Updates on Approaches to Increase the Residence Time of Drug in the Stomach for Site Specific Delivery: Brief Review

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ABSTRACT
In the field of oral drug delivery system, a gastroretentive system is gaining popularity day by day. Numerous of research work and extensive literature are published in past few years on gastroretentive drug delivery system. It is the one of the best and appropriate approaches for increasing the residence time of drug in the stomach and diffuses drug slowly in the sustained manner which helps in the site-specific delivery of the drug as well also increases the bioavailability at site-specific of delivery. This helps in many challenges associated with conventional oral drug delivery system. Different ways are used for approaching gastroretention viz. swelling and expandable system, high-density system, magnetic system, bioadhesive system and buoyant system with or without gas generating agents. During data mining well in vitro characterization and in vivo characterization including gamma scintigraphic and MRI techniques are well established and reported. But, still, today in vivo characterization technique is major challenging for the researcher due to its limitation. The documented literature explains the use of animal models like beagle dogs, rabbits and human subjects for in vitro evaluation parameter but it leads to increase in variation that’s why this delivery system is limited in the market. This paper contains the latest literature compilation and various techniques used for gastroretention with its pros and cons. This review paper helps the researcher to take an overview of basics of gastroretentive drug delivery system and helps in understanding the basics of the system.

Key Words: gastroretentive system, site-specific delivery, bioavailability, gastroretention.

INTRODUCTION
The human stomach is divided into three main distinct parts: fundus, body, and antrum (pylorus) which is pictorially depicted in figure 1. The part of fundus and the body acts as a storage for any undigested materials and antrium acts as an important site for mixing action. The main role of antrum acts as a propelling pump for gastric emptying because it is situated in the lower part of the stomach. Pylorus acts as storage for undigested food material and also provides a gastric residence time (Streubel et al., 2006; Nayak et al., 2010).

PHYSIOLOGY OF STOMACH
The physiology and disease state of the stomach has an important effect on the design of suitable drug delivery system (dosages form) because the drug is absorbed and enters into the site of action to the systemic circulation (table 1). Drug release and absorption in the stomach is affected by pH nature, volume of gastric secretion and gastric mucosa (Horter et al., 2003; DeSesso et al., 2001).

pH
Internal microclimate pH affects the bioavailability of orally administered drugs. A heavy mass of fluid administered with oral dosage form changes the pH of the abdomen. This change attributed due to the stomach does not have adequate time to get sufficient quantity of acid before emptying of liquid from the abdomen.

Volume of stomach
The resting volume of the stomach ranges from 25-52 ml. Gastric volume plays a significant role for in vivo dissolution of the dosage forms.

Gastric Secretion by stomach
Secretory enzymes of the stomach are acids, pepsin, gastrin, mucus and some other enzymes. Normal adults produce a secretion up to 60ml with approximately 4 milimole (4 mmol) of hydrogen ions per hour. Other important stimulators of gastric acid are the hormone such as gastrin, peptides, amino acids and gastric distention.

Effect of Food on Gastric Secretion
Type of meal and its caloric content, volume of the meal, viscosity of meal and administered drugs affect gastric secretions and gastric emptying time. The rate of gastric emptying time primarily depends on caloric contents of the repast. By and large, gastric emptying is slowed down because of increased acidity, osmolarity, and caloric values of nutrient.

MIGRATING MOTOR COMPLEX (MMC)
The gastric motility is different for the fast and fed state. The gastric motility is classified into the cycles of activity during fast and fed state. The time duration of each phase runs from 90 to 120 minute. The motion pattern of the stomach called as migrating motor complex (MMC) which maintain and regulates the gastrointestinal motility pattern (Awasthi et al., 2016). It consists of four phases: Phase I called as base or immediate phase, Phase II called as preburst phase, Phase III called as burst phase and Phase IV called as transition phase intervals (Figure 2). Phase I the immediate period, lasts from 30 to 60 min which is distinguished by a lack of secretory, electrical, and contractile activity. Phase II exhibits intermittent action for 20–40 min, also to continuous gastric emptying process through the
The oral route of administration is the easiest and convenient route for disposal of a drug to the patient (Zhang et al., 2002). Oral controlled/sustained release system has been increasing in the pharmaceutical manufacture to achieve better therapeutic benefits and merits like the ease of dosing, better patient compliance and suppleness for the formulator for designing and development of dosage form (Sastry et al., 2000). The main barrier in controlled/sustained release system is that not all drugs absorbed uniformly throughout the gastrointestinal tract. Some drugs are absorbed uniformly throughout the entire gastrointestinal tract or some absorbed to a different extent in various segments of the gastrointestinal tract, such drugs are said to have an absorption window in a particular region. So the drug releases its active content in a particular absorption window for absorption. This gene plays an important role in dosages form to increase the bioavailability in the stomach for site-specific targeting. After crossing the absorption window the drug shows negligible or no response. Gastric emptying time is also the major problem of the dosage form, decrease in gastric emptying time leads to decrease in the residence time in the stomach which ultimately involves the drug bioavailability for site specific action (Singh et al., 2000). To increase the gastric residence in the stomach several approaches are designed by formulat- ors such as bioadhesive, raft forming, expanding and single/multiple units floating drug delivery system (figure 3). Over the last three decades, these are the focusing fields to localize the drug at the site of drug targeting site to give site-specific discourse (Singh et al., 2000; Rocca et al., 2003).

The stomach is the major site for achieving gastroretention for the drugs. It is located in the left upper part of the abdominal cavity immediately under the diaphragm part. The size of the stomach varies according to the quantity of food and volume of fluid intake. After intake of meal size up to 1500 ml, in a collapsed state after emptying of stomach its volume is 25-52 ml (Nayak et al., 2010). The prerequisite parameter for achieving gastroretention is that formulation must withstand the forces of peristaltic waves created during the motility process, churning and grinding mechanism in the stomach. It must be having resistance to resist premature gastric emptying time; once the gastric retention is achieved it must be easily removable (Arora et al., 2005).

Gastroretentive drug delivery system (GDDS) has a bulk density lower than the gastric content i.e. 1.064 g/cm³, therefore, remain buoyant in the stomach for the prolonged period of time (Awasthi et al., 2016). At last residual system is evacuated from the abdomen. Gastric emptying is much faster in fasting state as compared to fed state, the possible reason for such type of phenomenon is due to the floating system depends to a large extent on the presence of food to retard gastric emptying time and provide sufficient liquid for effective buoyancy (Arora et al., 2005; Verma et al., 2016).

Since 1960, different approaches have been taken up by the researcher to increase the residence time of drug in the stomach. The concept of a high-density system (2.5 to 3.0 gm/ml) was taken by the researcher in the past to increase the residence time of the drug by using polymers which are having high viscosity. These systems with stand in vivo peristaltic movement and remained intact in the stomach for the desired period of time (Verma et al., 2016). Average gastrointestinal transit time (GTT) ranges from 5.8 hours to 25 hours (table 3) in the different gastroretentive dosage form (Talukder et al., 2004). Components like barium sulfate, iron oxide, titanium dioxide and zinc oxide were added in the formulation to increase the density of the system. Chawla et al., 2003 reported that achieving gastric retention for high-density system high drug loading was required, which was the drawback of this system (Chawla et al., 2003). Another approach was employed for achieving gastroretention in the stomach by using magnetic fields. Such type of system should contain magnetically active compounds. The external magnet was required to put along the abdomen over the positioning of the stomach to retain the loaded drug. Lack of patient compliance is the major drawback of this system (Murphy et al., 2009). As the

**Figure 1:** Diagram of human stomach (Mandal et al., 2016).

**Figure 2:** Motility patterns of GIT in the fasted state (Awasthi et al., 2016).
research progresses swelling and expandable system attracts the researcher and it achieves significant success in vitro as well as in vivo (Garg et al., 2008). Bolton et al. (1989) reported about ‘plug-type system’ which expands in the stomach when coming in contact with gastric juice by using hydrophilic swelling polymers, these polymers hydrates, and swells. After swelling, size increases to the diameter of pyloric sphincter and remain intact in the stomach for the desired period of time. Selection of swellable polymers depends on its molecular weight, changing in grades etc. This swelling property of polymers affects the retardation of the drug from its swollen polymeric structure (Bolton et al., 1989). Chordiya et al. (2013) introduced the use of novel porous hydrogel polymers, which causes the swelling of polymer within a minute when it gets in contact with gastric juice. Rapid swelling property of the porous hydrogel polymer depends on its pore size more than 100 µm which causes an increase in capillary wetting through the interconnected pores after coming to the gastric fluid.

Rosenzweig et al. (2013) developed and characterized buoyant gastroretentive dosage form. These systems have the density lower than the gastric fluid (1.064 gm/cm³). Lag time depends upon the hydration, swelling, and characteristics of polymer (molecular weight, viscosity, and grade) of the polymers used in the formulation. The mentioned parameters also affect the retardation lag time and duration of floatation of formulations. Floatation time of formulation also depends on the physiological state of patients like disease state, fast and fed state, amount of gastric fluid content etc. After retention for a desired period of time, the system emptied out from the stomach. For improvement of floating time, including lag time of formulation efervescence generating agents was incorporated in the formulation. The various gas generating agents like calcium carbonate, citric acid, and tartaric acid was used. These gas generating agents when comes in contact with gastric fluid liberates CO₂ as a result of a chemical reaction. This CO₂ entrapped inside the polymeric structure of the polymer and creates density lesser than the utility i.e. 1.064.

<p>| Table 1: Anatomical and physiological feature of the gastrointestinal tract (DeSesso et al., 2001; Chawla et al., 2003). |</p>
<table>
<thead>
<tr>
<th>Section</th>
<th>Avg length (cm)</th>
<th>Dia (cm)</th>
<th>Villi present</th>
<th>Absorption mechanism</th>
<th>pH</th>
<th>Major constituents</th>
<th>Food Transit time (Hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>15-20</td>
<td>10</td>
<td>-</td>
<td>Convective transport and passive diffusion mechanism</td>
<td>5.2-6.8</td>
<td>Amylase, maltase, pylin and mucin</td>
<td>short</td>
</tr>
<tr>
<td>Esophagus</td>
<td>25</td>
<td>2.5</td>
<td>-</td>
<td>Not reported</td>
<td>5.0-6.0</td>
<td>-</td>
<td>Very short</td>
</tr>
<tr>
<td>Stomach</td>
<td>20</td>
<td>15</td>
<td>-</td>
<td>Convective transport and passive diffusion mechanism</td>
<td>1.2-3.5</td>
<td>HCl, pepsin, trypsin, rennin, lipase</td>
<td>-</td>
</tr>
<tr>
<td>Duodenum</td>
<td>25</td>
<td>05</td>
<td>*</td>
<td>Passive diffusion, convective, Active, facilitated transport, ion pair, pinocytosis mechanism</td>
<td>4.6-6.0</td>
<td>Bile, trypsin, chyotrypsin, 1-2 amylase, malate lipase, nuclease, CYP3A4</td>
<td>-</td>
</tr>
<tr>
<td>Jejunum</td>
<td>300</td>
<td>5</td>
<td>**</td>
<td>Passive diffusion, convective, Active, facilitated transport mechanism</td>
<td>6.3-7.3</td>
<td>Amylase, maltase, lipase, Sucrose, CYP3A5</td>
<td>Not reported</td>
</tr>
<tr>
<td>Ileum</td>
<td>300</td>
<td>2.5-5.0</td>
<td>**</td>
<td>Passive diffusion, convective, active, facilitated transport, ion pair, pinocytosis mechanism</td>
<td>7.6</td>
<td>Nuclease, nucleotidase, enterokinase</td>
<td>1-10</td>
</tr>
<tr>
<td>Cecum</td>
<td>10-30</td>
<td>7</td>
<td>*</td>
<td>Passive diffusion, convective, active transport, pinocytosis mechanism</td>
<td>7.5-8.0</td>
<td>-</td>
<td>short</td>
</tr>
<tr>
<td>Colon</td>
<td>150</td>
<td>5</td>
<td>*</td>
<td>Passive diffusion, convective transport mechanism</td>
<td>7.9-8.0</td>
<td>-</td>
<td>4-20</td>
</tr>
<tr>
<td>Rectum</td>
<td>15-19</td>
<td>2.5</td>
<td>-</td>
<td>Passive diffusion, convective transport mechanism</td>
<td>7.5-8.0</td>
<td>-</td>
<td>Variable</td>
</tr>
</tbody>
</table>

- Represents villi are absent, *Represents villi are scarcely present and **Represents villi are abundantly present.

| Table 2: Four phases of Migrating Motor Complex (MMC) (Mandal et al., 2016). |
| Phase | Description | Time (minutes) |
| Phase I (Basal phase) | Idle state without any contraction | 30 to 60 |
| Phase II (Pre-burst phase) | Intermittent contraction | 20 to 40 |
| Phase III (Burst phase) | The regular contraction at the maximal frequency causes the material to migrate distally | 10 to 20 |
| Phase IV (Transition phase) | Transition phase between phase III and phase I | 0 to 5 |
Figure 3: (a) representing human stomach (b) Gastroretentive drug delivery system representing high density system (c) Gastroretentive drug delivery system based on polymer swelling (d) Gastroretentive drug delivery system representing magnetic field (e) Gastroretentive drug delivery system based on principle of mucoadhesion (f) Gastroretentive drug delivery based on dual combination of polymer swelling and effervescence (Mandal et al., 2016).

Figure 4: Working principle of HBS (Nayak et al., 2010).
Table 3: Transit Time of various dosage forms across the segments of the GIT (Chawla et al., 2003).

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>Transit time (Hours)</th>
<th>Stomach</th>
<th>Small intestine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets</td>
<td>2.7 ± 1.5</td>
<td>3.1 ± 0.4</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>Pellets</td>
<td>1.2 ± 1.3</td>
<td>3.4 ± 1.0</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>Capsules</td>
<td>0.8 ± 1.2</td>
<td>3.2 ± 0.8</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Solution</td>
<td>0.3 ± 0.07</td>
<td>4.1 ± 0.5</td>
<td>4.4</td>
<td></td>
</tr>
</tbody>
</table>

gm/cm³. Combination of swelling and effervescence helps in the flotation and retention of formulation inside the stomach. Bioadhesive or mucoadhesive systems were also used in gastroretentive drug delivery system. Dosage form was made to be sequestered inside the lumen of the stomach wall and survive in the stomach for the desired period of time (Chen et al., 2010; Prinderre et al., 2011). Mucoadhesive polymers like chitosan, Hydroxypropyl methylcellulose (HPMC), lecithins, polycarbophil, carboxymethylcellulose (CMC) are used (Andrews et al., 2009; Sharma et al., 2011). The combination of mucoadhesion, swelling and flotation mechanism follows by the mucoadhesive gastroretentive system.

In situ raft type system was likewise applied for achieving gastroretention. These systems are fluid at room temperature contains sodium alginate as in situ gel forming polymers with carbonates or bicarbonates as effervescent agents. When ingested orally they swell and forms highly viscous gels contain entrapped CO₂ inside the polymeric structure. This entrapped CO₂ responsible for providing buoyancy to the formulation. This type of system used for the treatment of gastroesophageal reflux treatment. This type of system has an advantage of producing layer over the upper section of gastric fluid (Prapapati et al., 2013; Tiwari et al., 2015).

Hydrodynamically Balanced System (HBS) is the simplest gastroretentive dosage form. HBS composed of gel-forming polymers with drug filled in the hard gelatin capsule shell. After immersion in the solution (in vitro) or swallowing (in vivo), the shell of the swollen hydrogel is formed. This hydrogel-like structure controls the release of drug and maintains the integrity of HBS system and low density of the system than the utility (1.064g/cm³) which ensures the flotation of the HBS system. Such systems are suited for drugs having a better solubility in an acidic environment and for the drugs having a specific site of absorption in the upper part of the intestine (Verma et al., 2016).

History of HBS system was first to design, originated and described by Seth and Tossounian in year 1978. This system contained a mixture of drug and gel-forming polymers, which upon contact with gastric fluid acquired and maintained a bulk density of less than 1.064g/cm³ and remained buoyant over a gastric content until all the drug was released. Further, in the year 1979 same authors filed a US patent describing the development of HBS sustained release tablets containing drug and hydrophilic gel-forming polymer, which on contact with gastric fluids at body temperature formed a soft gelatinous mass on the outer surface of the system and creates an impermeable colloidal gel barrier (figure 4). This impermeable colloidal gel barrier is the rate-limiting step for the retardation of the drug also developed gelatinous mass which remained buoyant over gastric fluids (Sheth et al., 1978; Seth et al., 1979).

Further added there are lots of works are done on the HBS-capsule system like Kumar et al. (2013) prepared floating capsule which remained buoyant for a prolonged period of time without showing any lag time and retards the release of drug for sufficient period of time. Upon extensive literature survey, we found that drugs like Bismuth salts, Metronidazole, Ciprofloxacin, Clarithromycin, Amoxicillin, Cephalexin etc. are delivered with the help of HBS system (Verma et al., 2016). Xu et al. (1991) developed Gentamicin sulfate sustained release HBS system. Gamma scintigraphic technique was employed to study the residence time of the system with the comparison to the conventional system under fast and fed condition (Xu et al., 1991). Ali et al. (2006) developed HBS system for sustained delivery of ofloxacin in the stomach for achieving local action against H. Pylori infection. It is prepared by physical blending of different grades of Hydroxypropyl Methylcellulose (HPMC) and poly (ethylene oxide) (PEO) alone as well as in combination. Cellulose acetate phthalate, liquid paraffin and ethyl cellulose used as release modifiers and these releases the drug for the time period of 12 hours (Ali et al., 2006). Mouzam et al. (2011) developed novel floating ring cap delivery system in cross-linked by formaldehyde to hard gelatin capsule bearing Levofloxacin for the treatment of H. Pylori infection filled with Carbopol which is a hydrophilic polymer. This system exposed to acidic dissolution medium, a cap of gelatin capsule shell quickly dissolves and as a consequence, the formulation mixture gets exposed to the acidic environment only from a side. This exposed dry mixture of formulation gets hydrated and gradually erodes or swells, and at the same time drug dissolves in the gel and diffuses slowly to the aqueous acidic environment. Alessandra et al. (2016) developed floating drug delivery system bearing two antibiotics namely Amoxicillin and Clarithromycin and they were combined in a single dosages form to float over gastric content and to sustain the delivery of drugs in the gastric region. These modules having a disc form with curved bases were formulated as hydrophilic matrices. Two modules of Clarithromycin were assembled by sticking the concave base of one module to the concave base of the other, creating an internal void chamber. The assembled system showed immediate in vitro floatation at pH 1.2 for the time period of 5 hours. In summation, an in vivo absorption study performed on beagle dogs confirmed the slow release of clarithromycin and amoxicillin from the assembled system during the assembly permanence in the stomach for at least 4 hours (Rossi et al., 2016). Soni et al. (2016) prepared HBS system for nonsteroidal anti-inflammatory drugs (NSAIDs) with different grades of Chitosan (Low, medium and high molecular weight), Hydroxypropyl Methylcellulose (K4M and K15M). When these polymers come in contact with acidic dissolution media they develop a hydrogel-like structure and retard the release of Piroxicam and also impart the buoyancy to the formulation. Soni et al. (2017) developed HBS gastro-retentive system for Metoprolol Succinate bearing gel-forming polymer (High Molecular Weight Chitosan, Hydroxypropyl Methylcellulose K15M, and Crushed Puffed Rice). This system retards the release of Metoprolol Succinate for more than 05 hours, which follows zero-order kinetics and fickian diffusion of kinetics.
FACTORS AFFECTING GASTRIC RETENTION OF DRUG

Density of dosage forms
The density of a dosage form affects the retention of drug in the stomach and determines the location of the gastroretentive system in the stomach. Dosage forms having a density lower than the gastric contents i.e. 1.064 g/cm$^3$ can remain buoyant over the surface, while high density systems sink to bottom of the stomach (Arora et al., 2005; Barddonnet et al., 2006).

Shape and size of the dosage form
Shape and size of the dosage forms are important parameter for design and development for gastroretentive single unit dosage forms. The average gastric residence times (GRT) of non-floating systems are extremely variable and greatly dependent on their size, which may be large, medium and small units. In most cases, the larger the size of dosage forms the greater will be the GRT due to the larger size of the dosage form would not allow this to quickly pass through the pyloric antrum. Gastroretentive system having a diameter of should be below 5 mm show a better GRT compared with one having 9.9 mm. Ring-shaped and tetrahedron-shaped system have a better GRT as compared to size and shape (Arora et al., 2005; Barddonnet et al., 2006).

Food intake and its nature
Food intake, viscosity of the meal, the volume of food, caloric content of food, and frequency of administration of food has an effect on the gastric retention of dosage forms. The presence or absence of food in the gastrointestinal tract (GIT) affects the gastric retention time (GRT) of the dosage form. Normally, the presence of food in the gastrointestinal tract (GIT) improves the gastric retention time (GRT) of the dosage form and thus, the drugs absorption increases by allowing its stay at the absorption site for a longer period. Again, increase in acidity and caloric value slows down gastric emptying process, which can improve the gastric retention of dosage forms (Arora et al., 2005; Barddonnet et al., 2006).

Table 4: Drugs used for gastroretentive drug delivery system (Streubel et al., 2006; Arora et al., 2005; Nayak et al., 2014).

<table>
<thead>
<tr>
<th>Gastroretentive dosages form</th>
<th>Drugs for delivery through gastroretentive system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroretentive floating tablets (HBS-tablet)</td>
<td>Diltiazem, Fluourouracil, Isosorbide dinitrate, Isosorbid mononitrate, p-Aminobenzoic acid (PABA), Prednisolone, Nimodipine, Sotalol, Theophylline, Verapamil Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captoril, Cinerzine, Chlorpheniramine maleate and Ciprofloxacim</td>
</tr>
<tr>
<td>Gastroretentive floating capsule (HBS-capsule)</td>
<td>L-DOPA, Benserazide, Nicardipine, Misoprostol, Propranolol, Pepstatin, Metoprolol Succinate, Metoprolol Tartarate, NSAIDs, Chlorhidazexepoxide HCl, Diazepam and Furosemide,</td>
</tr>
<tr>
<td>Gastroretentive floating microspheres</td>
<td>Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terlenadine, Tranilast</td>
</tr>
<tr>
<td>Gastroretentive floating granules</td>
<td>Diclofenac sodium, Indomethacin, Prednisolone</td>
</tr>
<tr>
<td>Gastroretentive floating powders</td>
<td>Several basic powder drugs</td>
</tr>
<tr>
<td>Gastroretentive floating films</td>
<td>Cininerazine</td>
</tr>
</tbody>
</table>

Table 5: Polymers and ingredients which can be incorporated into HBS dosage form (Streubel et al., 2006; Arora et al., 2005; Nayak et al., 2014).

<table>
<thead>
<tr>
<th>Polymers and other ingredients</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocolloids (20-75%)</td>
<td>Acacia, Pectin, Chitosan, Agar, Casein, Bentonite, Yeegum, HPMC (K4M, K100M and K15M), Gellan gum (Gelrite®), Sodium Carboxy methyl cellulose, Hydroxypropyl Methylcellulose</td>
</tr>
<tr>
<td>Inert fatty materials (5-75%)</td>
<td>Beeswax, fatty acids, long chain fatty alcohols, Gelucires® 39/01 and 43/01.</td>
</tr>
<tr>
<td>Effervescent agents</td>
<td>Sodium bicarbonate, citric acid, tartaric acid, Di-Sodium Glycine Carbonate, Citroglycine.</td>
</tr>
<tr>
<td>Release rate accelerants (5-60%)</td>
<td>Lactose, Mannitol</td>
</tr>
<tr>
<td>Release rate retardants (5-60%)</td>
<td>Dicalcium phosphate, Talc, Magnesium Stearate</td>
</tr>
<tr>
<td>Buoyancy increasing agents (up to 80%)</td>
<td>Ethyl cellulose, calcium carbonate, low molecular weight chitosan</td>
</tr>
<tr>
<td>Low density material</td>
<td>Polypropylene foam powder (Accurel MP 1000®).</td>
</tr>
</tbody>
</table>
Effect of gender, posture and age

Generally, females have slower gastric emptying rates as compared to male. The effect of posture does not have any significant difference in the mean gastric retention time (GRT) for individuals in the upright, ambulatory and supine state. In case of elderly persons, gastric emptying is slowed down (Arora et al., 2005; Barddonnet et al., 2006).

**SUITABLE DRUG CANDIDATES FOR GDDS**

An ideal drug for gastroretentive drug delivery system should have the following properties (Streubel et al., 2006; Arora et al., 2005; Nayak et al., 2014):

1. Drugs which are locally active in stomach example: misoprostol, antacids etc.
2. Drugs which are primarily absorbed from the duodenum and upper jejunum segments example: Metroprol Succinate etc.
3. Drugs which have absorption window in the upper part of intestine example: L-DOPA, p- Amino Benzoic Acid (PABA), riboflavin, furosemide etc.
4. Drugs which are unstable in intestinal and colonic pH example: Captopril etc.
5. Drugs which exhibits low solubility at high pH values example: verapamil HCl, chlordiazepoxide, diazepam etc.
6. NSAIDs drugs can also be administered through an HBS system with gel-forming polymers, this property of polymer helps in prevention of gastric lesions.

**UNSUITABLE DRUG CANDIDATES FOR GDDS**

The unsuitable drug for gastroretentive drug delivery system may have one or more of the following properties (Streubel et al., 2006; Arora et al., 2005; Nayak et al., 2014):

1. Drugs which are unstable in gastric pH.
2. Drugs which undergo significant first pass effect (i.e., metabolize in the liver before entering in the systemic circulation; example: Nifedipine etc.).
3. Drugs which cause very low acidic solubility example: phentoin etc.

**ADVANTAGES OF GDDS**

The advantages of gastroretentive drug delivery system can be listed as below (Streubel et al., 2006; Arora et al., 2005; Nayak et al., 2014):

1. The bioavailability of therapeutic moiety can be increased, especially for those which get metabolized in the upper GIT by gastroretentive drug delivery technique in comparison to the administration of non-gastroretentive drug delivery.
2. For drugs with a short half-life, a sustained release may result in a flip-flop phenomenon and also enable the reduced frequency of dosing with better patient compliance.
3. It can be used to overcome the problem of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain buoyant in the gastric fluid without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric fluids (1.064g/cm³).
4. Gastroretentive drug delivery can produce prolonged and sustain the release of drugs from dosage forms which offer the local drug targeting in the stomach and small intestine. Hence, they are useful in the treatment of disorders related to stomach and small intestine.
5. Gastroretentive dosage forms minimize the fluctuation of drug concentrations in plasma and its effects. This feature is important for the drug which has a narrow therapeutic index.

6. Reduction of variation in drug concentration makes it possible to obtain improved selectivity in receptor activation.
7. The sustained mode of drug release from gastroretentive doses forms enables extension of the time over a critical concentration and therefore enhances the pharmacological effects and improves the chemical outcomes.

**CHALLENGES ASSOCIATED WITH GDDS**

The primarily challenge associated with gastroretentive drug delivery system is the retention in the stomach and the upper part of the small intestine until the drug is released at a predetermined period of time. There is variation in the gastric emptying process. It depends heavily on the condition of the stomach like a change in pH state (fast and fed state) and shape of the dosage form. Gastric retention more in the fed state compared to the fasted state. Another, a barrier which obstructs the gastric retention like the type of food, volume and time of fluid intake, caloric content, gender, and age. High caloric content food, fat content in food prolongs the gastric retention of drug in the stomach. Indigestible polymers and fatty acid salts also affect the movement of food and drug in the stomach under fed state and reduce the gastric emptying rate (Mandal et al., 2016). Mojaverian et al., 1988 reported that the variability in the gastric emptying rate depends on gender and age of patients. The role of pylorus plays a significant role in achieving gastric retention. The pylorus size is 2 to 3 mm during the digestive phase and the diameter becomes 12.8 ± 7.0 mm during the inter-digestive phase. Hence, all the system size of the gastroretentive system should be below 5 mm so that they can pass through the pylorus to the duodenum. Size and shape of the dosages form, disease state, and patient body mass index are the others factor which affects the gastric emptying rate. The single unit gastroretentive drug delivery system shows an improved and predictable drug release as compared to multiple unit gastroretentive drug delivery systems due to loading or entrapment of drug. It is reported that multiple unit systems are ultimately exiting the stomach before the dosages form become functional. Hence to develop an optimum gastroretentive drug delivery system is a challenging task for a formulator to overcome factors like gastric emptying rate of the stomach together with maintaining an appropriate drug release rate for an extended period of time before it gets metabolized in the system (Illum et al., 2001).

**DRUGS FOR GDDS FORMULATION**

The commonly used drugs for gastroretentive drug delivery system are summarized in Table 4.

**EXCIPIENTS FOR HBS DOSAGES FORMS**

Following types of polymer and other ingredients can be incorporated into HBS dosage form in addition to the drugs depicted in table 5.
Table 6: Some US Patents on gastroretentive drug delivery system.

<table>
<thead>
<tr>
<th>Patent Number</th>
<th>Patent Title</th>
<th>Field of Invention</th>
<th>Inventors Name</th>
<th>Priority Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>US9128002B2</td>
<td>Gastric release pulse system for drug delivery (Flanner et al., 2015)</td>
<td>Disclosed are pharmaceutical products for providing pulses of at least one pharmaceutically active ingredient from a patient’s stomach, or from a subsequent gastrointestinal site proximal thereto, for absorption thereof at a site(s) more distal in the gastrointestinal tract than the patient’s stomach, or than the subsequent gastrointestinal site proximal thereto. The product comprises first, second, and third pharmaceutical dosage forms, each of which comprises at least one pharmaceutically active agent and a pharmaceutically acceptable carrier. The product is formulated such that at least two of the first, second, and third pharmaceutical dosage forms further comprise means for providing temporary gastric-retention of the at least two of the first, second, and third pharmaceutical dosage forms within the patient’s stomach, or at the subsequent gastrointestinal site proximal thereto.</td>
<td>Henry H. Flanner, Donald Treacy, Sanna Tolle-Sander, Scott Brahim, Marcus Schestopol, Beth A. Burnside</td>
<td>08-09-2015</td>
</tr>
<tr>
<td>US6207197</td>
<td>Gastroretentive controlled release microspheres for improved drug delivery (Illum et al., 2001)</td>
<td>Invention relates to a novel method for retaining pharmaceutical agents in the stomach of a mammal, in order to provide local treatment of diseases of the stomach, or to improve the intestinal absorption of drugs which have a limited absorption capacity in the small intestine of such a mammal.</td>
<td>Illum; Lisbeth (Nottingham, GB), Ping; He (Miami, FL)</td>
<td>27-03-2001</td>
</tr>
<tr>
<td>US5972389</td>
<td>Gastric-retentive, oral drug dosage forms for the controlled-release of sparingly soluble drugs and insoluble matter (Shell et al., 1999)</td>
<td>Invention relates generally to the field of pharmacology and, in particular, to drug dosage forms that are retained in the stomach and gradually deliver sparingly soluble drugs or insoluble, particulate matter over a time period of several hours. More particularly, the present invention provides swellable polymer systems designed to deliver sparingly soluble drugs, insoluble or particulate matter and soluble drugs rendered less soluble by hydrophobicity enhancing agents into the gastrointestinal (G.I) tract. The drug or particulate matter is released into the stomach as the polymer gradually erodes and, thus, the rate at which the drug or insoluble, particulate matter is delivered is determined by the rate of polymer erosion.</td>
<td>Shell; John W. (Hillsborough, CA), Louie-Helm; Jenny (Union City, CA)</td>
<td>19-09-1996</td>
</tr>
<tr>
<td>US5443843</td>
<td>Gastric retention system for controlled drug release (Curatolo et al., 1995)</td>
<td>Invention relates to an oral drug delivery system having delayed gastrointestinal transit. More specifically it relates to a gastric retention system for controlled release of drugs to the gastrointestinal tract. The system comprises one or more non-continuous compressible elements, i.e., retention arms, and an attached controlled release device and which in the expanded form resists gastrointestinal transit. It further relates to a modular system for use therein comprising one or more non-continuous compressible elements and an attached receptacle means for receiving and holding a drug-containing orally administrable controlled release device and which in the expanded form resists gastrointestinal transit.</td>
<td>Curatolo; William J. (Niantic, CT), Lo; Jeelin (Old Lyme, CT)</td>
<td>22-08-1995</td>
</tr>
<tr>
<td>US5232704</td>
<td>Sustained release, bilayer buoyant dosage form (Franz et al., 1993)</td>
<td>Disclosed is a sustained release pharmaceutical dosage form including a drug and adapted to release the drug over an extended period of time. The dosage form comprises a capsule including a non-compressed bi-layer formulation; one layer comprising a drug release layer and the other a buoyant or floating layer, the pharmaceutical dosage form providing extended gastric residence time of the bi-layer formulation so that substantially the entire drug is released in the stomach over an extended period. The dosage form has a large diameter in relation to its size and an initial density of less than 1. The floating layer of the described pharmaceutical dosage form is formulated to provide buoyancy to the dosage form and diametral increase, the floating layer including a polymer which has the properties of a gelling agent and which upon contact with gastric fluid hydrates and forms a gelatinous barrier. The pharmaceutical dosage form is buoyant in gastric fluid for a period up to about 13 hours.</td>
<td>Franz; Michel R. (Brussels, BE), Oth; Marianne P. (Brussels, BE)</td>
<td>19-12-1990</td>
</tr>
</tbody>
</table>
Buoyant controlled release pharmaceutical powder formulation is provided which may be filled into capsules and releases a pharmaceutical of a basic character at a controlled rate regardless of the pH of the environment, which formulation includes a basic pharmaceutical, up to about 45% by weight of a pH dependent polymer which is a salt of alginic acid, such as sodium alginate, up to about 35% by weight of a pH-independent hydrocarbon gelling agent having a viscosity of up to about 100,000 centipoises in 2% solution at 20°C and excipients.

Dennis; Andrew (Merseyside, GB2), Timmins; Peter (Merseyside, GB2), Lee; Kevin (Cheshire, GB2) 23-10-1991

Non-compressed sustained release tablets which will float on gastric fluid are described. The tablets comprise a hydrocolloid gelling agent,(Cresskill, NJ), therapeutically acceptable inert oil, the selected therapeutic agent and Desai; Subhash (Plainsboro, NJ) 21-03-1989

A drug delivery device retained in the stomach comprising a planar figure made from an erodible polymer that may release a drug associated therewith over a controlled, predictable and extended period of time.

Caldwell; Larry J. (Lawrence, KS), Gardner; Colin R. (Lawrence, KS), Cargill; Robyn C. (Lawrence, KS) 30-08-1988

A novel sustained release formulation for the preparation of tablets for oral administration is disclosed. The formulation is hydrodynamically balanced to be buoyant in gastric juice thereby remaining in the stomach for an extended period of time.

Sheth; Prabhakar R. (Pearl River, NY), Tossounian; Jacques L. (Pine Brook, NJ) 13-02-1976

Sustained release pharmaceutical capsules suitable for oral administration and particularly suitable for sustained release therapy with certain benzodiazepines, e.g. chlordiazepoxide and diazepam, are disclosed. The formulation contained in the disclosed capsules is hydrodynamically balanced to be buoyant in gastric fluid thereby remaining buoyant in the gastric fluid until substantially the entire medicament therein has been released.

Sheth; Prabhakar 21-11-1978

Rovhe Products, USA

Hoffmann-LaRoche, USA

GlaxoSmithKline, India

Peerre Fabre Drug, France

Ranbaxy, India

Ranbaxy, India

Pharmacia, USA
**EXPERT OPINION**

On the basis of extensive literature and data survey, author’s opinion for gastroretentive drug delivery system is great importance for the drugs, which are locally, deliver the drug in the upper part of stomach (site-specific targeting), have narrow absorption window in the stomach and upper part of intestine, and have low solubility at higher pH. An adequate control of gastric residence time with time controlled drug release can significantly improve the pharmacotherapy. Several approaches are adopted for achieving gastroretention which is explained by the authors like floating, bio adhesion, effervescence, high density, magnetic, swelling system etc. The works on above mentioned gastroretentive system are well investigated by the researchers and very promising in vitro and in vivo results are published in the literature. On the basis of the literature survey, lots of work shifted towards the use of swelling polymers which forms a hydrogel-like structure which holds the active moiety for a desired period of time whereas residence time increase in the stomach by using bioadhesive polymers. Selection of polymers for achieving gastroretention is an important parameter. On the commercial scale, it is growing slowly as an important novel drug delivery system due to many challenges associated with it. In terms of delivering the drugs to the systemic circulation with enhanced effectiveness, the gastroretentive system will become more popular in coming years. However, it is necessary to correlate the in vitro and in vivo data due to complexity in pharmacokinetic and pharmacodynamic parameters.

**ACKNOWLEDGEMENT**

Authors are thankful to the Sardar Bhagwan Singh PG Institute of Biomedical Sciences and Research, Dehradun, India.

**CONFLICTS OF INTEREST**

None.

**REFERENCES**


