Review

Gastroretentive drug delivery systems: A review

Satinderkakar, Ramandeep Singh and Shalusandhan*
Himachal institute of Pharmacy, Paonta Sahib, India.
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Oral administration has only limited use for important drugs from various pharmacological categories, that have poor oral bio-availability due to incomplete absorption and/or degradation in the gastrointestinal tract (GIT). Drugs that are easily absorbed from the gastrointestinal tract (GIT) and have a short half-life are eliminated quickly from the blood circulation, so they require frequent dosing. To avoid this drawback, the oral sustained-controlled release formulations have been developed in an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the serum for longer period of time. However, such oral drug delivery devices have a physiological limitation of gastric retention time (GRT), variable and short gastric emptying time can result in incomplete drug release from the drug delivery system (DDS) in the absorption zone (stomach or upper part of small intestine), leading to diminished efficacy of the administered dose. The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. This idealized objective points to the two aspects most important to the drug delivery; namely spatial placement and temporal delivery of a drug. Spatial placement relates to targeting a drug to a specific organ or a tissue while temporal delivery refers to controlling the rate of drug delivery to that specific organ or a Tissue.

Key words: Gastroretentive, drugdelivery, controlled.

INTRODUCTION

Oral administration is the most convenient mode of drug delivery and is associated with superior patient compliance as compared to other modes of drug intake (Hofman A et al;2004). Approximately 50% of the drug delivery systems available in the market are oral drug delivery systems which have more advantages due to patient acceptance and ease of administration(Das, 2000). The oral absorption of drugs is often limited due to short gastric retention time (GRT), that is, the time required for the content of the stomach to enter small intestine(Shargel and Andrew,1999). Drugs that are easily absorbed from the GIT and have a short half-life are eliminated quickly from the blood circulation, so they require frequent dosing. To avoid this drawback, the oral sustained-controlled release formulations have been developed in an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the serum for longer period of time (Ma et al., 2008). However, such oral drug delivery devices have a physiological limitation of gastric retention time (GRT), variable and short gastric emptying time can result in incomplete drug release from the drug delivery system.

*Corresponding author. E-mail: shalinisandhan1990@gmail.com
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formulated but the oral route still remains preferable.

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. This idealized objective points to the two aspects most important to the drug delivery, namely; spatial placement and temporal delivery of a drug. Spatial placement relates to targeting a drug to a specific organ or a tissue while temporal delivery refers to controlling the rate of drug delivery to that specific organ or a tissue (Lee and Robinson, 2000). Controlled drug release technology represents one of the frontier areas of science which involves multidisciplinary scientific approach, contributing to human health care. These drug delivery systems have a great potential of solving the problems associated with the conventional multiple dosing systems like strict adherence to timely dosing, flip-flop plasma concentrations, associated side effects due to systemic accumulation of drug and patient non-compliance. Thus, there are numerous advantages such as improved efficacy, reduced toxicity, improved patient compliance and convenience etc.(Lalla,1991).

An appropriately designed sustained or controlled release drug delivery system can be a major advance toward solving the problems associated with the existing drug delivery systems(Khan,2001). Thus, a number of approaches are being developed. The common thread running through the approaches is the concept of self-administered, targeted, controlled release systems with increased bio-availability. However, incomplete release of the drug and a shorter residence time of dosage forms in the upper gastrointestinal tract, a prominent site for absorption of many drugs, will lead to lower bio-availability. Efforts to improve oral drug bio-availability have grown in parallel with the pharmaceutical industry. As the number and chemical diversity of drugs has increased, new strategies are required to develop orally active therapeutics. The past two decades have been characterized by an increased understanding of the causes of low bio-availability and a great deal of innovation in oral delivery technologies, marked by an unprecedented growth of the drug delivery industry (Orellana and Isabel, 2005). Thus, gastro retentive dosage forms which prolong the residence time of the drugs in the stomach and improve their bio-availability have been developed.

Oral delivery of drugs is by far the most preferable route of drug delivery due to ease of administration, patient compliance and flexibility in formulation. Development of oral controlled-release systems has been a challenge to formulation scientists because of their inability to restrain and localize the system in the targeted area of the gastrointestinal tract. Controlled/sustained release preparations using alternative routes have been formulated but the oral route still remains preferable.

When the drug is formulated with a gel forming polymer such as semisynthetic derivatives of cellulose, it swells in the gastric fluid with a bulk density less than one. It then remains buoyant and floats in the gastric fluid, and prolongs GRT (Patel et al., 2006).

Single-unit formulations are associated with problem being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation. On the other hand, a floating system made of multiple unit forms have relative merits compared to a single-unit preparation. On each subsequent gastric emptying, sunk particles will spread out over a large area of absorption sites, increasing the opportunity for drug release profile and absorption in a more or less predictable way. Moreover, since each dose consists of many sub-units, the risk of dose dumping is reduced (Gadad et al., 2009).

Gastric emptying of dosage form is an extremely variable process and its ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a long period of time than conventional dosage forms. Several difficulties are faced in designing controlled released systems for better absorption and enhance the bio-availability. Conventional oral dosage forms such as tablets, and capsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. Although single-unit floating dosage forms have been extensively studied, these single-unit dosage forms have the disadvantage of a release all or nothing during emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral controlled drug delivery and led to development of gastro retentive floating microspheres. This floating dosage form enhance bio-availability, having a dissolution and/or stability problem in the small intestine fluids, being locally effective in the stomach, being absorbed only in the stomach and/or upper part of the intestine (Sharma and Pawar, 2006).

STOMACH

An overview

The stomach is located in the upper left-hand portion of the abdomen just below the diaphragm(Tortora and Grabowski,2000). It occupies a portion of the epigastric and left hydrochondriac region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Due to its small surface area, very little absorption takes place from the stomach (Ross and Wilson, 2001).
### Table 1. pH range of various organs.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>pH range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>1-3</td>
</tr>
<tr>
<td>Small intestine</td>
<td>5-7.5</td>
</tr>
<tr>
<td>Large intestine</td>
<td>7.9-8</td>
</tr>
<tr>
<td>Rectum</td>
<td>7.5-8</td>
</tr>
</tbody>
</table>

**Structure**

The stomach has four main regions. The main function of fundus and body is storage, whereas that of cardia is mixing or grinding. The fundus adjusts the increased volume during eating by relaxation of the fundus muscle fibers. The fundus also exerts a steady pressure on the gastric contents pressing them towards the distal stomach. To pass through the pyloric valves into the small intestine, particles should be of size of 1 to 2 mm called chime. Anatomy of stomach is shown in Figure 1.

**Functions of stomach**

The stomach carries three major functions. It stores food, digest food and delivers food to the small intestine at a rate that the small intestine can handle.

1. Acts as a reservoir for holding food before it release into the small intestine.
2. Secrete gastrin into the blood.
3. Secretes gastric juice, which contains hydrochloric acid, pepsin, intrinsic factor and gastric lipase.
4. Mixes food and gastric juice to form chyme.

The pH range is shown in Table 1.

**Regulation of gastric secretion and motility**

Both neural and hormonal mechanisms control the secretion of gastric juice and the contraction of smooth muscles in the stomach wall. Events in gastric secretion occur in three overlapping phases; cephalic phase, gastric phase and intestinal phase.

**Cephalic phase**

The cephalic phase refers to the influence of the brain on secretion. Even before food enters the stomach, the sight, taste or thought of food initiate this phase, the secretion is brought about through stimulation of the nerve. This leads to presence of acid and pepsin in the stomach even before food enters the stomach (Saravanan et al., 2004).

**Gastric phase**

The gastric phase of secretion is brought about by the presence of food in the stomach. It is controlled by the hormone gastrin which is produced in the mucosa of the pyloric region of the stomach. Gastrin is released in response to stretching of the antrum caused by the presence of food in this region or in response to specific substances in the food; particularly proteins, alcohol and coffee are also potent stimulants of gastrin release. Once released, the gastrin is transported through the blood to stomach where it stimulates the secretion of hydrochloric acid and pepsinogen (Costa and Lobo, 2001).

**Intestinal phase**

The intestinal phase of acid secretion refers to the influence of the small intestine on gastric secretion. If the material present in the duodenum of the small intestine is too acidic, a hormone is released by the intestinal mucosa. This hormone is carried out by the blood to the body of the stomach where it inhibits further acid secretion. This serves as a protective device for the small intestine which is not as well protected against acid as the stomach. The total volume of gastric secretion in response to all the stimuli mentioned above is approximately 2 to 3 L per day (Kulkarni et al., 2004).

**Gastric emptying**

The process of gastric emptying occurs both during fasting and fed states. However, the pattern of motility differs markedly in the two states. In the fasted state, it is characterized by an inter-digestive cycle both through the stomach and small intestine, every 2 to 3 h. This activity is called the inter-digestive myoelectric cycle or migrating myoelectric complex (MMC). It is composed of four phases (Arora et al., 2005). The activities during gastric emptying is shown (Table 2).

1. Phase I (basal phase) lasts from 40 to 60 min with rare contractions.
2. Phase II (preburst phase) lasts for 40 to 60 min with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 min. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
4. Phase IV lasts for 0 to 5 min and occurs between phases III and I of 2 consecutive cycles.

**Factors affecting gastric retention**

Gastric residence time of an oral dosage is affected by several factors.
Table 2. Activities during phases of gastric emptying.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I (basal phase)</td>
<td>Period of rare contraction lasting from 40 to 60 min</td>
</tr>
<tr>
<td>Phase II (pre-burst phase)</td>
<td>Period intermittent contraction and of similar duration of 60 min</td>
</tr>
<tr>
<td>Phase III (burst phase)</td>
<td>Period of regular contraction at the maximal frequency lasting from 4 to 6 min</td>
</tr>
<tr>
<td>Phase IV</td>
<td>Period of transition between phase III and Phase I and last for 0 to 5 min</td>
</tr>
</tbody>
</table>

Figure 1. Anatomy of stomach.

1. Volume of meal: the larger the bulk of meal, the longer will be the gastric emptying time.
2. Composition of meal: fats promote the secretion of bile, which has an inhibitory effect on gastric emptying time.
3. Physical state of food and dosage form: viscous material empty slowly than less viscous materials.
4. Exercise: Retards gastric emptying time.
5. Emotion: Stress and anxiety promotes gastric motility where as depression retards it.
6. Circadian rhythms: Cardiac rhythms are increased in day time and less during night also affect the gastric retention time.
7. Size of the dosage form: Greater the energy content of meal (carbohydrate and high fat content), longer the duration of emptying.
8. Density of oral dosage form: The density of gastric fluid is reported to be 1.2g/cm³. The density of the dosage form should be less than this for buoyancy so that it is retained in the stomach for longer period of time.
9. Diseased state: state of the stomach also affects the environment for the dosage form as in case of ulcers, flatulence and spasms (Brahmankarand Jaiswal,2006).
10. Drug therapy: It also plays an important role in gastric emptying e.g. prokinetic drugs like cisapride and mosapride increase gastric emptying time whereas imipramine and atropine retards it.
11. Age: Increase in age decreases gastric motility there by increasing the gastric emptying time.
12. Posture: Gastric emptying is favored while standing and by lying on right side since normal curvature of the stomach provides a downhill path whereas lying on the left side or in supine position retards it.

GASTRO RETENTIVE DRUG DELIVERY SYSTEMS (GRDDS)

It is evident from the recent scientific and patent literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of the time exists today in academic and industrial research groups (Gargand Gupta, 2008).

Criteria for selection of drug candidate for GRDDS

The gastro retentive drug delivery systems are suitable for following types of drug therapy:

1. Drugs those are locally active in the stomach e.g.
misoprostol, antacids etc.
2. Drugs that have narrow absorption window in gastrointestinal tract (GIT) for example, LDOPA, paraaminobenzoic acid, furosemide, riboflavin etc.
3. Drugs that are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.
4. Drugs that disturb normal colonic microbes e.g. antibiotics against Helicobacter pylori.
5. Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide, verapamil HCl (Nayak et al., 2010).

Advantages of GRDDS

1. Enhanced bio-availability.
2. Reduced frequency of dosing.
3. Targeted therapy for local ailments in the upper GIT.
4. Patient compliance.
5. Improved therapeutic efficacy (Singh and Kim, 2000).

Gastro-retentive drug delivery system (GRDDS) greatly improves pharmacotherapy of the stomach through local drug release leading to high drug concentrations at gastric mucosa (eradicating helicobacter pylori from the sub mucosal tissue of the stomach), making it possible to treat stomach and duodenal ulcers, gastritis, and esophagitis, reduce the risk of gastric carcinoma, controlled release antacid formulations. GRDDS can be used as carriers for drugs which are absorbed from absorption windows in stomach. For example various antibiotics, antiviral and antifungal agents etc. (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides and tetracyclines, etc.) are taken up only from very specific sites of the GI mucosa.

Disadvantages of GRDDS

There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions and slow release of such drugs in the stomach is unwanted. Thus drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastro retentive systems. Furthermore, other drugs such as isosorbindinitrate that are absorbed equally well throughout the GIT will not be suitable for incorporation into a gastric retention system (Deshpandeet al., 1997). Also GRDD’s have some limitations such as:

1. Requirement of high levels of fluids in stomach for the delivery system to float and work efficiently.
2. Requires the presence of food to delay gastric emptying.
3. Drugs, which undergo significant first pass metabolism, may not be desirable candidates for floating drug delivery system since the slow gastric emptying.

4. May lead to alter systemic bioavailability.
5. Drugs having solubility or stability problems in the highly acidic gastric environment or which are irritants to gastric mucosa cannot be formulated as GRDDS.

On the other hand, violent gas generation, disintegration of dosage forms, burst release, dose dumping and alkaline micro-environment are the limitations of floating alginate beads. In case of bio-adhesive systems, the acidic environment, thick mucus as well as high turnover rate of mucus prevents bond formation at the mucous polymer interface. For swell-able systems, the dosage form must maintain a size larger than the aperture of the resting pylorus for required time period.

Applications of GRDDS

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 (Shirwalkar et al., 2006). Marketed products of GRDDS are shown in Table 4.

APPROACHES TO GASTRIC RETENTION

A number of approaches have been used to increase GRT of a dosage form in stomach by employing a variety of concepts. These Includes.

Sustained drug delivery

Hydro-dynamically balanced systems (HBS) 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 a bulk density less than 1 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 (Mayavanshi and Gajjar, 2008).

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, for example riboflavin and furosemide.

Absorption enhancement

Drugs that have poor bio-availability because of site
specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption (Deepa and Karthikeyan, 2009). This is illustrated in Figure 2.

**Floating systems**

Floating drug delivery systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system floats on gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in gastric retention time and a better control of fluctuations in plasma drug concentrations. Floating systems can be classified into two distinct categories, no effervescent and effervescent systems (Rajinikanth et al., 2008).

**Bio/muco-adhesive systems**

Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending gastric residence time of drug delivery system in stomach, by increasing the intimacy and duration of contact of drug with the biological membrane. Binding of polymers to mucin/epithelial surface can be divided into three broad categories, name; Hydration-mediated adhesion bonding-mediated adhesion and receptor-mediated adhesion.

**Swelling and expanding systems**

These are dosage forms, which after swallowing, swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in stomach for a long period of time. These systems may be named as “plug typesystem”, since they exhibit tendency to remain logged at the pyloric sphincter (Fursule et al., 2008) Various types of floating drug delivery systems are shown in Table 3.

**High density systems**

These systems with a density of about 3 g/cm³ are retained in the rugae of stomach and are capable of withstanding its peristaltic movements. A density of 2.6 to 2.8 g/cm³ acts as a threshold value after which such

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**Table 3. Various types of floating drug delivery systems**

<table>
<thead>
<tr>
<th>Dosage forms</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets</td>
<td>Acetaminophen, acetylsalicylic acid, amoxicillin, atenolol, chlorpheniramine, diltiazem, Isosorbidenononitrate, Prednisolone, Theophylline, Sotalol, Prednisolone, Quinidine gluconate, Piretanide</td>
</tr>
<tr>
<td>Capsules</td>
<td>Diazepam, furosemide, misoprostol, benserazide, L-Dopa</td>
</tr>
<tr>
<td>Films</td>
<td>Cinnarizine</td>
</tr>
<tr>
<td>Granules</td>
<td>Diclofenac sodium, indomethacin, prednisolone</td>
</tr>
<tr>
<td>Microspheres</td>
<td>Aspirin, ibuprofen, griseofulvin, tranilast</td>
</tr>
<tr>
<td>Powders</td>
<td>Basic drugs</td>
</tr>
</tbody>
</table>
systems can be retained in the lower parts of the stomach. High density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc.

Incorporation of passage delaying food agents

Food excipients like fatty acids, for example 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 to C14 (Rokhade et al., 2007).

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 in contrast to the uncoated beads, which will sink quickly.

Osmotic regulated 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 intra-gastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. Osmotic system is shown in Figure 4. The osmotic controlled drug delivery device consists of two components—drug reservoir compartment and osmotically active compartment (Srivastava et al., 2005).

FLOATING DRUG DELIVERY SYSTEMS (FDDS)

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are; effervescent system and non-effervescent system. Intragastric floating drug delivery devices are shown in Figure 7.

Effervescent systems

These buoyant delivery systems are prepared with swellable polymers such as methocel or polysaccharides for example, chitosan and effervescent components, e.g. sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature. The matrices are fabricated so that upon contact with gastric fluid, carbon dioxide is liberated by the acidity of gastric contents and is entrapped in the gelled hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy (Arora et al., 2005). The effervescent systems are classified into:

Multiple-unit oral floating drug delivery system

Recently a multiple-unit type of floating pill, which generates carbon dioxide gas, has been developed (Figure 3). The system consisted of sustained release pills as seeds surrounded by double layers. The inner layer is an effervescent layer containing both sodium bicarbonate and tartaric acid. The outer layer was a
swell-able membrane layer containing mainly polyvinyl acetate and purified shellac. Moreover, the effervescent layer was divided into two sub layers to avoid direct contact between sodium bicarbonate and tartaric acid. Sodium bicarbonate was contained in the inner sub layer and tartaric acid was in the outer layer. When the formed swollen pills, like balloons, with a density much lower than 1.004 g/cm³. The reaction was due to carbon dioxide generated by neutralization in the inner effervescent layer with the diffusion of water through the outer swell-able membrane layer (Yeole, 2005).

The system was found to float completing within 10 min and approximately 80% remained floating over a period of 5 h irrespective of pH and viscosity of the test medium. A floating system utilizing ion-exchange resins have been developed. The system consisted of resin beads, which were loaded with bicarbonate and a negatively charged drug that was bound to the resin. The resultant beads were then encapsulated in a semi permeable membrane to overcome rapid loss of carbon dioxide. Upon arrival in the acidic environment of stomach, an exchange of chloride and bicarbonate ion took place, as was expected. As result of this reaction, carbon dioxide was released and trapped in the membrane, thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads. In contrast, the uncoated beads sank quickly. Radioactivity measurement by scintigraphy showed that gastric residence was substantially prolonged, compared with a control, when the system was given after a light, mainly liquid meal. Furthermore, the system was capable of slow release of drug. A property which widens the scope of such floating system for SR preparation of drugs possessing negative charge since they can be easily bound to the resin in combination with bicarbonate ions. Two patents on FDDS issued to the Alza Corporation disclosed drug delivery devices for the controlled and continuous administration of medicinal agents (Garg and Sharma, 2003).

**Inflatable gastrointestinal drug delivery system**

The residence time of the drug delivery device in the stomach can also be sustained by incorporation of an inflatable chamber, which contains a liquid, e.g. ether that gasifies at body temperature to cause the chamber to float in the stomach.

**Intragasricosmotically controlled drug delivery system**

It is comprised of an osmotic pressure controlled drug delivery and an inflatable floating support in a bio-erodible capsule. When the drug delivery device reaches the site of drug administration e.g. the stomach, the capsule quickly disintegrates to release the
Intragastricosmotically controlled drug delivery device. The inflatable floating support is made from a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. This system is shown in Figure 7.

**Osmotic controlled drug delivery system**

Although single unit floating dosage forms have been extensively studied, these single unit dosage forms have the disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral controlled drug delivery and led to development of gastro-retentive floating microsphere (Vyasand Khar, 2002).

**Non-effervescent systems**

Commonly used excipients, here are gel-forming or highly swell-able cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polycrylate, polymethacrylate and polystyrene. One of the approaches to the formulation of such floating dosage forms involves intimate mixing of drug with the gel-forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than 1 and thus remains buoyant in the gastric fluid inside the stomach for up to 6 h. System is illustrated in Figure 5.

**Principle of hydrodynamically balance system**

**Bilayer tablet**

A bilayer tablet can be prepared to contain one immediate-release layer and one sustained-release layer. After the initial dose is delivered by the immediate release layer, the sustained release layer absorbs the gastric fluid and forms a colloidal gel barrier on its surface. This produces a bulk density less than that of the gastric fluid and remains buoyant in the stomach for extended period of time (Altaf et al., 2008). Bilayer tablet is shown in Figure 6.

**Intragastic floating gastrointestinal drug delivery system**

A gastrointestinal drug delivery system (GIDS) can be made to float in the stomach by incorporating a floatation chamber, which may be a vacuum or filled with a harmless gas (Rahman et al., 2006). A drug reservoir is encapsulated inside a microporous compartment with apertures along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the stomach mucosal surface with the undissolved drug. In the stomach the floatation chamber causes the GIDS to float in the gastric fluids. Fluids enter through the apertures, dissolve the drug, and carry and drug solute out of the drug delivery system for controlled transport to the intestine for absorption (Bolourtchian et al., 2008).

**Hollow/floating microspheres**

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres are in strict sense, spherical empty particles without core. These microspheres are prepared by incorporating a high level (20 to 75% w/w) of one or more gel-forming hydrocolloids, for example hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose and sodium carboxymethylcellulose into the formulation and then compressing these granules into a tablet (or encapsulating into capsules). On contact with gastric fluid the hydrocolloid in this intragastric floating device start to become hydrated and forms a colloid gel barrier around its surface with thickness growing with time. This gel barrier controls the rate of solvent penetration into the device and the rate of drug release from the device (Indian Pharmacopoeia Commission, 2007). It maintains a bulk density of less than 1 and thus remains buoyant in the gastric fluid inside the stomach for up to 6 h. System is illustrated in Figure 5.
characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer. Solid bio-degradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs (Xuet al., 2006). Gastro retentive floating microspheres are low density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration (Gryllaki et al., 2007). Preparation of floating microspheres by solvent evaporation method is shown in Figure 8.

### List of polymers used in hollow microspheres

Cellulose acetate, chitosan, eudragit, acrycoat, methocil,
Figure 7. Intra gastric floating drug delivery devices.

Figure 8. Preparation of floating microspheres using the solvent evaporation method.

Table 4. Marketed products of GRDDS

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Drug</th>
<th>Company,Country</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citran OD®</td>
<td>Ciprofloxacin (1 g)</td>
<td>Ranbaxy, India</td>
<td>Gas generating floating tablets</td>
</tr>
<tr>
<td>Madopar®</td>
<td>Levodopa (100 mg)</td>
<td>Roche products, USA</td>
<td>Floating controlled release capsule</td>
</tr>
<tr>
<td>Valrelease®</td>
<td>Diazepam (15 mg)</td>
<td>Hoffmann LaRoche, USA</td>
<td>Floating capsule</td>
</tr>
<tr>
<td>Topalkan®</td>
<td>Al-Mg antacid</td>
<td>Pierre Fabre Drug, France</td>
<td>Floating liquid alginate preparation</td>
</tr>
<tr>
<td>Oflin OD®</td>
<td>Ofloxacin (400 mg)</td>
<td>Ranbaxy, India</td>
<td>Gas generating floating tablet</td>
</tr>
<tr>
<td>Conviron</td>
<td>Ferrous sulphate</td>
<td>Pharmacia, India</td>
<td>Colloidal gel forming FDDS</td>
</tr>
<tr>
<td>Cytotec®</td>
<td>Misoprostol (100 µg/200 µg)</td>
<td></td>
<td>Bilayer floating capsule</td>
</tr>
<tr>
<td>Liquid Gaviscon®</td>
<td>Aluminium hydroxide (95 mg), Magnesium carbonate (358 mg)</td>
<td>Glaxosmithkline, India</td>
<td>Effervescent floating liquid alginate preparation</td>
</tr>
</tbody>
</table>

polyacrylates, polyvinyl acetate, carbopol, agar, polyethylene oxide, polycarbonates, acrylic resins and polyethylene oxide (Gupta et al., 2007).

Advantages of hollow microspheres

1. Improves patient compliance by decreasing dosing frequency.
2. Bioavailability enhances despite first pass effect because fluctuations in plasmadrug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.
3. Gastric retention time is increased because of buoyancy.
4. Enhanced absorption of drugs which solubilize only in
stomach
5. Drug releases in controlled manner for prolonged period.
6. Site-specific drug delivery to stomach can be achieved (Basavaiah and Prameela, 2004).
7. Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
8. Avoidance of gastric irritation, because of sustained release effect.
9. Better therapeutic effect of short half-life drugs can be achieved (Reymond et al., 1986).

LIMITATIONS
Floating drug delivery system requires sufficiently high level of fluids in stomach for the drug delivery to float and to work efficiently. It is not suitable for those drugs that have solubility or stability problems in gastric fluids. Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergoes significant first-pass metabolism may not be desirable candidates for FDDS, since the slow gastric emptying may lead to reduce systemic bioavailability of FDDS for drugs that are irritant to gastric mucosa (Nilkumhang and Basit, 2009).

Methods of preparation of hollow microspheres
Hollow microspheres are prepared by solvent diffusion and evaporation methods to create the hollow inner core. Polymer is dissolved in an organic solvent and the drug is either dissolved or dispersed in the polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing polyvinyl alcohol to form oil in water emulsion. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring. The solvent removal leads to polymer precipitation at the o/w interface of droplets, forming cavity and thus making them hollow to impart the floating properties (Basavaraj et al., 2008).

Mechanism of floating microspheres
When microspheres come in contact with gastric fluid the gel formers, polysaccharides, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. However a minimal gastric content needed to allow proper achievement of buoyancy. Hollow microspheres of acrylic resins, eudragit, polyethylene oxide, and cellulose acetate; polystyrene floatable shells; polycarbonate floating balloons and gelucire floating granules are the recent developments (Mastiholimath et al., 2007).

CONCLUSION
The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body and also to achieve and maintain the desired plasma concentration of the drug for a particular period of time. However, incomplete release of the drug, shorter residence times of dosage forms in the upper GIT leads to lower oral bio-availability. Such limitations of the conventional dosage forms have paved way to an era of controlled and novel drug delivery system.

Conflict of interest
Authors have none to declare.

REFERENCES