Review Article

GASTRORETENTIVE DRUG DELIVERY SYSTEMS: NOVEL APPROACHES AND ITS EVALUATION - A REVIEW

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ABSTRACT

There are different types of dosage forms, which are being administered through different routes. However oral route is the most preferred route of administration because of its patient compliance. Now days, oral controlled release systems are designed offering a number of advantages including improvement in patient compliance, therapeutic efficacy and safety. Gastric retention time is one of the important factors, which adversely affect the performance of these drugs when administered simply by an oral controlled drug delivery system. The purpose of this review is to provide complete information on the gastroretentive drug delivery systems (GRDDS) such as role and properties of gastrointestinal (GI) tract, factors affecting the gastric retention time, classification of gastroretentive dosage form and its evaluation parameters.

Keywords: Gastroretentive, floating, mucoadhesive, drug delivery systems, gastrointestinal.

INTRODUCTION

Drug delivery systems (DDS) are used for maximizing the therapeutic index of the drug and also targeted for reduction in the side effects. All over delivery systems the oral drug delivery has become the mainstay of treatment due to higher patient compliance and reduced patient discomfort.

Controlled drug delivery usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient[1]. Controlled drug delivery implies the predictability and reproducibility to control the drug release, drug concentration in target site and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose.

The main objective of the oral controlled drug delivery systems is to achieve more predictable and increased bioavailability[2]. The common property of conventional controlled release (CR) technologies is that a large part of the drug load is released in the colon, where the dosage form (DF) stays for a relatively longer period of time. This delivery approach, while suitable for many molecules, was found to be inappropriate for drugs that are poorly absorbed from the lower part of the GI tract.

Under certain circumstances prolonging the gastric retention of a DDS is desirable for achieving greater therapeutic benefit of the drug. For example, drugs that are absorbed in the proximal part of the gastrointestinal tract (GIT), and the drugs that are less soluble or are degraded by the alkaline pH may benefit from gastric retention[3]. In addition, for local and sustained drug delivery to the stomach and the proximal small intestine to treat certain conditions, prolonging gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailability, therapeutic efficacy and possible reduction of the dose size[4].

Drugs suitable for Gastric retention:

i. Narrow absorption window at upper part of gastrointestinal tract (e.g. levodopa, riboflavin, calcium, repaglinide, atenolol, theophylline, diltiazem, risedronate)

ii. pH-dependant absorption from stomach (acidic drugs). (e.g. furosemide)

iii. Drugs which are acting locally in the stomach. (e.g. antacids, antibiotics used for bacterial ulcers)

iv. Drugs which are primarily absorbed in the stomach. (e.g. albuterol)

v. Degradation at higher pH (higher stability at lower pH) (e.g. captopril)

vi. Drugs which are poorly soluble at an alkaline pH. (e.g. verapamil)

vii. Drugs which are absorbed rapidly from the GI tract. (e.g. amoxicillin)

viii. Drugs which degrade in the colon. (e.g. metoprolol)

Drugs those are unsuitable for gastroretentive drug delivery systems include

i. Limited acid solubility e.g. phenytoin

ii. Instability in the gastric environment e.g. erythromycin

iii. Intended for selective release in the colon e.g. 5-amino salicylic acid and corticosteroids.

GASTRO RETENTIVE DOSAGE FORM

Role of GI tract: Stomach

The stomach is J-shaped organ located in the upper portion and left side of the abdomen, just below the diaphragm. It occupies a portion of the epigastric and left hydrochondriac region (Fig 1). 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. It provides barrier to the delivery of drugs to small intestine[5].

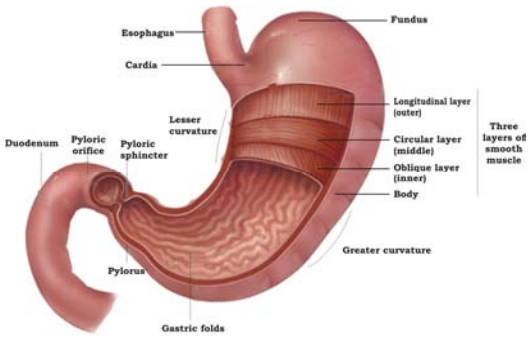


Figure 1: Anatomy of Stomach

The stomach is divided into three anatomical regions. I) Fundus ii) Body and iii) Pylorus (or antrum). The proximal stomach consisted of fundus and body, which serves as a reservoir for ingested materials, whereas the distal region (pylorus) is the major site of mixing motions, acting as a pump to propel gastric contents for gastric emptying[6]. Gastric emptying occurs both in fasting as well as fed states.

Gastric emptying occurs as a result of gastric contractions, the nature of which depends upon the contents of the stomach. Thus gastric emptying can be conveniently classified into gastric emptying of liquid, digestible solids and indigestible solids. Liquids can be emptied from the stomach because of the intragastric pressure generated by slow muscular contractions occurring mainly from the proximal stomach i.e. the upper body of the stomach[7]. Digestible solids can be empty from the stomach only when they have been changed to thick, creamy substance called chime. Sequence of gastric contractions removing a portion of digestible solids and liquefied food from the stomach is shown in the Fig 2. Peristaltic waves are contractions in the distal stomach i.e. the lower body of the stomach that is responsible for mixing and grinding solid food to the form required for emptying[8]. Indigestible solids including oral dosage forms are empty from the stomach in the fasting state by electromechanical activity through stomach and small intestine in every 2-3 hr[9]. This electrical activity is termed as interdigestive migrating myoelectric cycle (IMMC) or migrating myoelectric complex (MMC), which is further divided into four[10].

Phase I (Basal): Period of no contraction. (Duration: 45-60 min)

Phase II (Preburst): Period of intermittent contraction. (Duration: 30-45 min)

Phase III (Burst): Period of regular contractions at the maximal frequency that migrate distally. (Duration: 5-15 min)

Phase IV: Period of transition between phase III and phase I. (Duration: 0-5 min)

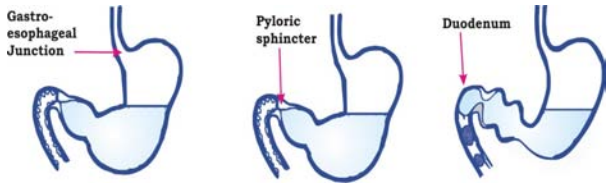


Figure 2: Sequence of gastric contractions responsible for gastric emptying of digestible solids and liquefied food from the stomach.

Some of the important aspects of the physiology of the gastric emptying process are as follows[11]

- The rate of movement of the dosage form from stomach to intestine is affected by the multiple chemical factors and the physical size of the medication.
- The chemical components of the gastric fluid will interact with the intestinal receptors. These receptors will control the rate of gastric emptying by neuronal or hormonal means.
- Emptying of the dosage form is also influenced by whether it is taken on an empty stomach, in an interdigestive state (with or soon after a meal), or in a digestive state
- Small particles, regardless of size, density, or texture that are ingested during the interdigestive state become coated by mucus and these coated dosage forms are emptied uniformly from the stomach.
- During the digestive state, the larger particles are retained in the stomach until the meal is essentially emptied.
- Emptying of the solid dosage forms range from 5 min to 5 h depending on the size of the medication and whether the individual is in the interdigestive or digestive state when medication is administered.

Thus, an understanding of the physiology of gastric emptying is important in developing the floating drug-delivery systems.

PROPERTIES OF THE GI TRACT

Gastrointestinal Transit time

One of the unique properties of the GI tract is that the food content remains in each segment of the GI tract for different time periods. Table 1 shows the residence times of both liquid and solid food in each segment of the GI tract. The values given in the table should be taken as relative rather than absolute, and are intended to point

out the general differences among different segments of the GI tract. Since most drugs are absorbed from the upper intestine i.e. stomach, duodenum, jejunum and ileum as shown in the table, the total effective time for drug absorption is 3 to 8 hours[12].

Table 1: Transit time in each segment of the GI tract

Segment	Type of food	
	Liquid	Solid
Stomach	10 – 30 min	1 – 3 hrs
Duodenum	< 60 sec	< 60 sec
Jejunum and Ileum	3 hrs ± 1.5 hrs	4hrs ± 1.5 hrs
Colon	---------	20hrs – 50 hrs

Factors Controlling Gastric Retention Time

The gastric retention time of a dosage form is mainly depends upon the factors like density, size of the dosage form, food nature, age, posture, sex and condition of the patient.

Density of the dosage form

Dosage forms having a density lower than that of gastric fluid experience floating behaviour and hence gastric retention. Density <1.0 gm/cm^3 of the dosage form is required to exhibit floating property. However, the floating tendency of the dosage form usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium[13].

Size of the dosage form

Size of the dosage form is also one of the factors which influence the gastric retention dramatically. The mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size. In fed conditions, the smaller units get emptied from the stomach during the digestive phase and the larger units during the housekeeping waves. In most cases, the larger the size of the dosage form, the greater will be the gastric retention time because the larger size would not allow the dosage form to quickly pass through the pyloric antrum into the intestine. Thus the size of the dosage form appears to be an important factor affecting gastric retention[14].

Nature of food

Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the GIT influences the GRT of the dosage form. Usually the presence of food in the GIT improves the 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 shows down GET, which can improve the gastric retention of dosage forms[15].

Effect of age, posture, sex and condition of the patient

Elderly people, especially those over 70 yrs have a significantly longer GRT. A study by Mojaverian et al found that females showed comparatively shorter mean ambulatory GRT than males, and the gastric emptying in women was slower than in men. The authors also studied the effect of posture on GRT, and found no significant difference in the mean GRT for individuals in upright, ambulatory and supine state[16]. On the other hand, in a comparative study in humans by Gansbeke *et al*, the floating and non-floating systems behaved differently. In the upright position, the floating systems floated to the top of the gastric contents and remained for a longer time, showing prolonged GRT[17]. But the non-floating units settled to the lower part of the stomach and underwent faster emptying as a result of peristaltic contractions, and the floating units remained away from the pylorus. However, in supine position, the floating units are emptied faster than non-floating units of similar size[18].

Single or multiple unit formulation

Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms[19].

Fed or unfed state

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 3 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer[20].

Gastrointestinal pH

Gastric emptying is retarded at low stomach pH and promoted at higher or alkaline pH. Chemicals that affect gastrointestinal pH also alters drug release. The inhibitory effect of various acids on gastric emptying decreases with increase in molecular weight and is in the following order: HCl > acetic > lactic > tartaric > citric. With alkaline solutions, a low base concentration (1% $NaHCO_3$) increases the gastric emptying rate more than the one of higher concentration (5%) [21].

Nature of meal

Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release[22].

Caloric content

GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.

Frequency of feed

The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

Concomitant drug administration

Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride increases the GRT.

Considerations for Gastroretentive Drug Delivery Systems Design

Drug absorption window

The specificities of drugs being only absorbed in specific regions of the GIT may be attributed to various factors, including drug solubility due to varying pH values, enzymatic degradation of the drug, interaction of the drug with endogenous compounds such as bile, and the necessity for active drug transport mechanisms which are selectively present at specific regions of the GIT[23] (Fig 3). Drugs which display a narrow absorption window also have a poor bioavailability when administered orally by conventional immediate release drug delivery systems. This results in poor drug therapeutic efficacy. Majority of narrow absorption window drugs are absorbed in the proximal region of the small intestine or duodenum like metformin, captopril, acyclovir, ciprofloxacin, levodopa and nitrofurantoin[24]. There are a few drugs however, that are not suitable for use as a gastroretentive delivery system. These include drugs that have adverse effects on the gastric mucosal lining or are absorbed equally throughout the entire GIT. Drugs that are suitable for incorporation into gastroretentive delivery systems usually posses one or more of the following characteristics: drugs that are suitable for local therapeutic action within the stomach, the primary drug absorption site is within the stomach, the drug is poorly soluble or unstable in the alkaline environment of the small and large intestine, the drug is classified as a NAW drug and those drugs that undergo rapid absorption from the GIT.

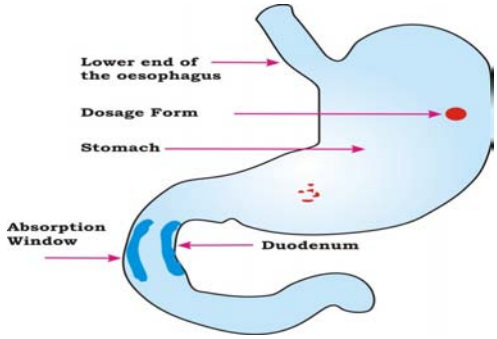


Figure 3: Absorption window in Gastro Intestinal Tract

APPROACHES TO ACHIEVE GASTRIC RETENTION

While many attempts have been made to develop gastro retentive dosage forms, few have been successful as a platform for oral controlled release dosage forms. To formulate a successful gastro retentive dosage form several techniques are currently used as mentioned in Table 2.

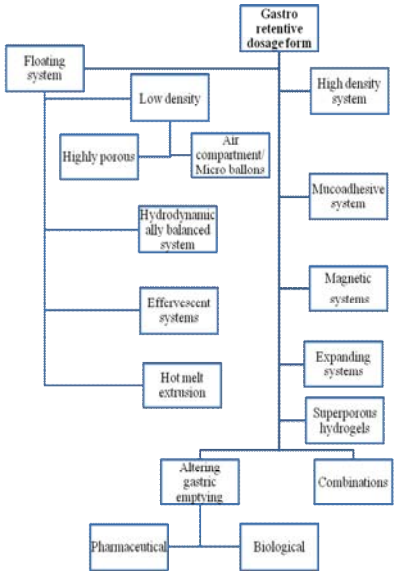
Floating system

Floating drug delivery systems are most commonly used technique for achieving gastric retention. This delivery system is desirable for drugs with an absorption window in stomach or in the upper small intestine[24]. Floating drug delivery systems can be subdivided into low density systems, hydrodynamically balanced system, effervescent system and hot melt extrusion system as mentioned in the Table 2.

Low density system

Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a longer period of time. While the system floats over the gastric contents, the drug is released in desired rate, which results gastric retention and reduces the fluctuation in the plasma drug concentration. Low density systems sub classified into highly porous system and air compartment system (Fig 4 (a&b).).

Table 2: Classification of the Gastroretentive dosage form



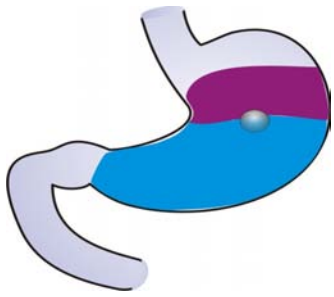


Figure 4 (a): Intragastric floating system (density <1gm/cc)

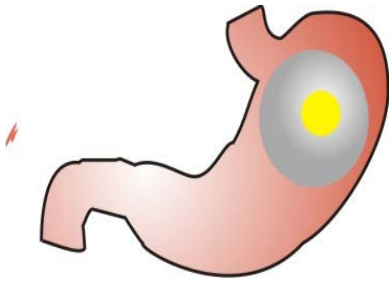


Figure 4 (b): Low density systems

i. Highly porous system

The inclusion of low density polymeric carriers in a formulation may result in a matrix with a density of less than 1g/cm^3, thereby becoming buoyant. There are numerous low density polymeric carriers available, including porous silicon dioxide, polypropylene foam, magnesium aluminometa silicate, porous calcium silicate and polypropylene foam powder[25]. These porous carriers possess certain characteristics which add to their attractiveness for use in drug delivery systems design, including a high surface area, tunable pore sizes with narrow distributions, stable uniform porous structures and well-defined surface properties thus allowing for the absorption of drugs and drug release in a reproducible and predictable manner[26] (Fig 5).

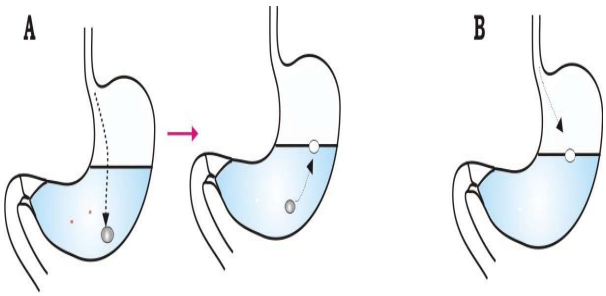


Figure 5: Floating systems with density lower than 1gm/cm^3. A) The density of the system can be lower after administration to the stomach B) Lower density from the beginning.

ii. Air compartment/Micro balloons

In order to achieve immediate buoyancy of a drug delivery system, an air compartment (or buoyancy chamber) can be incorporated within the system. This process is generally complex and complicated. Kawashima Y *et al.* were successfully designed a hollow microsphere or micro balloons as they are termed. A polymer and drug solution in an organic solvent was poured into an aqueous poly (vinyl alcohol) solution[27]. Precipitation of the organic solvent resulted in the formation of a polymeric membrane surrounding organic solvent droplets (Fig 6). Different polymers were investigated, with the most promising results obtained from hydroxyproppyl methylcellulose (HPMC). *In vivo* results of these microballoons revealed that gastric retention of up to 5 hours was achieved[28].

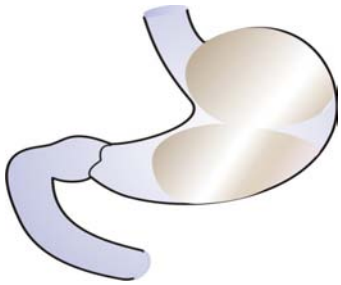


Figure 6: Intragastric balloon system

El-Gibaly was able to develop hollow chitosan microspheres through the interaction with a negatively charged surfactant, sodium dioctyl sulphosuccinate leading to the formation of chitosan gel sacs that were insoluble at a low pH.[29] Hollow microspheres are currently considered to be one of the most promising systems intended to maintain buoyancy. This is due to their inherent superior buoyancy in combination with a multi-unit system[30].

iii. Hydrodynamically balanced systems

It is a single unit drug delivery system containing one or more gel forming hydrophilic polymers. The polymer is mixed with drugs and usually administered in a hydrodynamically balanced system (HBS) capsule. The capsule shell dissolves in contact with gastric fluids and the mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period. Because, continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form[31] (Fig 7). Various polymers can be incorporated in order to delay the drug release like hydroxypropyl methylcellulose (HPMC), hydroxethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans, alginic acid, polyethylene oxide (PEO) etc.

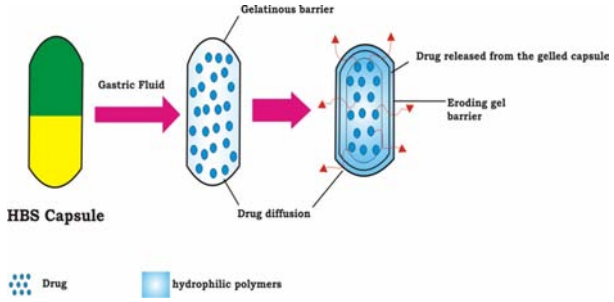


Figure 7: Working principle of hydrodynamically balanced system

The potential limitation of this approach is that the floating concept in an HBS is rather passive i.e. it mainly depends upon the air captured in the dry mass inside the hydrating gelatinous surface layer.

iv. Effervescent systems

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds like sodium

bicarbonate, tartaric acid and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

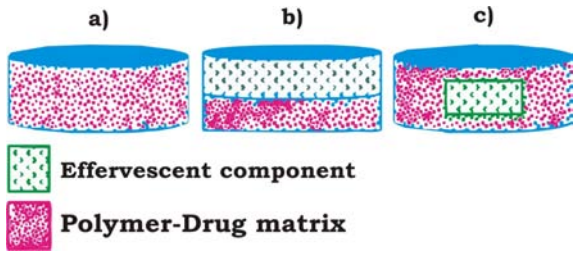


Figure 8: Schematic of a) a single layer tablet matrix, b) a bi-layered tablet and c) A bi-layered tablet with a central effervescent core.

This effervescent system may be composed of single or multi layers in various geometries such as membranes or spheres[32]. CO2 generating components are incorporated into a tablet matrix in one of two forms, either intimately incorporated within the matrix, or separated within its own layer as depicted in Fig 8. Alternatively the gas generating unit can be loaded inside micro particles such as ion exchange resin beads, which can be loaded with bicarbonate and coated with a semi permeable membrane[33]. On contact with gastric fluid CO_2 is released which causes floatation of the device (Fig 9).

The results of *invivo* studies employing gas generating floating drug delivery systems have not been consistent. The main problem here is that the persistence of the buoyant property not has been carefully examined in most of the devices. For this reason, it was suggested that the initial bulk density of the dosage unit and changes of the floating strength with time should be characterized prior to *invivo* comparison between floating and non floating units. Whether dosage form is buoyant or not, are expected to be emptied from the stomach in fasted condition due to housekeeper waves. Human studies using γ- scintigraphy showed the floating tablets, capsules have shorter gastric retention in fasted condition (< 2 hrs) than fed conditions (> 4 hrs). Thus, it appears that, as with other devices, the presence of food prolongs the gastric retention time of the floating devices. Most human studies with monolithic floating dosage form showed the same trend in the presence of food[34].

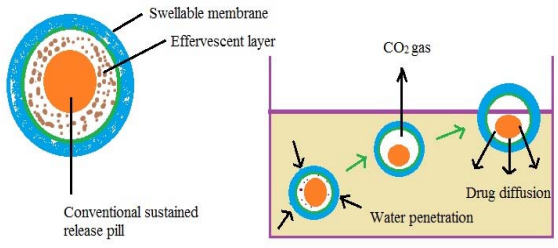


Figure 9: Structural characteristics (left) and floating mechanism (right) of the effervescent floating system.

v. Hot Melt Extrusion

Hot melt extrusion is a method of continuous mixing and design of mouldable materials. It is possible to produce tablets, microspheres, granules, transdermal and transmucosal delivery system through this approach. The polymers used for this technique are polymethacrylate polymers due to their thermoplastic properties. Selection of polymer is mainly depends upon its glass transition temperature, melt viscosity and stability under high temperature. This technique has produced several advantages includes fewer processing steps, absence of solvents, no need of compression and proper mixing of the formulation components[35].

vi. High density system

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/cm3) 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 diameter of the pellets, although many conflicting reports stating otherwise also abound in literature[36]. High density system includes coated pellets. These formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulphate, zinc oxide and titanium oxide etc. They are retained in the antrum of stomach as shown in Fig. 10. But, effectiveness of this system in human beings was not observed and no system has been marketed.

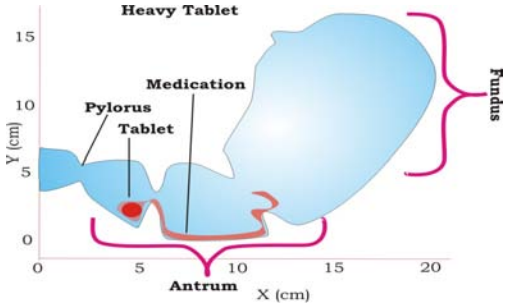


Figure 10: Graphic of heavy tablet which is denser than the stomach fluid and therefore sinks to the antrum.

vii. Mucoadhesive systems:

The mucoadhesive systems are intended to extend the GRT by adhering the dosage form to the gastric mucous membrane. Bioadhesive drug delivery systems are used to deliver the drug within the lumen to enhance drug absorption in a site specific manner. Several natural or synthetic polymers have been exploited to control as well as to prolong the gastric retention of the delivery systems by adhesion to the smooth muscle[37]. The adhesion of the polymers with the mucous membrane may be mediated by hydration, bonding, or receptor mediated[38]. In hydration mediated adhesion, the hydrophilic polymers

become sticky and mucoadhesive upon hydration. Bonding mediated adhesion may involve mechanical or chemical bonding. Chemical bonds may involve covalent or ionic bonds or Vander Waals forces between the polymer molecules and the mucous membrane. Receptor mediated adhesion takes place between certain polymers and specific receptors expressed on gastric cells. The polymers could be anionic or cationic or neutral. Table 3 is a brief description of the classification of these polymers. Basic action of the mucoadhesive drug delivery systems is shown in the Fig 11.

Table 3: Classification of bioadhesive polymers.

Anionic	Cationic	Neutral
Carboxymethylcellulose	Polylysine	Polyethylene glycol
Chondroitin sulphate	Polybrene	Polyevinyl pyrrolidone
Poly acrylic acid		Dextran
Carageenan		
Pectin		
Chitosan		
Alginic acid		

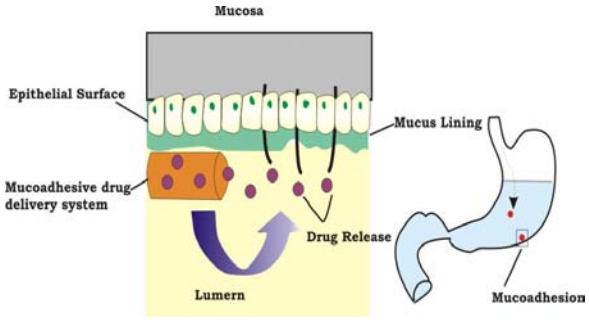


Figure 11: Basic action of Mucoadhesive drug delivery system

viii. Magnetic system

Magnetic system is one of the gastroretentive techniques, the principle involved in this is dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance.

Gröning *et al.* designed a gastroretentive drug delivery system incorporating a small magnet within the system that could be guided with an extracorporeal magnet attached to the abdomen[39]. The capsule was effectively delayed within the stomach therefore extending the gastric residence time and increasing the absorption of the drug at its specific absorption window. It was however found that results differed depending on whether the patient was in a fed or fasting state. Clinical investigations were conducted, involving three different delivery systems. The first system involved the magnetic depot tablet with the use of an extracorporeal magnet, the second system excluded the use of an extracorporeal magnet and the third system was an immediate release formulation. A gastric retention time of 12 hours was obtained, and drug plasma concentrations showed an increase in drug absorption associated with the magnetic depot tablet when an extracorporeal magnet was used. The most probable system limitation associated with a magnetic system is the reduced patient compliance due to the precision with which the magnet must be placed externally.

ix. Expanding system

The technology involved in this technique is, the devices that are small enough for easy swallowing and expandable upon contact with gastric fluid to a size sufficient to cause the retention of the dosage form in the stomach i.e. to a size too large to pass through the pylorus (Fig 12). This type of systems are made to a size slightly larger than the diameter of the pyloric canal, is about 1-4 cm, usually 2 cm in humans, until completion of the prescribed therapeutic regimen. Because the systems have to be removed from the stomach eventually, they have to be made either degradable or deflatable[39].

The main principle in this system is the swelling of the device and unfolding of the system in stomach (Fig 13 & 14).

a) Swelling of the system: It can be achieved by

- ❖ Hydrogels that swell upon contact with water,
- ❖ Wrapping the osmotic expanding agents like sugar, salt or swellable expanding agents like swellable resins and hydrocolloids with semi permeable membranes that are substantially nonhydratable but permeable to both drug and body fluids.
- ❖ Solidified or liquefied gas at ambient temperature can be used as swelling agent. Ex: diethyl ether, methyl formate, n-peptane etc.,

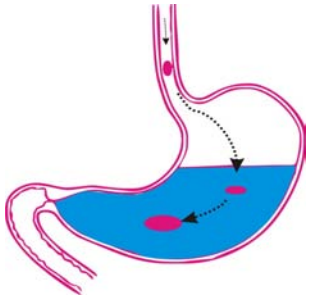


Figure 12: The expandable device can swell in the stomach either by absorbing water from the gastric fluid or by evaporation of solidified or liquefied gas present in the device.

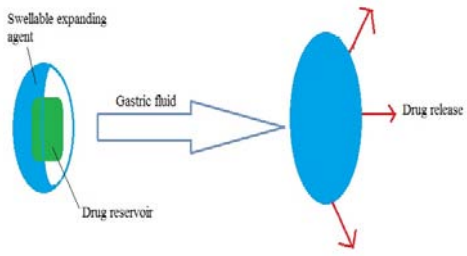


Figure 13: Mechanism of swelling system

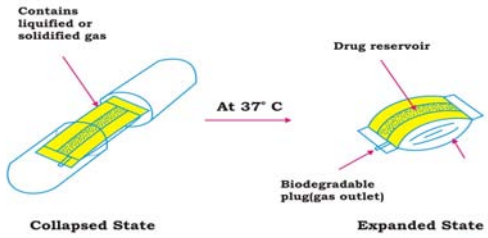


Figure 14: Expanding system based on gas evaporation.

b) Systems unfolding in the stomach

Systems that unfold in the stomach have one or more non continuous compressible retention arms. The retention arms are initially folded to make the whole system smaller. With the arms folded, the system can be fit into gelatine capsules. In the stomach, folded arms are expanded to make the system too large to resist the gastric transit. These shapes included the tetrahedron, ring or planar membrane.

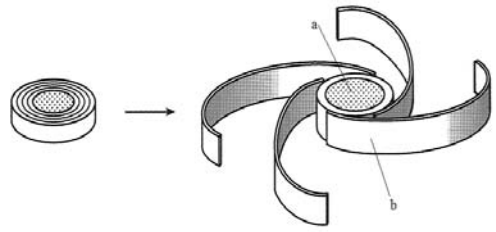


Figure 15: The system with the coiled arms (left) can unfold the arms (right) in the stomach. a) The spiral configuration unfolding system and b) the unfolding 'Y' system.

An unfolding "Y" system demonstrating prolonged shape memory was developed (Fig. 15). The centre of the "Y" comprised a polymer which was able to maintain its shape memory for an extended period of time, while the limbs of "Y" comprised a drug-loaded erodible material, the rate of erosion of which determines the residence time. A third component provided the link between the centre and the limbs. A spiral configuration comprising four short shape memory arms arranged concentrically around a tablet was also developed. As seen in Fig. 15, a shape memory material a), which assures unfolding, is connected to the erodible material which serves as a drug reservoir b) and whose rate of degradation controls the gastric retention time. Both of these systems achieved a gastric retention of longer than 24 hours in *in vivo* animal studies. Fig 16 describes another type of expanding system in tetrahedral dorm.

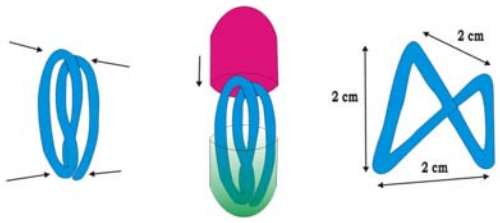


Figure 16: The tetrahedral form of the device is compressed (left), encapsulation (centre), tetrahedral form is restored for extended gastric retention.

Superporous hydrogels

This approach is based on the swelling of the hydrogel system. The main difference from the previous swelling systems is that the extent of swelling of superporous hydrogels is far beyond that obtained by other systems. The swelling ratio can be over 1000 compared with the only 2-50 fold increases obtained with other expanding system. The superporous hydrogel, when dried, contains open pores which form capillary channels. Through these open pore channels, water is rapidly absorbed, allowing swelling to take place within a few minutes, up to a few hundred times its original volume. The average pore size of the superporous hydrogel is in the range of a few hundred micrometers. On hydration, water is taken up by capillary wetting as opposed to diffusion. In order to increase the mechanical strength of the hydrogels and to withstand peristaltic pressure the superporous hydrogel composites were synthesized by adding excipients like croscarmellose sodium[40].

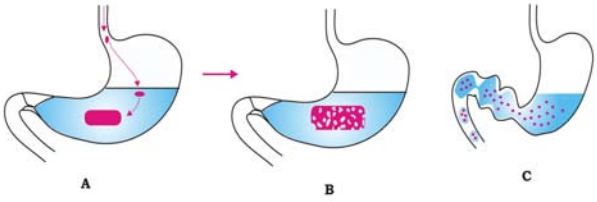


Figure 17: (A) superporous hydrogel swells to a huge size in the stomach. (B) Drug is released and hydrogel undergoing degradation. (C) Emptied from the stomach.

Superporous hydrogels can be divided into two groups basing upon their swelling ratio and their mechanical stability. A superporous hydrogel is a soft polymer which swells very quickly, but has poor mechanical stability, whereas a superporous hydrogel composite has a slower swelling rate, but is mechanically stable. The composite is therefore utilized as a retentive drug delivery system. Through the incorporation of biodegradable crosslinkers, the superporous hydrogel degrades in the body thus preventing obstructions within the GIT (Fig 17). *In vivo* animal studies demonstrate that the superporous hydrogel remained within the stomach for more than 24 hours after feeding. After approximately 30 hours there was evidence of fragmentation and the delivery system was cleared from the stomach.

ALTERING GASTRIC EMPTYING

a. Pharmaceutical

It's a simple method for gastric retention which involves the inclusion of either an excipient or pharmaceutical substance which possesses gastric motility retardation characteristics.

b. Biological

Some dietary components like fats, peptides and some amino acids play a major role in the gastric retention b prolonging the gastric emptying and intestinal transit. This phenomenon is known as the ileal brake, which is

believed to be a feedback process in order to improve digestion of dietary components. Components from other biological species have been investigated for their ability to delay gastric and intestinal transit. It is known that tapeworms decrease intestinal transit in hosts[41].

Combinations

There is a possible advantage of combining more than one mechanisms of gastro retention in order to achieve an additional enhancement and prolongation of gastric residence time. Fig 18 describes the way of drug getting absorbed by gastro retentive dosage form by all systems. Visualization is a vital step in the development of novel gastroretentive drug delivery systems. Numerous approaches have been used in order to explicitly view the positioning and characteristics of gastroretentive systems in the GIT. The techniques include Radio labelling and ϒ-scintigraphy, radiology, magnetic resonance imaging and alternate current biosusceptometry.

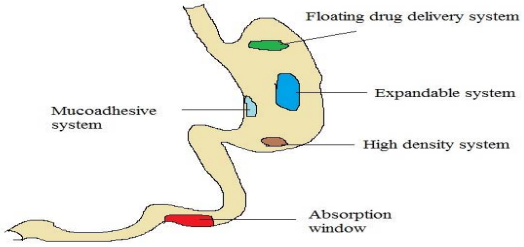


Figure 18: Drug absorption through various gastro retentive ways

EVALUATION PARAMETERS FOR GASTRO RETENTIVE DOSAGE FORM

Floating dosage forms

Floating dosage forms, also referred to as low density systems, remain buoyant in the gastric fluid for an extended period of time. Floating systems may be inherent low density type systems or may achieve their low density after coming into contact with the dissolution media. *In vitro* parameters that could be linked to *in vivo* gastro-retentive performance of the floating systems include lag time, density (porosity) and floating time.

Floating lag time

The Floating lag time is the time required by the dosage forms to emerge on the surface of the dissolution medium after placing it into the dissolution medium[42]. For liquid dosage forms like in situ gel forming formulations or raft, a small Petri dish (4.5 mm diameter) containing the required dose of liquid is put carefully into the dissolution vessel and the time required by the formulation to emerge on the surface is determined[43]. Irrespective of the drug, the ideal dissolution medium for evaluation of GRDDS is 0.1 N HCl or simulated gastric fluid (SGF) to mimic the in vivo conditions, while other media have not been defined for the more relevant fed condition, since floating GRDDS are only purported to be effective in the fed state.

Density/ Specific gravity of the dosage form

For a floating dosage form, density is an important parameter to predict its floatability. Tablet density[44] is the ratio of tablet weight (w) to tablet volume (v). Tablet volume is calculated by measuring tablet height (h) and diameter (m) using a micrometer gauge.

Specific gravity is determined by liquid displacement method, where a known mass of solid is filled into the pycnometer, followed by a liquid filling; and by using the value of specific gravity of the liquid, the volume of liquid displaced by solid is to be determined for calculating the specific gravity of the solid. Water, Benzene or n-Hexane may be used as solvent for displacing the medium.

Porosity

Porosity is one of the evaluation parameter which was calculated by measuring the true density (ρ_t) and particle density (ρ_p) as per the following equation.

$$\varepsilon = \left(1 - \frac{\rho_p}{\rho_t}\right) \times 100$$

Floating time/buoyancy time

Floating time, also referred to as buoyancy time, may be defined as the total time period between placing a dosage form in the dissolution medium to the time it remains floating. The test for buoyancy is usually determined in 900 ml of 0.1 N HCl maintained at 37°C using USP dissolution apparatus. Floating time duration could potentially be an indication of the gastric retention time of the dosage form.

Floating kinetics

Li *et al.* have developed a floating monitoring system based on the method to access the mucoadhesive force measurement[45]. As shown in Fig 19, a floating measuring probe consisting of a stainless steel basket is connected to a metal string, suspended from an electronic balance. The floating dosage form is kept in the basket and immersed at a fixed depth into the dissolution apparatus. The upward force can be measured by the balance and this measure is transmitted to an online computer by RS-232C cable. The data obtained are used to plot a floating kinetic curve where the floating kinetics are plotted against time at each 30 s interval. Researchers have utilised this system to optimise the formulations on the basis of residual floating force (resultant weight).

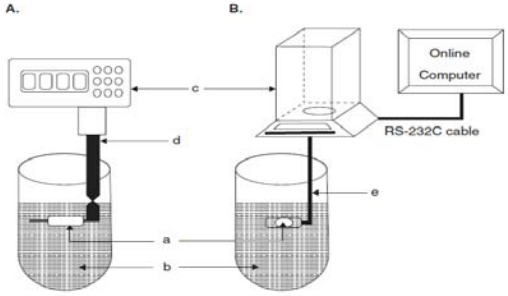


Figure 19: A. Resultant weight apparatus with force transmitter device (FTD). B. Continuous floating monitoring system.

a. Floating dosage form, b. dissolution medium, c. electronic weighing balance, d. force transmitter device with holder, e. metal string with basket.

Swelling index/water uptake

The swelling index represents the swelling capacity of the polymer when it comes into contact with the dissolution media[46]. The swelling index or water uptake (Q) of swellable tablets can be determined by following equation.

$$Q = \left(\frac{W_S - W_D}{W_D} \right) \times 100$$

Where W_S and W_D represent the weight of the swollen tablet and weight of the dry tablet (initial weight of tablet before swelling), respectively.

Exposed size parameter

The folded or coiled unit of an unfolding type of expandable system is filled into a capsule and on release the system unfolds to its maximum size to achieve gastro-retention[47]. Thus, the *in vivo* capability to unfold and the preservation of the shape and size as a function of time are the critical parameters to optimise the formulation for gastro-retention, which can be determined by 'exposed size parameter'. The X-ray contrast aluminium threads obtained from surgical gauze pads are incorporated in the formulation of unfolding GRDDS, generally on the periphery of the dosage form. The X-ray photographs are taken at regular time intervals and percentage exposed size parameter (% ESP) are calculated using following equation.

$$\%ESP = \left(\frac{L_S \times L_L}{S} \right) \times 100$$

Where L_S and L_L are the average length between parallel contrast threads in the shorter and longer dimensions, respectively. S is the maximum surface area of GRDDS before folding or coiling.

***In vitro* drug release**

GRDDS are intended to remain in the stomach and release the drug in the gastric fluid. Consequently, the *in vitro* drug release from GRDDS should be studied in SGF or in acidic media. The majority of researchers use USP dissolution apparatus I or II, depending upon the type of dosage form. SGF or 0.1 N HCl (pH 1.2), with or without enzymes and surfactants, have been used as a dissolution media for GRDDS.

In vivo evaluation

Although various in vitro techniques are available to evaluate the gastro-retentive performance of dosage forms, in vivo evaluation techniques are considered to be the most reliable. Therefore, various *in vivo* techniques to study the gastro-retentive performance of dosage forms are mentioned.

❖ ***Radio Labelling and ϒ Scintigraphy***

ϒ rays which were emitted by radioactive isotope is incorporated into the formulation. The most commonly used radioisotope is technetium (^{99m}Tc), which is prepared through the elution of pertechnetate (Na [^{99m}TcO4]) with a 0.9% sodium chloride solution from a molybdenum-99 generator. The major advantages of using ^{99m}Tc are its short half life of 6 hours, very low radiation dose and due to its easy availability in a sterile, pyrogen free and carrier free-state[48]. When the ϒ scintigraphy is performed, the location of the delivery system can easily be observed.

❖ ***Radiology***

Through the incorporation of radiopaque threads, such as barium sulphate (BaSO4), it is possible to determine the positioning and movement of delivery systems from x-rays taken at different time periods. Radiology is commonly used in preclinical trials due to its simplicity and cost effectiveness, however, due to health risks from high levels of exposure, its use has become limited and – scintigraphy may be preferred[49].

❖ ***Magnetic Resonance Imaging (MRI)***

MRI's may be performed in order to improve the visualization of delivery systems within the stomach. These scans are normally done in the supine position, and scans are taken in both the axial and coronal planes[50]. Sequential images may assist in the determination of gastric retention.

❖ ***Multichannel Superconducting Quantum Interference Device (SQUID)***

Newer, non-invasive and radiation free methods, known as biomagnetic techniques have been developed for the evaluation of delivery systems. Multichannel superconducting quantum interference device (SQUID) devices measure the magnetic field of an ingested delivery system which is magnetically marked. Although the SQUID has expensive operating costs, it is designed to detect extremely weak biomagnetic fields, in a magnetically shielded environment[51].

❖ ***Alternate Current Biosusceptometry (ACB)***

A new promising technique, the alternate current biosusceptometry (ACB) has shown accuracy in the evaluation of physiological properties of the GI tract. Induction coils are used to record the magnetic flux variation obtained by the response of an ingested magnetic material (ferrite — MnFe2O3). Continuous improvements of the ACB has allowed for the gradual increase of sensitivity[52].

Gastroretentive systems are gaining more popularity day-by-day, which can be easily seen by availability of a number of commercialized gastroretentive products in the market. Commonly used drugs in formulation of Gastroretentive dosage forms and some marketed products are listed in Table 4 and Table 5 respectively.

Table 4: Commonly used drugs in formulation of Gastroretentive dosage forms.

Dosage form	Drugs
Tablets/ Pills	Acetaminophen, Acetylsalicylic acid, Amoxicillin trihydrate, Ampicillin, Atenolol, Chlorpheniramine, Cinnazirine, Diltiazem, Fluorouracil, Isosorbide mononitrate, Isosorbide dinitrate, p-aminobenzoic acid, Piretanide, Prednisolone, Quinidine gluconate, Riboflavin-5'-phosphate, Sotalol, Theophylline, Verapamil HCl
Capsules	Chlordiazepoxide HCl, Diazepam, Furosemide, levodopa, benserazide, Misoprostol, Propranolol HCl, Furosemide, Ursodeoxycholic acid
Microspheres	Aspirin, Grisiofulvin, p-nitroanilline, Ibuprofen, Terfinadine, Tranilast.
Granules	Diclofenac sodium, Indomethacin and Prednisolone
Films	Cinnarizine

Advantages of GRDDS:

- Sustained drug delivery
- Site specific drug delivery
- Absorption enhancement
- Fewer doses
- Improved plasma levels
- Better bioavailability
- Less irritation
- Fewer side effects
- Low risk inactive ingredients
- Manufacturing ease
- Low cost

Limitations of GRDDS:

- The major disadvantage of floating systems is requirement of a sufficiently high level of fluids in the stomach for the drug delivery. However, this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach.
- The dosage form should be administered with a minimum of glass full of water (200-250 ml).
- Floating system is not feasible for those drugs that have solubility or stability problems in gastric fluids.
- The drugs, which are absorbed throughout GIT, which undergo significant first pass metabolism, are not desirable candidates.
- Some drugs present in the floating system causes irritation to gastric mucosa.

Table 5: Gastroretentive products available in the market

Active Ingredient	Products	Technology	Manufactured by
Ofloxacin	Zanocin OD	Effervescent floating system	Ranbaxy, India
Metformine HCl	Riomet OD	Effervescent floating system	Ranbaxy, India
Ciprofloxacin	Cifran OD	Effervescent floating Form	Ranbaxy, India
Siméthicone	Inon Ace Tablets	Foam based floating system	Sato Pharma, Japan
Gabapentin	Gabapentin GR	Polymer-based swelling technology: AcuForm™(In phase three clinical trial)	Depomed, USA
Ciprofloxacin	Proquin XR	Polymer-based swelling technology:AcuForm™	Depomed, USA
Metformin HCL	Glumetza	Polymer-based swelling technology:AcuForm™	Depomed, USA
Metformin HCL	Metformin GR™	Polymer-based swelling technology:AcuForm™	Depomed, USA
Prazosin HCl	Prazopress XL	Effervescent and swelling-based floating system	Sun Pharma, Japan
Metformin HCL	Metformin Hcl LP	Minextab Floating®	Galenix, France
Cefaclor	Cafeclor LP	Minextab Floating®	Galenix, France
Tramadol	Tramadol LP	Minextab Floating®	Galenix, France
Ciprofloxacin HCl and betaine	Cipro XR	Erodible matrix based system	Bayer, USA
Baclofen	Baclofen GRS	Coated multi-layer floating & swelling system	Sun Pharma, India
Carvedilol	Coreg CR	Gastro retention with osmotic system	Glaxosmithkline
Alginic acid and Sodium bicarbonate	Liquid gaviscon	Effervescent floating liquid alginate preparation	Reckitt Benckiser Healthcare, UK
Diazepam	Valrelease	Floating capsule	Roche, UK
Misoprostol	Cytotec	Bilayer floating capsule	Pharmacia Limited, UK
Aluminum magnesium antacid	Topalkan	Floating liquid alginate	Pierre Fabre Medicament, France

Table 6: Platform technologies

Company	Platform technology	Type of technology
Depomed	AcuForm	Polymer-based technology
Intec Pharma	Accordion Pill	Expandable film filled in capsule
Sun Pharma	Gastro Retentive Innovative Device (GRID)	Coated multilayer floating and swelling system
Merrion Pharma	Gastrointestinal Retention System (GIRES)	Gas generating inflatable pouch in capsule
Flamel	Micropump	Gastro-retention with osmotic system
Roche	Hydrodynamically Balanced System (HBS)	Matrix forming polymer-based floating system

Applications and Technologies:

i. Recent study indicated that the administration of diltiazem floating tablet twice a day might be more effective compared to normal tablets in controlling the blood pressure of hypertensive patient.

ii. Madopar® HBS- containing L-dopa and benserazide- here drug was released and absorbed over a period of 6-8 hour and maintain substantial plasma concentration for parkinson's patients.

iii. Cytotech® -- containing misoprostol, a synthetic prostaglandin- E1 analog, for prevention of gastric ulcers caused by non-steroidal anti-inflammatory drugs (NSAIDS).

iv. As it provides high concentration of drug within gastric mucosa, it is used to eradicate pylori (A causative organism for chronic gastritis and peptic ulcers).

v. 5-Fluorouracil has been successfully evaluated in patients with stomach neoplasm.

vi. Developing HBS dosage form for tacrine provides a better delivery system and reduces its GI side effects in alzheimer's patients.

vii. Treatment of gastric and duodenal cancers.

viii. Alza corporation has developed a gastroretentive platform for the OROS® system, which showed prolong residence time in a dog model as the product remain in the canine stomach at 12 hrs. post dose and was frequently present at 24 hrs.

Platform technologies

Some of the Gastroretentive technologies developed by various companies are mentioned in the Table 6.

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. Various techniques and approaches have been employed to develop GRDDS. All the gastroretentive systems have their positive aspects and drawbacks. All over the retentive systems gastric floating and mucoadhesive systems for modulation of oral controlled drug delivery was found to be great importance. These systems have special additional advantages for the drugs that are primarily absorbed from the upper segment of the GIT.

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