WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 8, 368-389. Review Article ISSN 2277– 7105

GASTRORETENTIVE DOSAGE FORMS AS ORAL CONTROLLED DRUG DELIVERY: A REVIEW

Pamu Sandhya[*1], C. V. S. Subrahmanyam[2] and K. S. K. Rao Patnaik [1]

[1]Department of Pharmacy, UCT, Osmania University, Telangana State, Hyderabad, 500004.

[2]Gokaraju Rangaraju College of Pharmacy, Bachupally, Hyderabad, 500090.

Article Received on
21 May 2016,

Revised on 12 June 2016,
Accepted on 03 July 2016

DOI: 10.20959/wjpr20168-6687

***Corresponding Author**
Pamu Sandhya
Department of Pharmacy,
UCT, Osmania University,
Telangana State, Hyderabad,
500004.

ABSTRACT

Profound research has began in the field of oral controlled drug delivery systems about 30 years ago, to deliver the drug to the affected site in a pre determined and predicted rate. Gastroretentive drug delivery systems are one of a kind, which offers several advantages besides providing better bioavailability to poorly absorbed drugs and a required release profile thus attracting interest of pharmaceutical formulation scientists. Here we have discussed about factors controlling gastric retention of dosage forms, motility patterns of the GIT, applications of floating drug delivery systems, floating drug delivery systems, bio/muco-adhesive systems, raft forming systems, swelling and expanding systems and magnetic systems which are aimed for gastric retention and various factors involved in their efficiency.

KEYWORDS: Gastroretentive drug delivery systems, bioavailability, floating drug delivery systems, bio/muco-adhesive systems, raft forming systems, swelling and expanding systems.

INTRODUCTION

Site and time specific oral drug delivery have been of great interest in pharmaceutical field to achieve improved therapeutic efficacy. Controlled drug delivery systems are aimed primarily to achieve more predictable and increased bioavailability of drugs. However, the developmental process is generally precluded by several physiological adversities such as inability to restrain and localize the drug delivery system within the desired regions of the gastrointestinal tract (GIT) and highly variable nature of gastric emptying process.[1,2,3] Depending upon the physiological state of subject and design of pharmaceutical formulation, the emptying process can last from few minutes to 12 h. This variability, in turn may leads to

unpredictable bioavailability and times to achieve peak plasma levels since the majority of drugs are preferentially absorbed in upper part of the GIT. Gastro retentive drug delivery systems have been developed for prolonged gastric residence time (GRT), extended release devices with reduced frequency of administration and also improved patient compliance. In recent scientific and technological advancement have been made in the research and development of rate controlled oral drug delivery systems overcoming physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET).[4,5,6] Furthermore, absorption windows in the proximal gut can limit the bioavailability of orally administered compounds and can be a major obstacle to the development of controlled release formulations for important drugs. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery system (FDDS), also known as hydrodynamically balanced systems (HBS), bio adhesive systems, swelling and expanding systems, modified shape systems and high density system.

Requirements for gastric retention

Physiological factors in the stomach, it must be noted that, to achieve gastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms.[7,8] To function as a gastric retention device, it must resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease.

Potential drug candidates for gastroretentive drug delivery systems

1) Drugs those are locally active in the stomach e.g. misroprostol, antacids etc.
2) Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. L-DOPA, para amino benzoic acid, furosemide, riboflavin etc.
3) Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.
4) Drugs that disturb normal colonic microbe's e.g. Antibiotics against Helicobacter pylori.
5) Drugs that exhibit low solubility at high pH values e.g. Diazepam, Chlordiazepoxide, Verapamil HCl.

Drugs those are unsuitable for gastroretentive drug delivery systems

1) Drugs that have very limited acid solubility e.g. Phenytoin etc.
2) Drugs that suffer instability in the gastric environment e.g. Erythromycin etc.

3) Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and Corticosteroids.

Factors controlling gastric retention of dosage forms

The stomach anatomy and physiology contain parameters to be considered in the development of gastroretentive dosage forms. To pass through the pyloric valve in to the small intestine the particle size should be in the range of 1 to 2 mm. The most important parameters controlling the gastric retention time (GRT) of oral dosage forms include :density, size and shape of the dosage form, food intake and its nature, caloric content and frequency of intake, posture, gender, age, sex, sleep, body mass index, physical activity and diseased states of the individual (e.g.chronic disease, diabetes etc.) and administration of drugs with impact on gastrointestinal transit time for example drugs acting as anticholinergic agents (e.g. atropine, propantheline), Opiates (e.g. codeine) and prokinetic agents (e.g. metclopramide, cisapride.). The molecular weight and lipophilicity of the drug depending on its ionization state are also important parameters.[9, 10]

Density of dosage forms: The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach. Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm/ cm3 is required to exhibit floating property.

Shape and size of the dosage form: Shape and size of the dosage forms are important in designing indigestible single unit solid dosage forms. The mean gastric residence times of non floating dosage forms are highly variable and greatly dependent on their size, which may be large, medium and small units. In most cases, the larger the dosage form the greater will be the gastric retention time (GRT) due to the larger size of the dosage form would not allow this to quickly pass through the pyloric antrum into the intestine. Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm. Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared with other shapes.

Effect of gender, posture and age: Generally females have slower gastric emptying rates than male. The effect of posture does not have any significant difference in the mean gastric retention time (GRT) for individuals in upright, ambulatory and supine state. In case of elderly persons, gastric emptying is slowed down.

Advantages of FDDS

1. Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine.
2. FDDS are advantageous for drugs meant for local action in the stomach e.g.: Antacids
3.FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhoea to keep the drug in floating condition in stomach to get a relatively better response.
4. Acidic substance like aspirin causes irritation on the stomach wall when come in contact with it hence; HBS/FDDS formulations may be useful for the administration of aspirin and other similar drugs.
5. The FDDS are advantageous for drugs absorbed through the stomach e.g.: Ferrous salts, Antacids.

Disadvantages of FDDS

1. Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.
2. Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergo significant first-pass metabolism, may not be suitable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.
3. One of the disadvantages of floating systems is that they require a sufficiently high level of fluids in the stomach, so that the drug dosages form float therein and work efficiently.
4. Drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastro retentive systems.

E.g., Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions.

Application of floating drug delivery system[11, 12]

1. Sustained Drug Delivery: HBS system 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 controlled release formulation, hence, can be overcome with these systems. These systems have bulk density of <1, as a result of which they can float on the gastric contents.

E.g. recently sustained release floating capsules of nicardipine were developed and 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 cap (8 hours).

2. Site specific drug delivery: These systems are particularly advantages for drugs that are specifically absorbed from stomach or the proximal part of the small intestine. Eg riboflavin atorvastatin and misoprostal. A bilayer floating capsule was developed for local delivery of misoprostol, which is a synthetic analog of prostaglandin E, used as protectant of gastric ulcer caused by administration of NSAIDs. By targeting slow delivery of misoprostol to the stomach, desired therapeutic level could be achieved and drug waste could be reduced.

3. Absorption Enhancement: Drugs that have poor bioavailability because of site specific absorption from the upper part of the GIT are potential cardidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

E.g. A significant increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablet (33.4%) and enteric coated LASIX-long product (29.5%).

4. Maintenance of Constant Blood Level: These systems provide an easy way of maintaining constant blood level with an ease of administration and better patient compliance.

5. Minimized 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 betalactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

6. Fewer Doses: Creating once daily formulations for improved patient compliance

7. Improved plasma levels: Both extends plasma concentration levels and provides a more linear release profile.

8. Better Bioavailability: Delivers the drug in the upper G.I. tract for optimal absorption[7]

9. Less Irritation: The polymer matrix acts as a buffer between harsh drug crystals and the stomach lining.

10. Fewer side effects: Keeps drugs out of the lower GI tract which can be harmful to intestinal flora. Lower peak concentrations can also reduce adverse pharmacological effects.

11. Low risk inactive ingredients: tablets are composed of well .understood polymers from the FDA.s inactive ingredients list. This keeps the regulatory risks and hurdles of the formulation to an absolute minimum.

12. Manufacturing ease: Tablets are made in standard high-speed tableting equipment .No special tooling or engineering is required. The enables high quality, consistent, rapid scale-up and technology transfer to our development and marketing partners.

13. Low cost: The ingredients used in these systems are commodity items produced in extremely large quantity and at very low cost.

Basic gastro-intestinal tract physiology: The GI tract is essentially a tube about nine metres long that runs through the middle of the body from the mouth to the anus. The wall of the GI tract has the same general structure throughout most of its length, with some local variations for each region. The stomach is an organ with a capacity for storage and mixing. Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus).[19] Under fasting conditions, the stomach is a collapsed bag with a residual volume of approximately 50 ml and contains a small amount of gastric fluid and air. Gastric emptying occurs during fasting as well as fed states. The GI tract is in a state of continuous motility consisting of two modes: inter-digestive motility pattern and digestive motility pattern. The former is dominant in the fasted state with a primary function of cleaning up the residual content of the upper GI tract, which cycle both through stomach and intestine every 2 to 3 hours. This is called the inter- digestive myloelectric cycle or migrating myloelectric cycle (MMC) and is organized in cycles of activity and quiescence.[13] 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 (Figure 1).

Physiology of the Stomach: The Gastrointestinal tract is essentially a tube about nine meters long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx), esophagus, stomach, small intestine (consisting of the duodenum, jejunum

and ileum) and large intestine (consisting of the caecum, appendix, colon and rectum). The wall of the gastrointestinal tract has the same general structure throughout most of its length from the esophagus 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.

Motility patterns of the GIT

The various phases are as below

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

Phase II (preburst phase)-Period of intermittent contractions (20-40 minutes),

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*-Period of transition between phase III and phase I (0-5 minutes).[14]

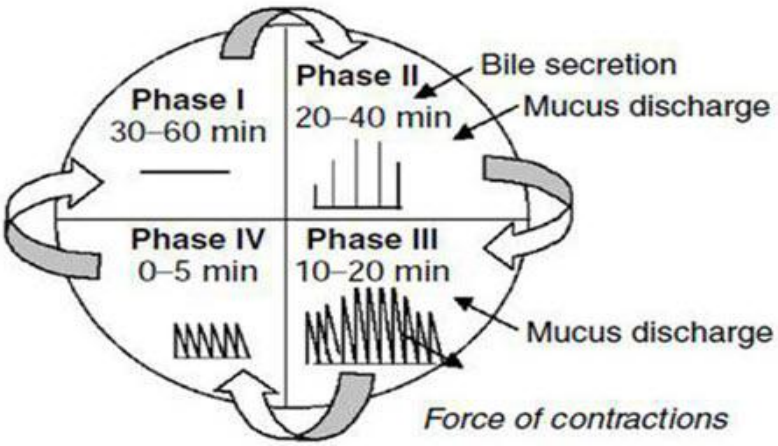

Figure 1: Motility patterns of the GIT in the fasted state

After the ingestion of a mixed meal, the pattern of contractions change from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1mm), which are propelled toward the pylorus in a suspension form. During the fed state, onset of MMC is delayed resulting in slowdown of gastric emptying rate. Orally administered controlled release dosage forms are subjected to basically 2complications that are, short gastric residence time and unpredictable gastric emptying rate. The ideal properties of GRDDS are shown in Figure 2.[14]

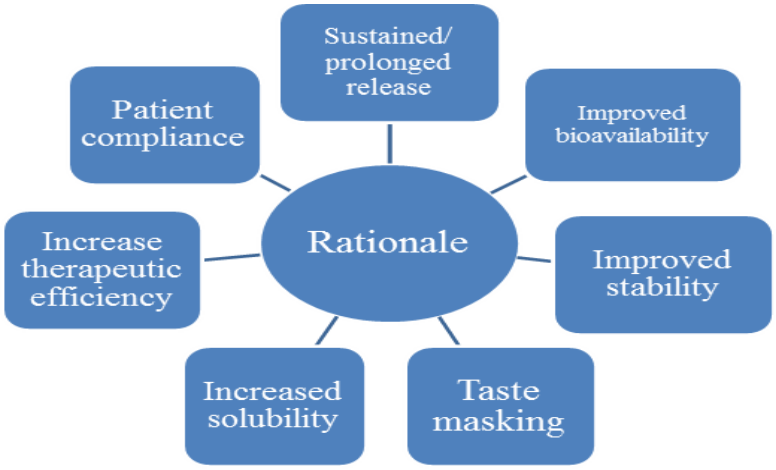

Figure 2: Rationale for the use of GRDD

TYPES OF GASTRORETENTIVE DOSAGE FORMS [16, 17, 18, 19]

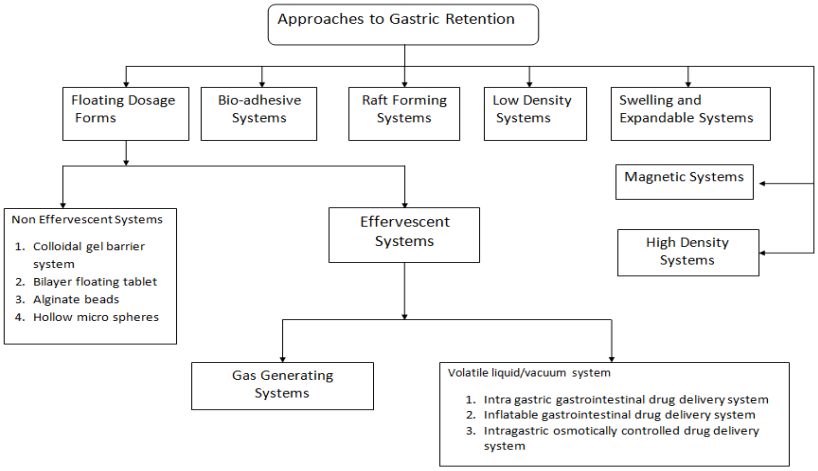

Figure 3: Approaches to gastric retention

Approaches to gastric retention

A. Floating Drug Delivery Systems: Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and 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 contents, the drug is released slowly at the desired rate from the system.[20] 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

I. Effervescent systems.

II. Non effervescent systems.

The effervescent systems further classified into two types.

1. Gas Generating systems
2. Volatile Liquid/Vacuum Containing Systems

The Non-Effervescent Systems further classified into two types

1. Colloidal Gel Barrier System
2. Micro porous Compartment System
3. Hollow Microspheres / Micro balloons
4. Alginate Beads

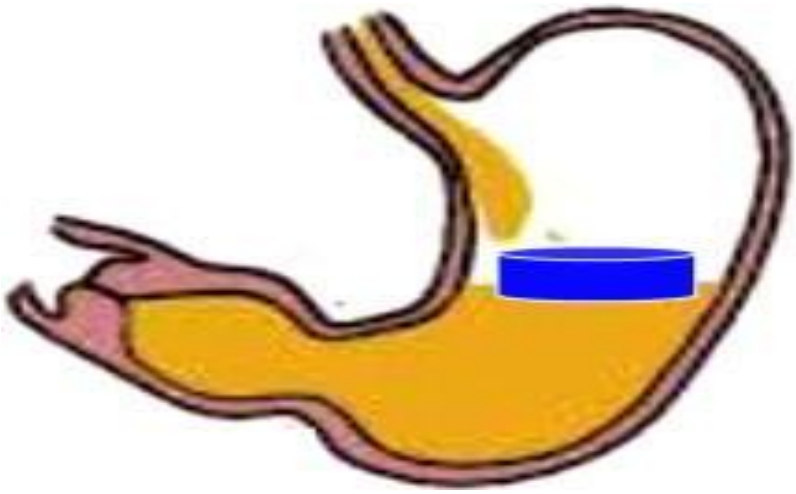

Figure 4: Floating system

I. Effervescent Systems[21, 22, 23]

1. Gas generating systems

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chime. These buoyant systems utilize matrices prepared with swellable polymers like methocel, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating, which is insoluble but permeable, allows permeation of water Thus, carbon dioxide is released, causing the beads to float in the stomach.[19,20]

a) Intra gastric single layer floating tablets or Hydrodynamically Balanced System (HBS)

These are formulated by intimately mixing the CO_2 generating agents and the drug within the matrix tablet (Figure 5). These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

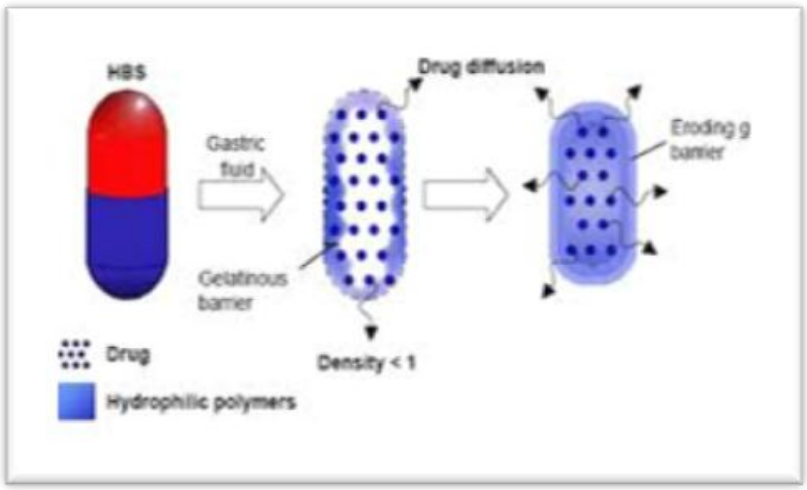

Figure 5: Hydrodynamically Balanced System (HBS)

b) Intra gastric bilayered floating tablets

These are also compressed tablets as shown in Figure 6 and contain two layers i.e

(i) Immediate release layer; ii) Sustained release layer.

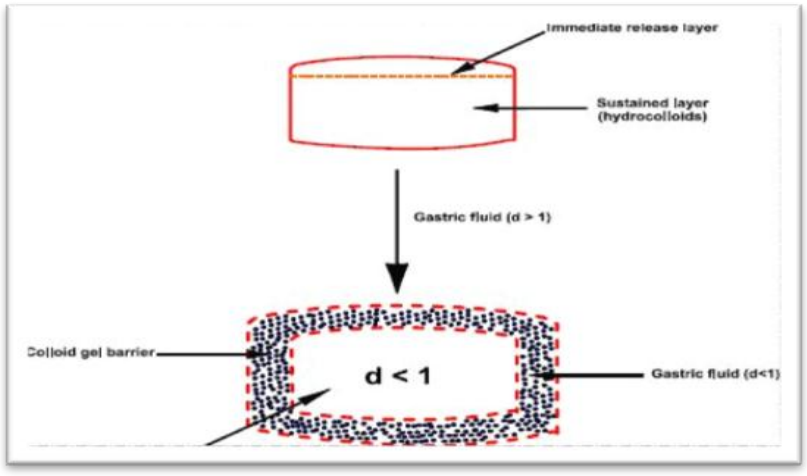

Figure 6: Intra gastric bilayer floating tablet

c) Multiple Unit type floating pills

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons, which float as they have lower density (Figure 7).

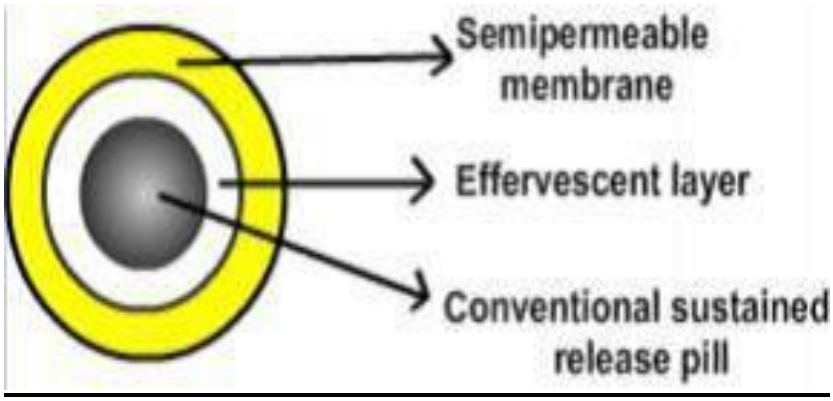

Figure 7: Multiple unit of oral FDDS

2. Volatile Liquid/Vacuum Containing Systems

a) Intragastric floating gastrointestinal drug delivery system

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporus compartment, as shown in Figure 8.

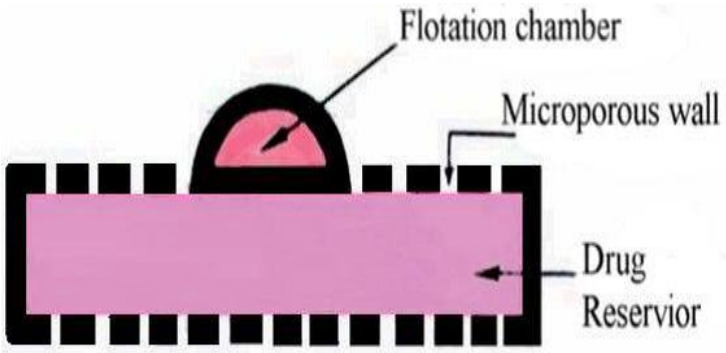

Figure 8: Intra gastric floating gastrointestinal drug delivery device

b) Inflatable gastrointestinal delivery systems

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug,

impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid (Figure 9).

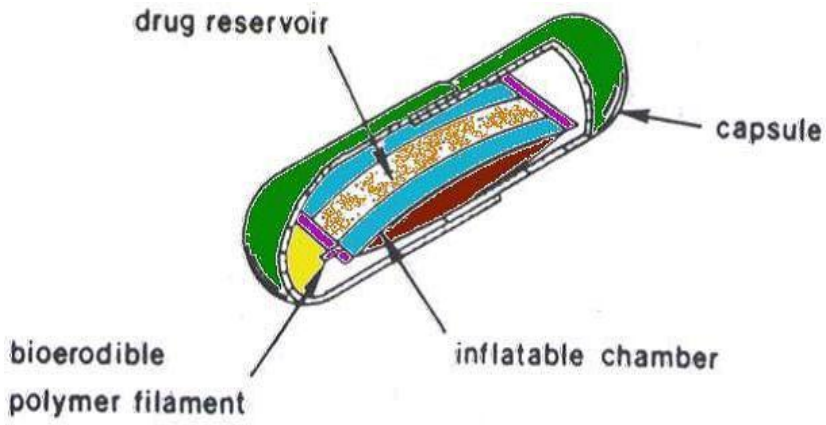

Figure 9: Inflatable gastrointestinal delivery system

c) Intragastric osmotically controlled drug delivery systems

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the 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 pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapor and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi permeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semi permeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice.[21] The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach (Figure 10).

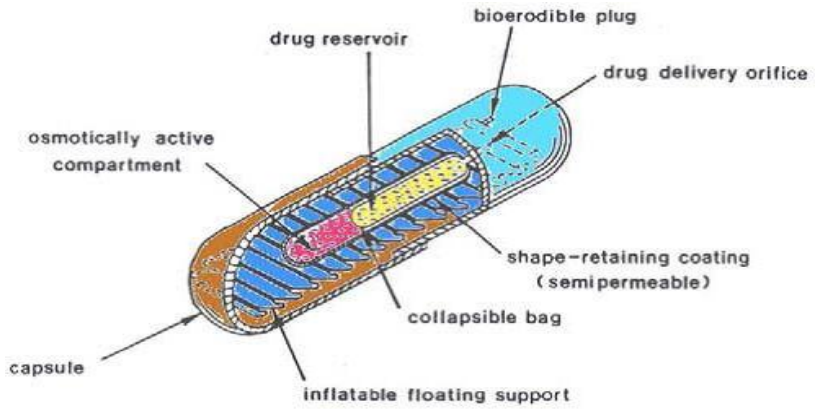

Figure 10: Intragastric osmotically controlled drug delivery system

II.Non-Effervescent Systems[24, 25, 26]

This type of system, after swallowing, swells Unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. One of the formulation methods of such dosage forms involves the mixing of the drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier18. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxylpropyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. This system can be further divided into four sub-types.

1. Colloidal Gel Barrier System

Sheth and Tossounian first designated this 'hydro dynamically balanced system'. Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption. This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g., hydroxyl propylcellulose, hydoxyethylcellulose, hydroxylpropyl methylcellulose (HPMC), polysaccharides and matrix-forming polymer such as polycarbophil, polyacrylate and polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface.

2. Microporous Compartment System

This technology is based on the encapsulation of a drug reservoir inside a micro porous compartment with pores along its top and bottom walls. The peripheral walls of the drug

reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

3. Hollow Microspheres / Micro balloons

Hollow microspheres loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent diffusion method. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The micro balloon floated continuously over the surface of an acidic dissolution media containing surfactant for More than 24 hr.

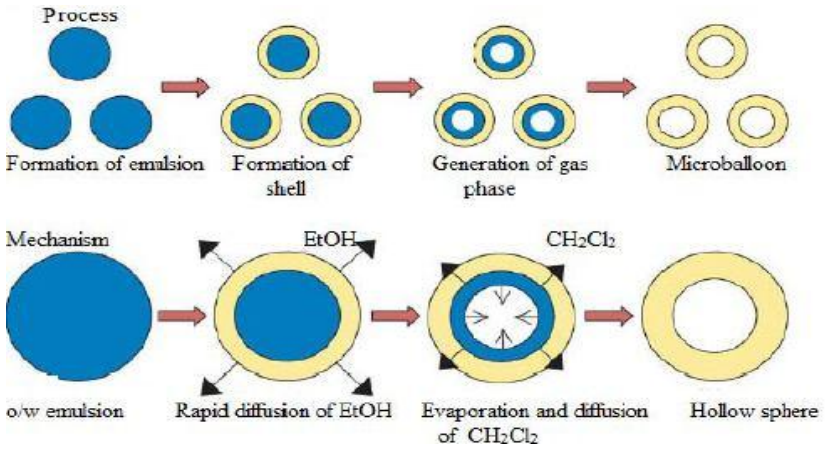

Figure 11: Micro balloons

4. Alginate Beads: Multiple unit dosage forms enjoy the advantage since they pass uniformly through the GIT to avoid the vagaries of gastric emptying and provide an adjustable release, thereby, reducing the intersubject variability in absorption and risk of local irritation. Current technologies, such as oral multiparticulate drug-delivery systems (MDDS), have gained immensely in importance, not only because of their ability to control drug release, but also for the modified drug-release profiles they facilitate**.** Lately, a wide variety of both natural and synthetic hydrophilic polyionic systems like alginates have been investigated for preparation of multiple-unit floating dosage forms (FDFs). The purpose of designing multiple-unit dosage form is to develop a reliable formulation that has all the

advantages of a single-unit form and also is devoid of any of the above-mentioned disadvantages of single unit formulations.

Mechanism The mechanism of drug release from multiparticulates can be occur in the following ways

Diffusion On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

Erosion Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle.

Osmosis In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating.

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate leading to formation of a porous system, when compared with solid beads, which gave a short residence, time of 1 hr, and these floating beads gave a prolonged residence time of more than 5.5 hr.

Figure 12: Floating alginate beads

B. Bio/Muco-Adhesive Systems: Bioadhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a site specific manner. This

approach involves the use of bioadhesive polymers, which can adhere to the epithelial surfacein the stomach. Gastric mucoadhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastro retentive force.[27, 28] Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan and gliadin, etc.

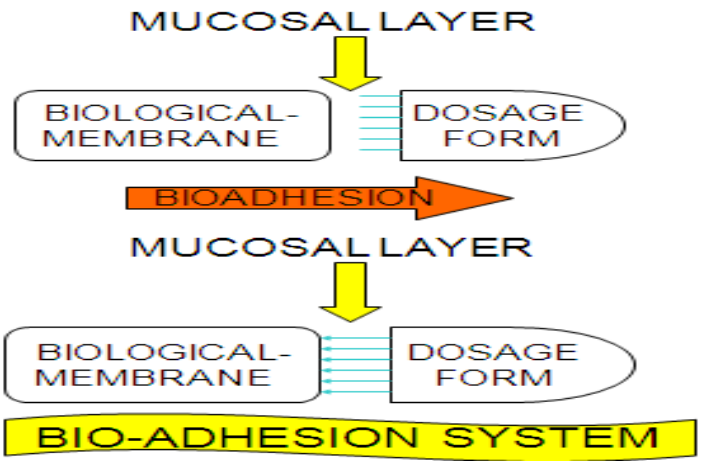

Figure 13: Bio/Muco-Adhesive Systems

C. Raft systems

Raft forming systems incorporate alginate gels. These have a carbonate component and, upon reaction with gastric acid, bubbles form in the gel, enabling floating.[29] These systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO_2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense and float on the gastric fluids.[29, 30] A patent assigned to Reckitt and Colman Products Ltd., describes a raft forming formulation for the treatment of *helicobacter pylori (H. Pylori*) infections in the GIT.

Figure 14: Barrier formed by a Raft Forming System

D. Swelling and expanding systems

These systems are sometimes referred to as plug- type systems because they tend to remain lodged at the pyloric sphincter. These polymeric matrices remain in the gastric cavity for several hours even in the fed state. Sustained and controlled drug release may be achieved by selecting a polymer with the proper molecular weight and swelling properties.[17,18] Upon coming in contact with gastric fluid, the polymer imbibes water and swells. The swollen system eventually will lose its integrity because of a loss of mechanical strength caused by abrasion or erosion or will burst into small fragments when the membrane ruptures because of continuous expansion. These systems also may erode in the presence of gastric juices so that after a predetermined time the device no longer can attain or retain the expanded configuration.The expandable GRDF's are usually based on three configurations: a small ('collapsed') configuration which enables convenient oral intake; expanded form that is achieved in the stomach and thus prevents passage through the pyloric sphincter; and finally another small form that is achieved in the stomach when the retention is no longer required i.e. after the GRDF has released its active ingredient, thereby enabling evacuation.[30]

Expandable gastro retentive dosage forms (GRDFs) have been designed over the past 3 decades. They were originally created for possible veterinary use but later the design was modified for enhanced drug therapy in humans. These GRDFs are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that prolong their GRT. After drug release, their dimensions are minimized with subsequent evacuation from the stomach. Gastro retentivity is enhanced by the combination of substantial dimensions with high rigidity of the dosage form to withstand the peristalsis and

mechanical contractility of the stomach. Positive results were obtained in preclinical and clinical studies evaluating the GRT of expandable GRDFs. Narrow absorption window drugs compounded in such systems have improved in vivo absorption properties.

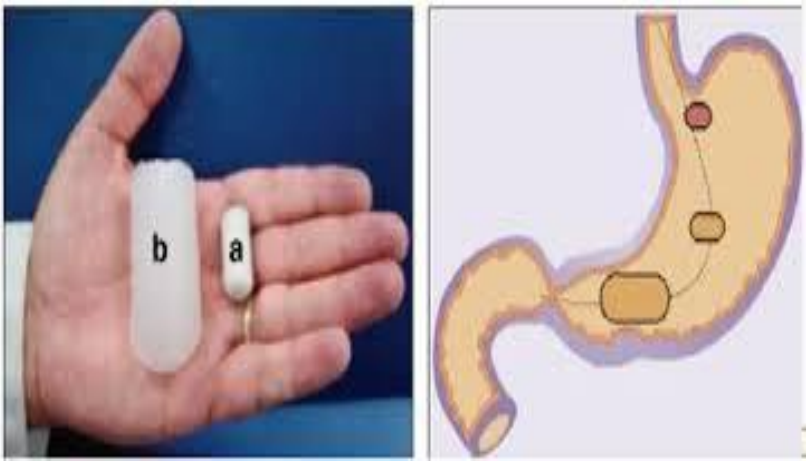

Figure 15: Swelling and expanding systems

E. Magnetic systems

This system is based on a simple idea that the dosage form contains a small internal magnet and a magnet placed on the abdomen over the position of the stomach. Ito *et al.* used this technique in rabbits with bioadhesive granules containing ultrafine ferrite (g-Fe2O3). They guided them to the oesophagus with an external magnet (1700 G) for the initial 2 min and almost all the granules were retained in the region after 2 h.[32] Although these systems seem to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance.

F. High-Density Systems

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Dense pellets (approximately 3g/cm-3) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on the diameter of the pellets. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to 1.5–2.4g/cm.

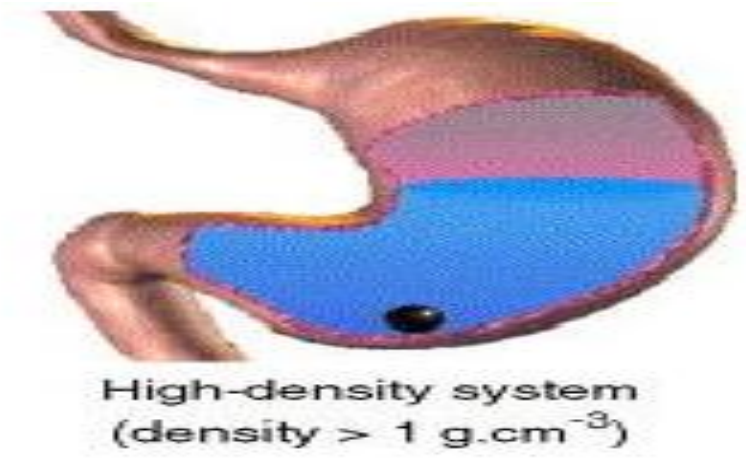

Figure 16: High-Density Systems

Other types of GRDDS

1. Large single unit dosage forms

These dosage forms are larger than the pyloric opening and so are retained in the stomach. There are some drawbacks associated with this approach. Permanent retention of rigid large-sized single-unit forms can cause bowel obstruction, intestinal adhesion and gastroplasty.

2. Incorporation of passage delaying food agents

Food excipients like fatty acids e.g. salts of myristic acid change and modify the pattern of stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C10-C14.

3. Ion exchange resins

Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads are then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide is released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads.

4. Osmotic regulated systems

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.

CONCLUSION

The major problem is the physiological variability such as gastrointestinal transit in addition to gastric retention time, as the later plays a dominating role in the overall transit of the dosage form. Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Over the last few decades, several gastro retentive drug delivery approaches being designed and developed. In future these novel drug delivery systems mentioned above, may lead to an important breakthrough in providing better bioavailability to poorly absorbed drugs, drugs used for bacterial infections in stomach like *H. Pylori* infections.

REFERENCES

1. Rocca JG, Omidian H, Shah K. Progresses in gastroretentive drug delivery systems. Business Briefing: Pharma Tech, 2003; 152–156.
2. Bardonnet PL, Faivre V, Pugh WJ, Piffaretti JC, Falson F. Gastroretentive dosage forms: Overview and special case of Helicobacter Pylori. J. Control. Release 2006; 111: 1-18.
3. Sharma N, Agarwal D, Gupta MK, Khinchi MP. Formulation and development of hydrodynamically balanced tablet of ranitidine hydrochloride. Asian J Pharm Health Sci., 2011; 1: 61-65.
4. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery system. Expert Opin Drug Deliv. 2006 Mar; 3(2): 217- 33.
5. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery system. Expert Opin Drug Deliv. 2006 Mar; 3(2): 217- 33.
6. Iannucelli V, Coppi G, Bernabei MT, Camerorni R. Air compertment multiple-unit system for prolonged gastric residence. Part-I. Formulation study. Int J Pharm. 1998; 174(1-2): 47-54.
7. Tortora GJ, Grabowski SR. Principles of anatomy and physiology. 8th ed. Harper Collins College Publishers, 1996; 658-669.

8. Wilson KJW, Waugh A. Anatomy and physiology in health and illness. 8th ed. (London): Churchill Livingstone, 1996.
9. Jain NK. Progress in Controlled and Novel Drug Delivery Systems, First Ed. CBS Publishers and Distributors, New Delhi, 2004; 84-85.
10. Wilson CG, Washington N. The stomach: its role in oral drug delivery. In: Rubinstein MH, ed. Physiological Pharmacetical: Biological Barriers to Drug Absorption. Chichester, UK: Ellis Horwood, 1989: 47-70.
11. Goyal M, Prajapati R, Purohit KK, Mehta SC. Floating Drug Delivery System. J. Curr. Pharm. Res. 2011; 5(1): 7-18.
12. Rouge N, Buri P, Doelker E. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. Int J Pharm. 1996; 136(1-2): 117 -139.
13. Hoichman D, Gromova LI, Sela J. Gastroretentive Controlled-Release Drugs. Pharmaceutical Chemistry Journal. 2004; 38: 621-4.
14. Mathur P, Saroha K, Syan N, Verma S, Nanda S, Valecha V. An overview on recent advancements and developments in gastro retentive buoyant drug delivery system. Der Pharmacia Sinica. 2011; 2(1): 161-169.
15. Vyas SP, Khar RK. Gastroretentive systems. In: Controlled drug Delivery. Delhi:Vallabh Prakashan editor; 2006; 197-217.
16. Bhowmik D, Chiranjib B, Chandira M, Jayakar,Kumar KPS. Floating Drug Delivery System-A Review. Der Pharmacia Lettre. 2009; 1(2): 199-218.
17. Chen J, Blevins WE, Park H, Park K. Gastric retention of superporous hydrogel composites. J Control Release. 2000, February, 14; 64(1): 39-51.
18. Chen J, Park K. Synthesis and characterization of superporous hydrogel composites. J Control Release 2000, March 1; 65(1-2): 73-82.
19. Huang Y, Leobandung W, Foss A, Peppas NA. Molecular aspects of muco- and bioadhesion: tethered structures and site-specific surfaces. J Control Release. 2000; 65(1-2): 63- 71.
20. Nayak AK,Malakar J, Sen KK. Gastroretentive drug delivery technologies: Current approaches and future potential. Pharm Educ Res. 2010; 1(1): 1-12.
21. Sing S, Joshi V, Barpete PK. Gastroretentive drug delivery systems: Current approaches. J Pharm Res. 2009; 2(5): 881-886.
22. Patil JM, Hirlekar RS, Gide PS, Kadam VJ. Trends in floating drug delivery systems. J Sci Ind Res. 2006 Janauary; 65: 11-21.

23. Hashim H, Li Wan Po A. Improving the release characteristics of water-soluble drugs from hydrophilic sustained release matrices by in situ gas-generation.Int J Pharm. 1987; 35: 201-206.
24. Katkam VK,Somagoni JM,Reddy S,Eaga CM.floating Drug Delivery:A review,Current Trends in Biotechnology and Pharmacy, 2010; 4: 610-20.
25. Jamil F, Kumar S, Sharma S, Vishvakarma P, Singh L. Review on Stomach Specific Drug Delivery Systems: Development and Evaluation. International Journal of Research in Pharmaceutical and Biomedical Sciences, 2011, December; 2(4): 1427-33.
26. Patel GM, Patel HR, Patel M. Floating drug delivery system an innovative approaches to prolong gastric retention.pharmainfo.net. 2007.
27. Gopalakrishnan S, Chenthilnathan A. Floating Drug Delivery Systems: A Review. Journal of Pharmaceutical Science and Technology. 2011; 3(2): 548-554.
28. Thakur N,Gupta BP, Patel D, Chaturvedi SK, Jain NP, Banweer J. A comprehensive review on floating oral drug delivery system. Drug Invention Today. 2010; 23: 328-30.
29. Mayavanshi AV, Gajjar SS. Floating drug delivery systems to increase gastric retention of drugs: A Review. Research J. Pharm. and Tech. 2008; 1(4): 345-8.
30. Nayak AK, Maji R, Das B. Gastroretentive drug delivery systems: a review. Asian J Pharm Clin Res. 2010; 3(1): 2- 10. Garg R, Gupta GD. Progress in Controlled Gastro retentive Delivery Systems. Trop J Pharm Res. 2008; 7(3): 1055-1066.
31. Chavanpatil M, Jain P, Chaudhari S, Shear R, Vavia P.Development of sustained release gastroretentive drug delivery system of ofloxacin: In vitro and In vivo evaluation. Int J Pharm. 2005; 304: 178-184.
32. Foda NH, Ali SM. Gastroretentive drug delivery systems as a potential tool For enhancing the efficacy of antibiotics: a review.International Journal of Pharma and Bio Sciences. 2011; 2: 94-104.
33. Indian Pharmacopoeia. Government of India, Ministry of Health and Family Welfare, vol II. Ghaziabad: The Controller of Publication, 2007; 457.