World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: http://www.wjpsonline.org/
Review Article

Gastroretentive drug delivery system therapeutic management of peptic ulcer in geriatric patient

Kajal A. Prajapati, Anil G. Raval, Yogesh K. Patel and Himanshu G. Agraval

Department of Pharmaceutics, Sharda School of Pharmacy, Pethapur, Gandhinagar, Gujarat

Received: 23-09-2018 / Revised Accepted: 20-10-2018 / Published: 26-10-2018

ABSTRACT

A peptic ulcer, stomach ulcer, or gastric ulcer, also known as peptic ulcer disease, is a very common chronic disorder of the stomach which is mainly caused by damage or impairment of the stomach lining. Various factors such as pepsin, gastric acid, H. pylori, NSAIDs, prostaglandins, mucus, bicarbonate, and blood flow to mucosa play an important role in causing peptic ulcers. In this review article, our main focus is on some important gastroretentive drug delivery systems (GRDDS) (floating, bioadhesive, high density, swellable, raft forming, superporous hydrogel, and magnetic systems) which will be helpful in gastroretention of different dosage forms for treatment of peptic ulcer. GRDDS provides a mean for controlled release of compounds that are absorbed by active transport in the upper intestine. It also enables controlled delivery for paracellularly absorbed drugs without a decrease in bioavailability. The above approaches are specific for targeting and leading to a marked improvement in the quality of life for a large number of patients. In the future, it is expected that they will become of growing significance, finally leading to improved efficiencies of various types of pharmacotherapies.

Keywords: Gastric retention, gastroretentive drug delivery systems, Floating dosage form, Drug delivery system

Address for Correspondence: Kajal A. Prajapati, Department of Pharmaceutics, Sharda School of Pharmacy, Pethapur, Gandhinagar, Gujarat, India; Email: kajuprajapati26@gmail.com

How to Cite this Article: Kajal A. Prajapati, Anil G. Raval, Yogesh K. Patel and Himanshu G. Agraval. Gastroretentive drug delivery system therapeutic management of peptic ulcer in geriatric patient. World J Pharm Sci 2018; 6(11): 71-83.

INTRODUCTION

Owing to tremendous curative benefits of the oral controlled release dosage forms are being preferred as the interesting topic of research over the past 3 decades[1-4]. The much obvious interest in this scenario is owing to its two fold advantage. Primarily, the oral controlled release dosage forms have the potential to upkeep an effective concentration in system for a longer duration.

Secondly, it is helpful in providing easy dosage administration to the patient, that further provides patient compliance on the part of the patient and ultimately providing an array of options in the final formulation. But the benefits are yet obstructed by the knock of short gastric retention time (GRT) and the unpredictable rapid gastric rate may cause partial drug release in the absorption zone of the patient's body hence, hampering the efficiency of the dosage. It has caused the awaited development in oral gastroretentive drug delivery systems (GRDDS).

An unaccustomed drug delivery system of gastroretentive dosage form has evolved. It has an upper hand owing to its ability of prolonged retaining ability in the stomach. This improves the gastric residence span of drugs in stomach. This elongated retention ability provides more benefits which may be enumerated as: improving activity span for short half-life drugs, bioavailability of drugs, exclusion of side effects, reduction in dosage periodicity, saving drugs owing to former benefit, improves solubility for drugs that are less soluble in a high pH environment, optimized therapy and ultimately easy compliance on the part of the patient.

Recent approaches to increase the gastric residence time of drug delivery systems include bioadhesive systems, floating systems (low density systems), non-floating systems (high density systems), magnetic systems, swelling systems, unfoldable and expandable systems, raft forming systems and superporous systems, biodegradable hydrogel systems.

CR delivery systems provide a uniform concentration/amount of the drug at the absorption site and thus, after absorption, allow maintenance of plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration. CR products are formulations that release active drug compounds into the body gradually and predictably over a 12 to 24 hour period and that can be taken once or twice a day. Typically, these products provide numerous benefits compared with immediate release drugs, including greater effectiveness in the treatment of chronic conditions, reduced side effects, greater convenience, and higher levels of patient compliance due to a simplified dosing schedule. Because of the above advantages, such systems form the major segment of the drug delivery market. A number of techniques are used to achieve controlled release of drugs via the oral cavity. GRDF is the one of these techniques reviewed briefly in this review.

Scope: The development of oral controlled release systems has been a challenge to formulation scientists due to their inability to restrain and localise the system at targeted areas of the gastrointestinal (GI) tract. Controlled drug delivery systems aim to maintain plasma concentration of drugs within the therapeutic window for a longer period of time, thereby to ensure sustained therapeutic action and for that reason an increasing interest in their development exist. Moreover, many of new therapeutics under development are large molecules such as peptides, proteins, oligonucleotides, and vaccines[5,6].

NEED FOR GRDDS[7]

- ✓ Conventional oral delivery is widely used in pharmaceutical field to treat diseases. However, conventional delivery had many drawbacks and major draw-back is non-site specificity.
- ✓ Some drugs are absorbed at specific site only. They require release at specific site or a release such that maximum amount of drug reaches to the specific site.
- ✓ Pharmaceutical field is now focusing towards such drugs which require site specificity.
- ✓ Gastro-retentive delivery is one of the site specific deliveries for the delivery of drugs either at stomach or at intestine.
- ✓ It is obtained by retaining dosage form into stomach and drug is being released at controlled manner to specific site either in stomach, duodenum and intestine.

ADVANTAGES OF GRDDS:[8,9]

- ✓ Increase in bioavailability and curative efficiency of drugs and economic usage of dosage.
- ✓ Minimised factor of risk in resistance in antibiotics owing to stabilised therapeutic levels over prolonged periods removing fluctuations.
- ✓ Optimised release in case of short half-life drugs, causes flip flop pharmacokinetics and also ensures patient compliance with reduced dosage frequency.
- ✓ They are advantageous against drawbacks of the gastric retention time (GRT) as well as the gastric emptying time (GET). The system

remains buoyant on gastric fluid because of lower bulk density than gastric fluids.

- ✓ These are efficient in repairing stomach and small intestine related problems. Its attributed to the fact that gastroretentive drug delivery sustains drug release and hence, avail local therapy in these organs.
- ✓ This method provides with a systematic and controlled drug delivery system which minimises chances of drug over exposure at the diseased site.
- ✓ Providing a narrow curative index, the gastroretentive dosage forms minimises variance in concentrations of drugs and effects.
- ✓ This system provides higher efficiency due to reduced counter activity by body.
- ✓ As the system provides with controlled rates of fluctuation, a wider array is provided for selectivity in receptor activation.

DISADVANTAGES OF GRDDS:[10,11]

- ✓ Need for increased level of fluids in the stomach.
- ✓ Unsuitable for such drugs as:
  a. Problematic with solubility in gastric fluid
  b. Causing G.I irritation
  c. Inefficient in acidic environment
- ✓ Drugs intended for selective release in the colon.
- ✓ Unpredictable adherence owing to state of constant renewal of mucus wall of stomach.
- ✓ GRDDS is fed into the system after the meal as time of stay in stomach depends on digestive state.
- ✓ The ability of the drug to remain in the stomach depends upon the subject being positioned upright.
- ✓ Hydrogel based swelling system takes longer time to swell.
- ✓ Upon multiple administrations, size increasing drug delivery systems pose the threat to life owing to possible hazard of permanent retention in stomach.
- ✓ Superporous systems having drawback like problematical storage of much easily hydrolysable, biodegradable polymers.

SUITABLE AND UNSUITABLE DRUGS CANDIDATES FOR GRDDS:[12]

Suitable and unsuitable drugs candidates for GRDDS are listed in **Table 1** and **Table 2** respectively.

TABLE 1: POTENTIAL DRUG CANDIDATES FOR GRDDS

Suitable Drug candidates	Example
Drugs acting locally in the stomach.	Antacids, Anti-ulcer drugs, drugs against *H. Pylori*, Misoprostol, Clarithromycin, Amoxicillin.
Drugs with narrow absorption window inGastrointestinal tract (GIT).	Cyclosporine, Methotrexate, Levodopa, Repaglindine, Riboflavin, Furosemide, Para-aminobenzoic Acid, Atenolol, Theophyllin,
Drugs having unstable properties in the intestinal or colonic environment.	Captopril, Ranitidine HCl, Metronidazole, Metformin HCl.
Drugs caused imbalance of normal colonic microbes.	Antibiotics against *H. Pylori*, Amoxicillin Trihydrate.
Drugs having low solubility at high pH values.	Diazepam, Chlordiazepoxide, Furosemide, Verapamil HCl.

TABLE 2: UNSUITABLE DRUG CANDIDATES FOR GRDDS

Unsuitable Drug Candidates	Example
Drugs having very limited acid solubility.	Phenytoin
Drugs that exhibits instability in the gastric environment.	Erythromycin
Drugs that are used for selective release in the colon.	5- amino salicylic acid and corticosteroids

PHYSIOLOGY OF THE STOMACH:[13]

The Gatrointestinal tract is essentially a tube about nine metres long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx), oesophagus, stomach, small intestine (consisting of the duodenum, jejunum and ileum) and large intestine (consisting of the cecum, appendix, colon and rectum). The wall of the Gatrointestinal tract has the same general structure throughout most of its length from the oesophagus to the anus, with some local variations for each region.

The stomach is an organ with a capacity for storage and mixing. The antrum region is responsible for the mixing and grinding of gastric contents. The interdigestive motility pattern is commonly called the 'migrating motor complex' ('MMC') and is organised in cycles of activity and quiescence. Each cycle lasts 90–120 minutes and consists of four phases. The concentration of the hormone motilin in the blood controls the duration of the phases. In the interdigestive or fasted state, an MMC wave migrates from the stomach down the GI tract every 90–120 minutes.

A full cycle consists of four phases, beginning in the lower oesophageal sphincter/gastric pacemaker, propagating over the whole stomach, the duodenum and jejunum, and finishing at the ileum. Phase III is termed the 'housekeeper wave' as the powerful contractions in this phase tend to empty the Stomach of its fasting contents and indigestible debris. The administration and subsequent ingestion of food rapidly interrupts the MMC cycle, and the digestive phase is allowed to take place. The upper part of the stomach stores the ingested food initially, where it is compressed gradually by the phasic contractions. The digestive or fed state is observed in response to meal ingestion. It resembles the fasting Phase II and is not cyclical, but continuous, provided that the food remains in the stomach. Large objects are retained by the stomach during the fed pattern but are allowed to pass during Phase III of the interdigestive MMC. It is thought that the sieving efficiency (i.e. the ability of the stomach to grind the food into smaller size) of the stomach is enhanced by the fed pattern or by the presence of food (Fig. 1 and 2).

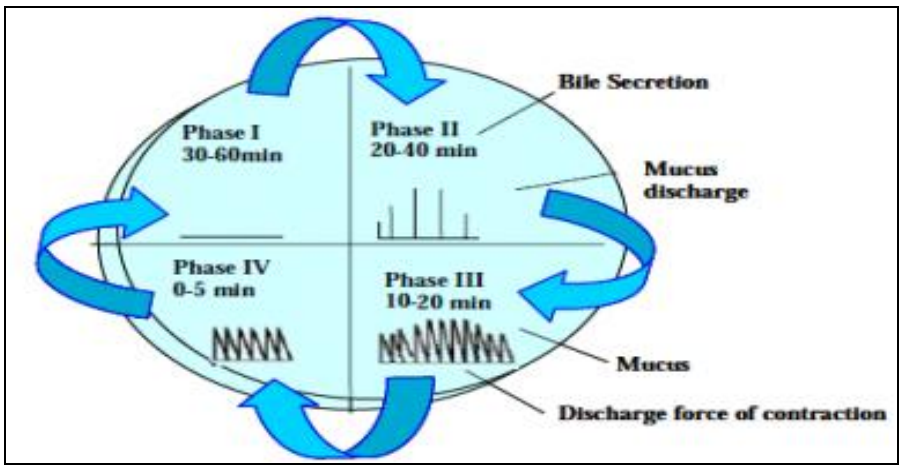

Figure 1: Phases of gastric cycle

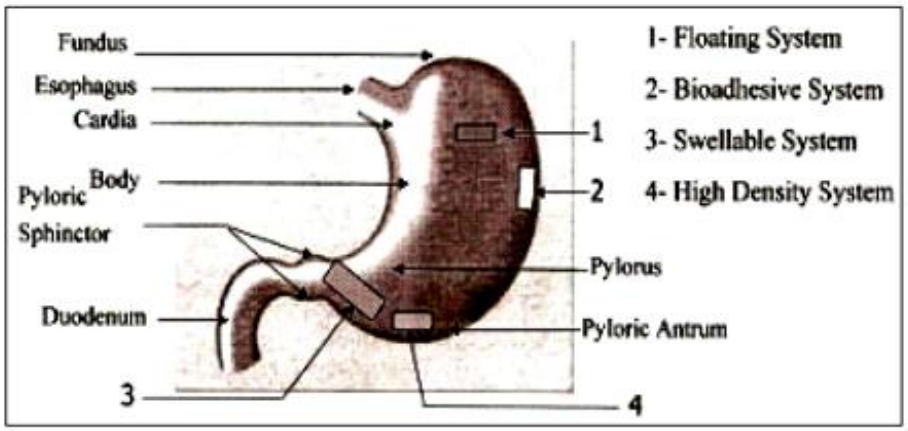

Figure. 2: Physiology of stomach

DIFFERENT FEATURES OF STOMACH[14,15]

GASTRIC PH:

- ✓ Fasted healthy subject 1.1 ± 0.15
- ✓ Fed healthy subject 3.6 ± 0.4
- ✓ Volume: Resting volume is about 25-50 mL
- ✓ Gastric secretion: Acid, pepsin, gastrin, mucus and some enzymes about 60 ml with approximately 4 mmol of hydrogen ions per hour.
- ✓ Effect of food on Gastric secretion: About 3 liters of secretions are added to the food.

FACTORS CONTROLLING GRDDS:[11,14,15]

- ✓ **Density:** Dosage form with lower density in the gastric content can float to the surface while high density sink to the bottom of the stomach. Suitable density required for floating property is less than 1.0 gm/ cm3
- ✓ **Size:** Size should be more than 7.5 mm in diameter.
- ✓ **Shape:** Either round or spherical shaped dosage form exhibit better property related to other shapes.
- ✓ **Single or multiple unit formulation:** Multiple units are desirable due to foretell release profile.
- ✓ **Fed or Unfed State:** Gastric retention time is less during fasting condition due to rise in gastric motility
- ✓ **Nature of Meal:** High amount of fatty acid and other indigestible polymers slow down the gastric retention time due to variation in gastric motility
- ✓ **Frequency of Feed:** Low frequency of migrating myoelectric complex (MMC) contributes to GRT upto 400 times which inturn depends on the frequency of food intake
- ✓ **Caloric Content:** A high protein and fat rich diet can increase GRT by 4 to 10h.
- ✓ **Gender:** Males have greater GRT than females
- ✓ **Age:** GRT is more in geriatric patients and less in neonates and children. Age above 70 (>70) exhibit longer GRT.
- ✓ **Posture:** GRT can vary between supine and upright ambulatory states of the patient.
- ✓ **Disease State:** Gastric disease such as diabetes, chron's disease, hypothyroidism, hyperthyroidism, duodenal ulcers etc fluctuates the GRT
- ✓ **Concomitant Intake of Drug:** Combination of some drugs along with gastric motility enhancers or depressants, affect GRT.

APPROACHES FOR GRDDS:[10,12,15,]

The following methods have been devised to improve period of retainment of oral dosage form in the stomach viz.

- ✓ ***Floating System***
- ✓ ***Swelling and Expanding System,***
- ✓ ***Bioadhesive System,***
- ✓ ***High Density System***

It is shown in Figure 3 and classification of GRDDS is shown in Figure 4.

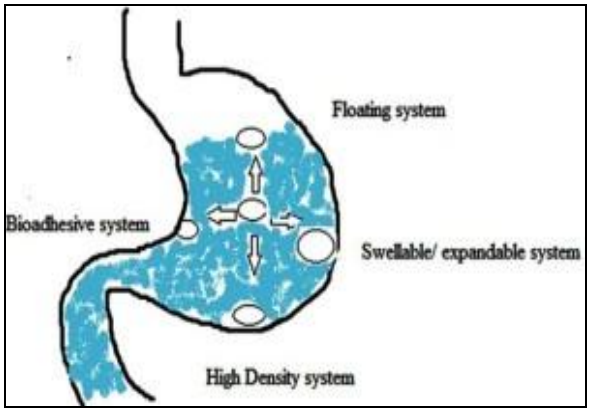

Figure 3: Approaches for GRDDS

MECHANISTIC APPROACHES OF GASTRIC RETENTIVE DRUG DELIVERY SYSTEM[15]

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. 4.

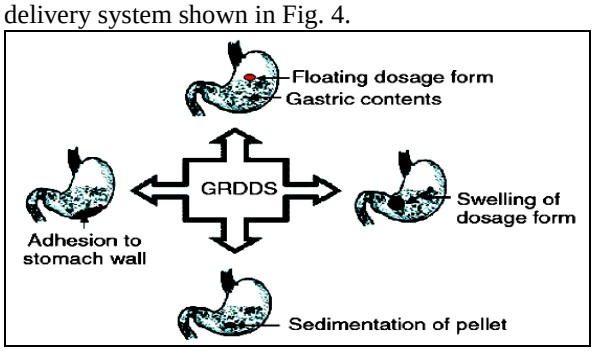

Figure 4: Classification of gastroretentive drug delivery system

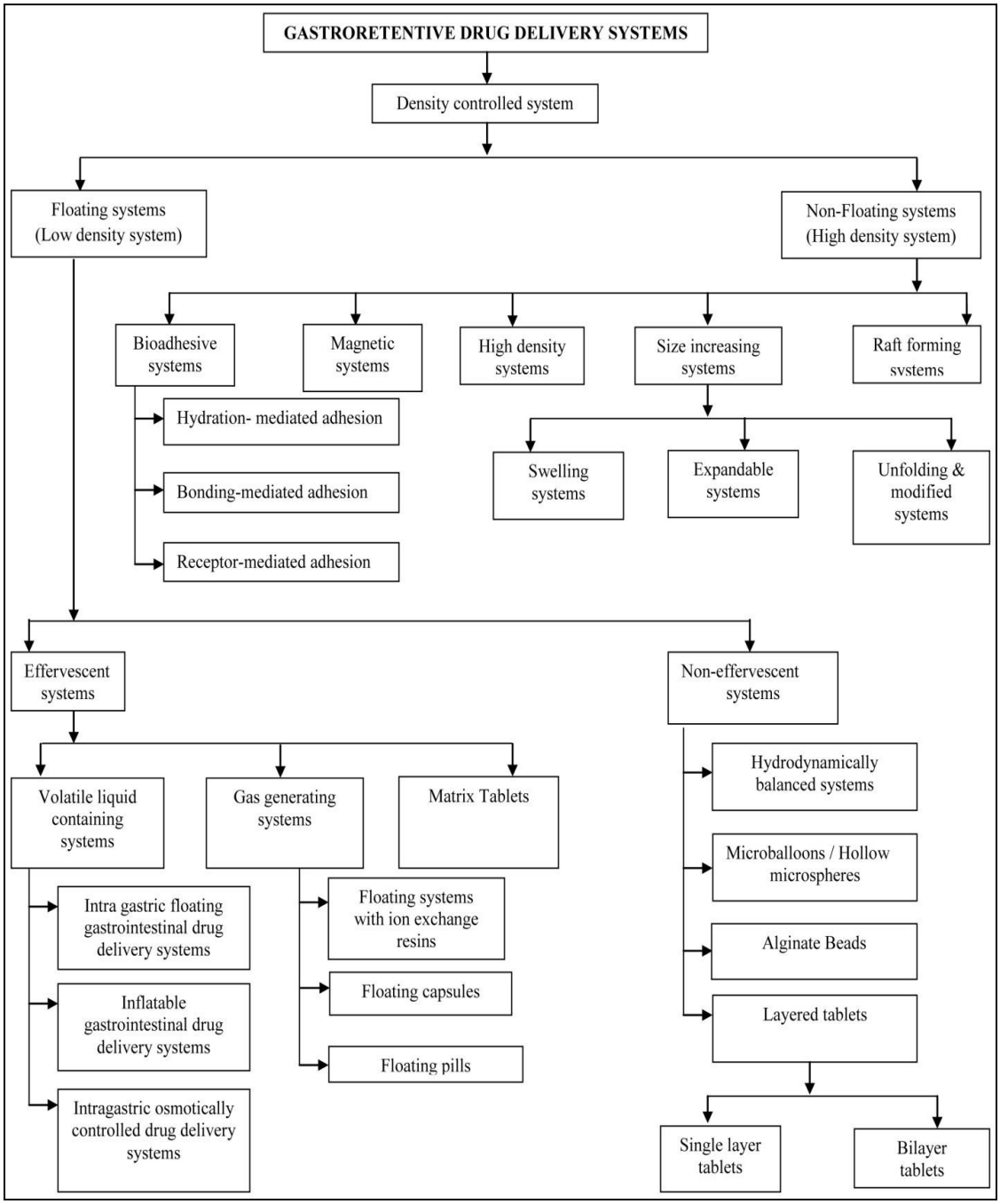

Figure 5: Classification of GRDDS

FLOATING DRUG DELIVERY SYSTEM (FDDS)[15,16]

Floating dosage form is also known as hydrodynamically balanced system (HBS). FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time while the system is floating on the gastric contents, the drug is released slowly at the desired rate. After release of drug, the residual system is emptied from the stomach.

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

A. 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. 6).

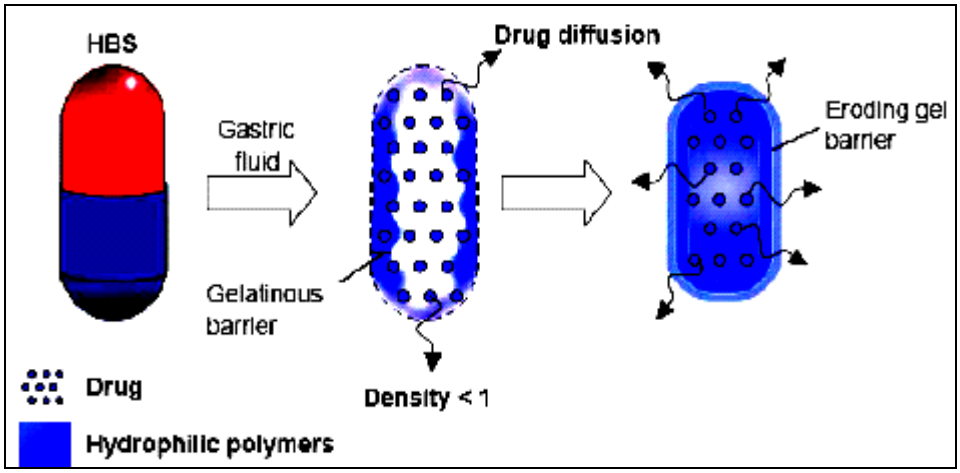

Fig. 6: Hydrodynamically based system (HBS)

(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. 7).

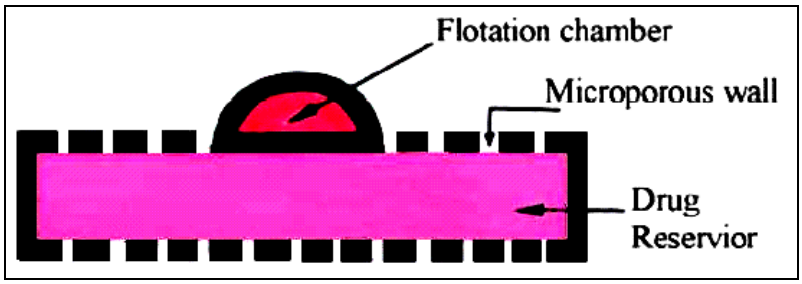

Fig. 7: Floating drug delivery device with microporous membrane andfloatation chamber

(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.

(iv)Hollow Microspheres: Hollow microspheres (microballoons), loaded with ibuprofen 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.

B. 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.

Volatile liquid containing systems

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. A deformable system consists of

two chambers separated by an impermeable, pressure responsive, movable bladder. The first chamber contains the drug and the second chamber contains volatile liquid. The device inflates and the drug is continuously released from the reservoir into the gastric fluid. The device may also consist of bioerodible plug made up of PVA, polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable system from the stomach (Fig. 8).

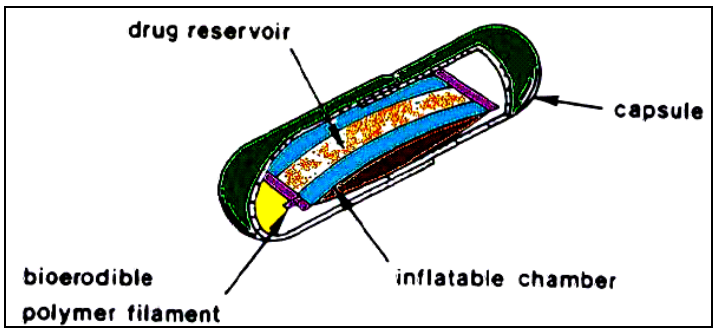

Fig. 8: Gastro inflatable drug delivery device

Gas generating systems: These buoyant delivery systems utilize effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2 which gets entrapped in the jellified hydrochloride layer of the system, thus decreasing its specific gravity and making it float over chyme. 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. 9).

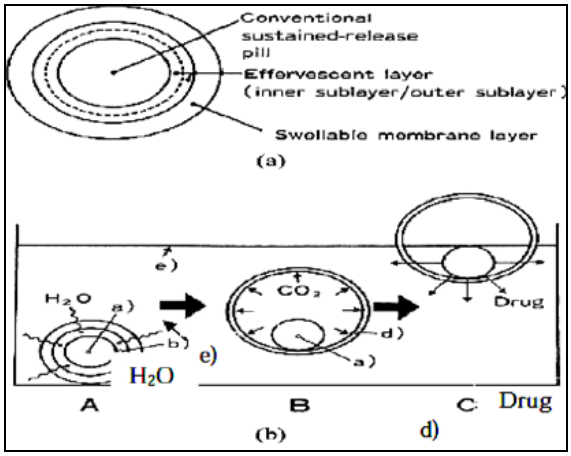

Fig. 9: The multiple units floating drug delivery system using gas generation technique

Bioadhesive DDS[16]

Bioadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as the potential means of extending the GRT of DDS in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane. The concept is based on self-protecting mechanism of GIT. Mucus secreted continuously by the specialized goblet cells located throughout the GIT plays a cytoprotective role. Bioadhesion is an interfacial phenomenon in which two materials, at least one of which is biological, are held together by means of interfacial forces. The attachment could be between an artificial material andbiological substrate, such as adhesion between a polymer and a biological membrane.

Swelling and expanding systems[17]

These are the dosage forms, which after swallowing, swell to an extent that prevent their exit from the pylorus. As a result, the dosage form is retained for a longer period of time. These systems may be named as "plug type systems", since they exhibit the tendency to remain lodged at the pyloric sphincter. On coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is due to the presence of physical/chemical cross-links in the hydrophilic polymer network. These cross-links prevent the dissolution of the polymer and hence maintain the physical integrity of the dosage form.

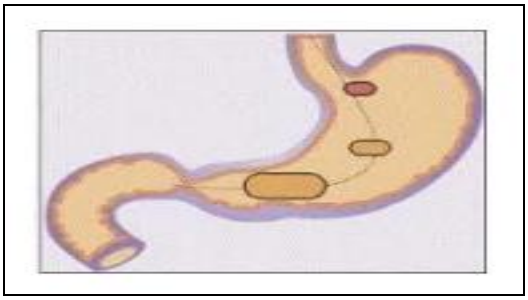

Fig. 10: Swelling and expanding systems

High density systems[17]

These dosage forms have a density (3 g/mL) far exceeding that of normal stomach contents (1 g/mL) and thus retained in region of the stomach and are capable of withstanding its peristaltic movements. High density formulations include coated pellets that have density greater than that of stomach contents (1.004 g/cm^3). This is accomplished by coating the drug with heavy inert materials such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc. The weighted pellet can then be covered with a diffusion controlling polymer membrane.

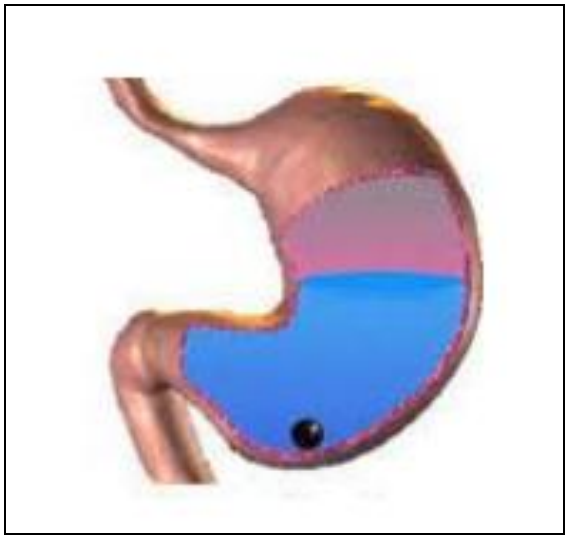

Fig. 11: High Density systems

PHARMACOKINETIC ASPECTS OF GRDDS[18,19]

Absorption window- that the drug is within the category of narrows absorption window agents: In general, appropriate candidates for CR-GRDF are molecules that have poor colonic absorption but are characterized by better absorptionproperties at the upper parts of the GI tract. In the case of absorption by active transporters that are capacity limited, the efficacy of thetransport activity may increase following sustained presentation of the drug to the transporting enzymes in comparison to non CR mode of administration.

Enhanced bioavailability: Once it has been ascertained that the compound in question is defined as narrow absorption window, the possibility of improving bioavailability by continuous administration of the compound to the specific site should be tested. For example, certain bisphosphonates, including alendronate, are absorbed directly from the stomach. However, the magnitude of this pathway remains modest even in the case where the prolonged gastric retention of the bisphosphonate in rats is produced by experimental/surgicalmeans.

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

Improved bioavailability due to reduced P-glycoprotein (P-gp) activity in the duodenum*:* In apparent contrast to the higher density of CYP3A4 at the upper part of the intestine, P-gpmRNA levels increase longitudinally along the intestine such that the highest levels are located in the colon. Therefore, for drugs that are P-gp substrate and do not undergo oxidative metabolism, such as digoxin, CRGRDF may elevate absorption compared to the immediate and CR dosage forms.

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.

Targeted therapy for local ailments in the upper GI tract: The prolonged and sustained administration of the drug from the GRDF to the stomach may be advantageous for local therapy in the stomach and the small intestine. By this mode of administration, therapeutic drug concentrations may be attained locally while the systemic concentrations, following drug absorption and distribution, are minimal.

PHARMACODYNAMICS ASPECTS[18,19]

Reduced fluctuations of drug concentration*:* Continuous input of the drug following CR-GRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

Improved selectivity in receptor activation: Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

Reduced counter-activity of the body: In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that

minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading tohigher drug efficiency.

Extended time over critical (effective) concentration: For certain drugs that have non-concentration dependent pharmacodynamics, such as beta lactam antibiotics, the clinical response is not associated with peak concentration, but rather, with the duration of time over a critical therapeutic concentration.

Minimized adverse activity at the colon: Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to development of microorganism's resistance.

EVALUATION PARAMETER OF GASTRORETENTIVE DRUG DELIVERY SYSTEM [19]

a) **Floating system:** 6 stage dissolution test apparatus is used. 0.1N, 900 ml HCl is used as dissolution media. The time required to emerge on surface of medium (Floating lag time) and Total duration of floating time is measured. *In-vitro* studies are done at temperature of 370C for duration as specified (approx. 8 hours).

b) **Mucoadhesive system:** Bio-adhesive strength is measured. Cellophane membrane is used, similar to mucosa of stomach or intact mucosa from rabbit is taken. When mucosa is there bio adhesive polymer sticks to it and force required to separate is measured. Force required to separate gives measure of strength of the polymer.

c) **Swellable system:** We check the water uptake. Water uptake gives idea of swelling index. We also check Weight, diameter and increase in thickness. Dissolution test is done using 0.1N HCl as dissolution fluid.

Swelling index (S.I) = (Wt - W0 / W0) X 100

Wt = Final weight after water uptake, Wo = Initial weight.

d) **Micro balloons:**

Fourier transform infra-red spectroscopy (FTIR) analysis: The FTIR analysis was done for the analysis of drug polymer interaction. FT-IR spectra of Pure Drug, Eudragit RS 100, HPMC and floating micro balloons were recorded using Shimadzu 8700 FTIR spectrophotometer.

Micromeritics: The prepared micro balloons were characterized for micromeritics properties, such as particle size, bulk density, tapped density, compressibility index and flow properties .

Morphology: The dried micro balloons were coated with gold film under vacuum using a sputter coater. The surface part of micro balloons was observed under scanning electron microscopy (Joel JSM-1600, Tokyo, Japan).

e) **Floating behavior:** Fifty milligrams of the floating micro balloons were placed in simulated gastric fluid (pH 1.2, 100 ml) containing 0.02 w/v% Tween 20. The mixture was stirred at 100 rpm in a magnetic stirrer. After 6h, the floating and the settled portion of micro balloons were recovered separately by filtration. The micro balloons were dried and weighed. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

f) **Buoyancy (%) = Wf / (Wf + Ws) × 100**

Where Wf and Ws are the weights of floating and settled micro particles.

g) ***In-vitro* release study:** The drug release rate from micro balloons was determined using USP XXIII basket type dissolution apparatus. A weighed amount of hollow microspheres equivalent to 20 mg drug was filled into a capsule (# 3) and placed in the basket. Simulated gastric fluid (SGF, pH-1.2) (900 ml) containing Tween 20 (0.02 w/v %) was used as the dissolution medium and maintained at 37± 0.5° C at a rotation speed of 100 rpm. Perfect sink conditions prevailed during the drug release studies. 5ml sample was withdrawn at each 1h interval, passed through a 0.5µm membrane filter (Millipore) and analysed spectrophotometrically at 296 nm to determine the concentration of drug present in the dissolution medium. The initial volume of the dissolution fluid was maintained by adding 5 ml of fresh dissolution fluid after each withdrawal. All experiments were conducted in triplicate.

h) **Stability study:** The prepared floating micro balloons, best formulation was selected on basis of buoyancy and the percentage drug released. The selected formulation was placed in borosilicate screw capped glass containers and stored at different temperatures (27±2°C), oven temperature (40±2°C) and in the refrigerator (5-8°C) for a period of 90 days. The samples were assayed for drug content (drug entrapment) at regular intervals.

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS[19]

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at

the site of absorption and thus enhances the bioavailability. These are summarized as follows,

A. Sustained Drug Delivery

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of G1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.

Recently sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours). Similarly a comparative study63 between the Madopar HBS and Madopar standard formulation was done and it was shown that the drug was released up to 8 hours in vitro in the former case and the release was essentially complete in less than 30 minutes in the latter case.

B. Site-Specific Drug Delivery

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, eg, riboflavin and furosemide. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets.

A bilayer-floating capsule was developed for local delivery of misoprostol, which is a synthetic analog of prostaglandin E1 used as a protectant of gastric ulcers caused by administration of NSAIDs. By targeting slow delivery of misoprostol to the stomach, desired therapeutic levels could be achieved and drug waste could be reduced.

C. Absorption Enhancement

Drugs that have poor bioavailability because of sitespecific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. A significant increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and entericcoated LASIX-long product (29.5%).

D. Minimize adverse activity at the colon

Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

E. Enhance bioavailability

The bioavailability of CR-GRDF is significantly enhanced in comparison to the administration of nonGRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.

F. Reduce fluctuations of drug concentration

Continuous input of the drug following controlled release gastro-retentive dosage form administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

CONCLUSION

Based on the literature surveyed, it may be concluded that gastroretentive drug delivery offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper gastrointestinal tract (GIT) and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability. Due to complexity of pharmacokinetics and pharmacodynamics parameters, in vivo studies are required to establish the optional dosage form for a specific drug. Another promising area of research for gastroretentive drug delivery system is eradication of Helicobacter pylori, which is now believed to be causative bacterium of chronic gastritis and peptic ulcers.

Although, this micro organism is highly sensitive to many antibiotics, its complete eradication requires high concentration of antibiotics be maintained within gastric mucosa for prolonged time period. An important feature to take into account is the stomach physiology. The time when the drug is taken (during or apart from the meal) is an important parameter. To develop an efficient gastroretentive dosage form is a real challenge to

pharmaceutical technology. Indeed, the drug delivery system must remain for a sufficient time in the stomach, which is not compatible with its normal physiology. All these 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. Now, a lot of work is running to develop different types of gastroretentive delivery systems of various drugs. In the future, it is expected that they will become of increasing importance, ultimately leading to improved efficiencies of various types of pharmacotherapies.

Table 3. List of Drugs Formulated as Single and Multiple Unit Forms of Floating Drug Delivery Systems.

Marketed products of FDDS

Brand Name	Delivery System	Drug Dose	Company Name
Val release®	Floating Capsule	Diazepam (15 mg)	Hoffmann-LaRoche
Topalkan®	Floating liquid alginate preparation	Al-Mg Antacid	Pierre Fabre Drug, France
Conviron®	Colloidal gel forming FDDS	Ferrous sulphate	Ranbaxy, India
Cytotech®	Bilayer floating capsule	Misoprostol (100µg/200µg)	Pharmacia, USA
Cifran OD®	Gas generating floating form	Ciprofloxacin(1gm)	Ranbaxy, India
Liquid Gaviscon®	Effervescent floating liquid alginate preparation	Al hydroxide (95mg), Mg Carbonate (358mg)	GlaxoSmithKline, India
Madopar HBS	Floating CR capsule	Levodopa & Benserazide	Roche product, USA

REFERENCES

1. Prajapati S and Dharamsi A: Floating drug delivery for prolonging gastric retention of dosage form. *Indian Journal of Novel Drug Delivery*, **2013**; 5:15-27.
2. Sharma N, Agarwal D, Gupta M and Khinchi M: A comprehensive review on floating drug delivery system. *International Journal of Research in Pharmaceutical and Biomedical sciences*, **2011**; 2:428-441.
3. Swetha S, Allena RT and Gowda DV: A comprehensive review on gastroretentive drug delivery systems. *International Journal of Pharmaceutical and Biomedical Research*, **2012**; 3:1285-1293.
4. Kawatra M, Jain U and Ramana J: Recent advances in floating microspheres as gastro-retentive drug delivery system: A review. *International Journal of Recent Advances in Pharmaceutical Research*, **2012**; 2:5-23.
5. Bhowmik D: Floating drug delivery system- A review. *Der Pharmacia Lettre***, 2009**; 1:199-218.
6. Pandey A, Kumar G, Kothiyal P and Barshiliya Y: A Review on current approaches in gastro retentive drug delivery system. *Asian Journal of Pharmacy and Medical Science*, **2012**; 2: 60-77.
7. Makwana A, Sameja K, Parekh H and Pandya Y: Advancements in controlled release gastroretentive drug delivery system: A review. *Journal of Drug Delivery and Therapeutics*, **2012**; 2:12-21.
8. Nayak KP and Upadhyay P: Gastroretentive drug delivery systems and recent approaches: A review. *Journal of Pharmaceutical Research and Opinion*, **2012**; 2:1-8.
9. Kagan L and Hoffman A: Selection of drug candidates for gastroretentive dosage forms: Pharmacokinetics following continuous intragastric mode of administration in a rat model. *European Journal of Pharmaceutics and Biopharmaceutics*, **2008**; 69:238–246.
10. Reddy BV, Navaneetha K: Gastroretentive drug delivery system- A review. *Journal of Global Trends in Pharmaceutical Sciences*, **2013**; 4: 018-1033.
11. Vasa S and Banji D: Approaches for gastrotentive drug delivery systems. *International Journal of Applied Biology and Pharmaceutical Technology*, **2010**; 1:589-601.
12. Bhardwaj L, Sharma PK and Malviya R:A short review on gastro retentive formulations for stomach specific drug delivery: special emphasis on floating *in-situ* gel systems. *African Journal of Basic and Applied Sciences*, **2011**; 3:300-312.

13. Rathee P, Jain M, Rathee S, Nanda A and Hooda A: Gastroretentive drug delivery systems: A review of formulation approaches. *The Pharma Innovation*, **2012**; 1:79-107.
14. Nayak AK, Maji R and Das B: Gastroretentive drug delivery systems: A review. *Asian Journal of Pharmaceutical and Clinical Research*, **2010**; 3:2-10.
15. Hardenia SS, Jain A, Patel R and kaushal A: Floating drug delivery systems: A review. *Asian Journal of Pharmacy and Life Science*, **2011**; 1:284-293.
16. Dhiman S, Singh TG and Sood S: Gastroretentive: a controlled release drug delivery system. *Asian Journal of Pharmaceutical and Clinical Research*, **2011**; 4:5-13.
17. Mishra J and Dash AK: Recent advances in gastro retentive drug delivery system: A review. *Mintage journal of Pharmaceutical and Medical Sciences*, **2013**; 2:25-27.
18. Mishra A and Gupta P: Gastro retentive drug delivery system: A review. *International Journal of Drug Development and Research*, **2012**; 4:28-39.
19. Brahmaiah B, Bhagath GP and Gudipati M: Formulation and evaluation of gastroretentive floating drug delivery system of metoprolol tartarate. *International Journal of Life Sciences Biotechnology and Pharma Research*, **2013**; 2:183-197.