U tube from reservoir beaker.

As medium is transfer from reservoir, amount of water transfer can be determined by observing loss in weight by digital balance.

B) *In vitro* dissolution tests

A. *In vitro* dissolution test is generally done by using USP apparatus with paddle and GRDDS is placed normally as for other conventional tablets. 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.

B. 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.

C. 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.

D. 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.

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

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.

F. Inspite of the various modifications done to get the reproducible results, none of them showed co-relation with the *in vivo* conditions. So a novel dissolution test apparatus with modification of Rossett-Rice test Apparatus was proposed.

Rossett-Rice test is used for predicting in-vitro evaluation of directly acting antacid (action

by chemical neutralization of acid), where HCl is added gradually to mimic the secretion rate of acid from the stomach.

In this modified apparatus as shown in figure, it has side arm from bottom of beaker such that it maintains volume of 70 mL in beaker and fresh SGF is added from burette at 2 mL/min rate. Thus sink condition is maintained. Stirring is done by magnetic stirrer at 70-75 RPM (Fig. 16).

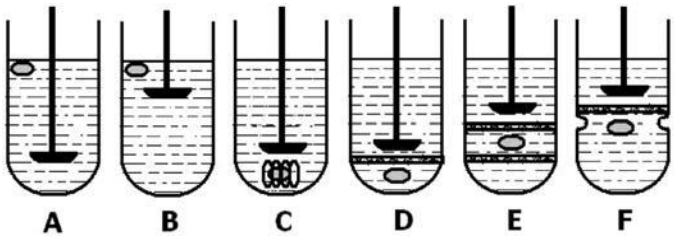


Fig. 16 *In vitro* dissolution tests

(C) In vivo evaluation

(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 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 99Tc.

(c) Gastroscopy:

Gastroscopy 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 that it 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:

13C Octanoic acid is incorporated into GRDDS. 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 upto 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.

CONCLUSION

Drug absorption in the stomach is a variable process which depends upon gastric emptying and other physiological factors. According to the literature survey, GRDDS enable prolonged and

continuous input of the drug to the upper parts of the gastrointestinal (GI) tract and improve the absorption & bioavailability of medications. All these different approaches for gastroretentive drug delivery systems (high density, floating, expandable or unfoldable or swelling, superporous, bioadhesive, magnetic systems etc.) are interesting and present their own advantages and disadvantages. GRDDS is much safer dosage form and have systemic, localized actions as well GRDDS do help in the treatment of chronic diseases like ulcers and carcinoma of GIT, and also reduces dose frequency there by minimize contra indication, systemic toxicity and drug dependence. In future it can be assumed that GRDD systems will become more popular in terms of delivering drug to the systemic circulation with improving efficiency of various type of pharmacotherapy approaches.

REFERENCES

1. M. N. V. Ravi Kumar, Handbook of Particulate Drug Delivery, American Scientific Publishers. Volume 2nd, 2008 123-128
2. L. Shargel, S. Wu-Pong, B.C. Yu., Applied Biopharmaceutics &Pharmacokinetics, McGraw-Hill Education Publication USA, Sixth Edition, 2012, 232-280
3. N. Rouge, P. Buri, E. Doelker; Drug Absorption Sites in the Gastrointestinal Tract and Dosage Forms for Site Specific Delivery; Int. Journal of Pharmacy; 1996; 136, 117-139
4. A.K. Nayak, R. Maji, B. Das; Gastroretentive Drug Delivery Systems: A Review; Asian Journal of Pharmaceutical and Clinical Research; 2010, 3(1), 2-10
5. A.D. Kajale, A.V. Chandewar; Recent Advancement in Gastro Retentive Drug Delivery System – A Review; Indo American Journal of Pharmaceutical Research, 2013, 3(7), 122-130
6. A.C. Guyton, Movement of food through the alimentary tract. In: Human Physiology and Mechanisms of Disease, W.B. Saunders Co., London, 1982, 3, 487-497
7. S. Kumar, F. Jamil, M. Rajput and S. Sharma; Gastro Retentive Drug Delivery System: Features and Facts; International Journal of Research in Pharmaceutical and Biomedical Sciences; 2012; 3 (1); 125-130
8. K. Vasava, R. Kaushik, L.L. Jha; A Review On Gastro Retentive Drug Delivery System With Special Emphasis On Formulation And Development Of Floating Microspheres; 2011, 11(2), 77-78
9. M.R. Kumar, B. Satyanarayana, N.D. Paladugu; A Comprehensive Review on Gastro Retentive Drug Delivery System; Acta Chim. Pharm. Indica; 2013, 3(2), 149-164, 277-288
10. A. Badoni, A. Ojha, G. Gnanarajan, P. Kothiyal; Review on Gastro Retentive Drug Delivery System; The Pharma Innovation; 2012, 1(8),32-42.
11. R.P. Singh, D.S. Rathore; Gastroretention: A Means to Address Local Targetting in the Gastric Region; Pharmacophore; 2012, 3(6), 287-300
12. J. Ramana, M. Kawatra, U. Jain, Recent Advances in Floating Microspheres as Gastro-Retentive Drug Delivery System: A Review; International Journal of Recent Advances in Pharmaceutical Research; 2012, 2(3), 5-23.
13. S. Sharma, A. Nanda, Progress in stomach specific drug delivery system features and facts; Int journal of Current pharma Research; 2010; 3(4), 48-52.

14. J. Swarbrick and J.C. Boylan; Encyclopedia of Pharmaceutical Technology, Drug Delivery – Oral Route, 3rd edition, volume 1, St. John's University, Jamaica, New York, (2007) 1253.
15. H. Soni, V.A. Patel; Gastro Retentive Drug Delivery System; Int. Journal of Pharmaceutical Sciences Review & Research; 2015; 31(1); 81-85
16. C.G. Wilson, N. Washington; The stomach: its role in oral drug delivery. In: Rubinstein, MH, editors. Physiological Pharmaceutical: Biological barriers to the drug absorption. Chichester, U.K: Ellis Horwood; (1989) 47-70
17. G. Chawla, P. Gupta, V. Koradia, A.K. Bansal; Gastroretention: A means to address regional variability in intestinal drug absorption; Journal of Pharmaceutical technology; 2003; 27(2): 50-68.
18. S. Arora, J. Ali, A. Ahuja, R.K. Khar, S. Baboota; Floating Drug Delivery Systems: A Review; AAPS Pharm Sci Tech; 2005, 6(3), 372-390
19. E.A. Klausner, S. Eyal, E. Lavy, M. Friedman, A. Hoffman; Novel Levodopa gastroretentive dosage form: in vivo evaluation in dogs; J. Controlled release. 2003; 88: 117-126.
20. B. Binoy, J. Nair; Floating Drug Delivery System-A new Approach In Gastric Retention- A Review; Journal Of Drug Delivery Research; 2012, 1(3), 18-31.
21. S.P. Vyas, R.K. Khar; Targeted and controlled drug delivery novel carrier system; CBS Publishers and distributors New Delhi; 1st ed., 2002, 196-217.
22. T. Shaik, M. Alagu Sundaram, K. Umasankar; Review on Gastroretentive Drug Delivery System; International Journal of Research in Pharmaceutical and Nano Sciences; 2014, 3(3), 177 – 185
23. A. Makwana, K. Sameja, H. Parekh, Y. Pandya; Advancements in Controlled Release Gastroretentive Drug Delivery System: A Review; Journal of Drug Delivery & Therapeutics; 2012, 2(3), 12-21
24. L.Yang, J. Esharghi, R. Fassihi; A new intra gastric delivery system for the treatment of helicobacter pylori associated gastric ulcers:In vitro evaluation; J. Cont. Rel.; 1999; 57:215-222.
25. S. Shinde , I, Tadwee, S. Shahi; Gastro retentive drug delivery system: A review. Int. J. Pharm. Res. & All. Sci.; 2012, 1(1), 01-13.
26. S. Swetha, R. Teja, D.V. Gowda; A Comprehensive Review on Gastroretentive Drug Delivery Systems; International Journal of Research in Pharmaceutical and Biomedical Sciences; 2012, 3(3), 1288-1290.
27. D.N. Bhavsar, N.M. Varde, V.H. Shah; "Advances In Grdds: Raft Forming System A Review"; Journal of Drug Delivery & Therapeutics; 2(5), 2012, 123-128.
28. S. Kakar, D. Batra, R. Singh, U. Nautiyal; Magnetic Microspheres as Magical Novel Drug Delivery System: A review; Journal of acute disease; 2013, 2(3), 1-12**.**
29. S. Desai, S. Bolton; A floating controlled release drug delivery systems: in vitro- in vivo evaluation; *PharmRes*. 10, 1993, 1321-1325.