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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 vivo* 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 atrium 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.*, 2001; 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.

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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

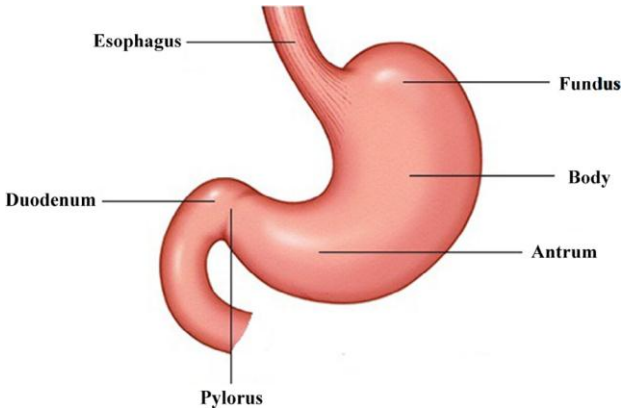

Figure 1: Diagram of human stomach (Mandal *et al.*, 2016).

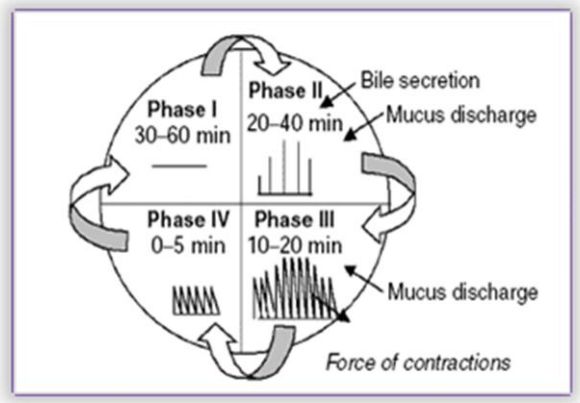

Figure 2: Motility patterns of GIT in the fasted state (Awasthi *et al.*, 2016).

pyloric sphincter in the fed state. During this, bile enters into the duodenum region, whereas gastric mucus discharge occurs during the latter phase of stage II and throughout the phase III period. Phase III is called a burst phase. The regular contraction at the maximal frequency causes the stuff to migrate (table 2). During this, housekeeper waves are generated which sweep out undigested food and material (drug). Phase IV is the transition phase between phase III and I which lasts for 0 to 5 minutes (Awasthi *et al.*, 2016; Vantrappen *et al.*, 1979; Talukder *et al.*, 2004).

APPROACHES FOR ACHIEVING GASTRIC RETENTION

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 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 formulators 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/cm^3, 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

Table 1: Anatomical and physiological feature of the gastrointestinal tract (DeSesso *et al.*, 2001; Chawla *et al.*, 2003).

Section	Avg length (cm)	Dia (cm)	Villi present	Absorption mechanism	pH	Major constituents	Food Transit time (Hr)
Oral cavity	15-20	10	-	Convective transport and passive diffusion mechanism	5.2-6.8	Amylase, maltase, ptylin and mucin	short
Esophagus	25	2.5	-	Not reported	5.0-6.0	-	Very short
Stomach	20	15	-	Convective transport and passive diffusion mechanism	1.2-3.5	HCl, pepsin, trypsin, rennin, lipase	0.25-3.0
Duodenum	25	05	*	Passive diffusion, convective, Active, facilitated transport, ion pair, pinocytosis mechanism	4.6-6.0	Bile, trypsin, chyotrypsin, amylase, maltase lipase, nuclease, CYP3A4	1-2
Jejunum	300	5	**	Passive diffusion, convective, Active, facilitated transport mechanism	6.3-7.3	Amylase, maltase, lipase, Sucrose, CYP3A5.	Not reported
Ileum	300	2.5-5.0	**	Passive diffusion, convective, active, facilitated transport, ion pair, pinocytosis mechanism	7.6	Nuclease, nucleotidase, enterokinase	1-10
Cecum	10-30	7	*	Passive diffusion, convective, active transport, pinocytosis mechanism	7.5-8.0		short
Colon	150	5	*	Passive diffusion, convective transport mechanism	7.9-8.0	-	4-20
Rectum	15-19	2.5	-	Passive diffusion, convective transport mechanism	7.5-8.0	-	Variable

*- 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

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/cm^3). 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 effervescence 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 CO_2 as a result of a chemical reaction. This CO_2 entrapped inside the polymeric structure of the polymer and creates density lesser than the utility i.e. 1.064

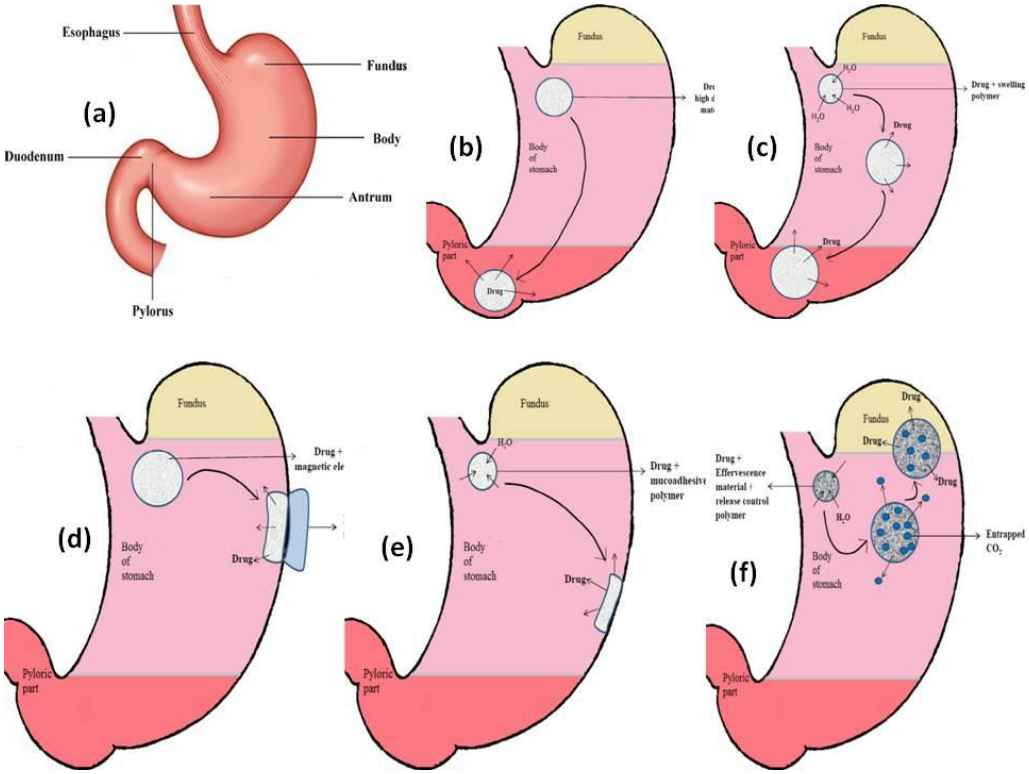

Figure 3: (a) representing human stomach **(b)** Gastroretentive drug delivery system representing high density system **(c)** Gastroretentive drug delivery system based on polymer swelling **(d)** Gastroretentive drug delivery system representing magnetic field **(e)** Gastroretentive drug delivery system based on principle of mucoadhesion **(f)** Gastroretentive drug delivery based on dual combination of polymer swelling and effervescence (Mandal *et al*., 2016).

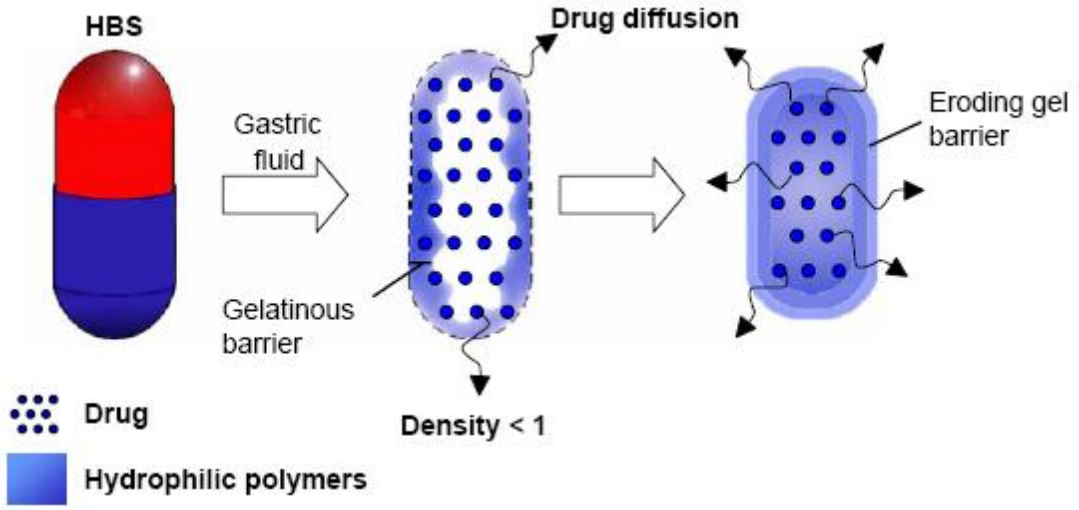

Figure 4: Working principle of HBS (Nayak *et al.*, 2010).

Table 3: Transit Time of various dosage forms across the segments of the GIT (Chawla *et al.*, 2003).

Dosage form	Transit time (Hours)		
	Stomach	Small intestine	Total
Tablets	2.7 ± 1.5	3.1 ± 0.4	5.8
Pellets	1.2 ± 1.3	3.4 ± 1.0	4.6
Capsules	0.8 ± 1.2	3.2 ± 0.8	4.0
Solution	0.3 ± 0.07	4.1 ± 0.5	4.4

gm/cm^3. Combination of swelling and effervescence helps in the floatation 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), lectins, polycarbophil, carbopols, carboxymethylcellulose (CMC) are used (Andrews *et al.*, 2009; Sharma *et al.*, 2011). The combination of mucoadhesion, swelling and floatation 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 CO_2 inside the polymeric structure. This entrapped CO_2 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 (Prajapati *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/cm^3) 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 Sheth 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 gloating 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.

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

Gastroretentive dosages form	Drugs for delivery through gastroretentive system
Gastroretentive floating tablets (HBS-tablet)	Diltiazem, Fluorouracil, Isosorbide dinitrate, Isosorbid mononitrate, p-Aminobenzoic acid (PABA), Prednisolone, Nimodipine, Sotalol, Theophylline, Verapamil Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerzine, Chlorpheniramine maleate and Ciprofloxacin
Gastroretentive floating capsule (HBS-capsule)	L-DOPA , Benserazide, Nicardipine, Misoprostol, Propranolol, Pepstatin, Metoprolol Succinate, Metoprolol Tartarate, NSAIDs, Chlordiazepoxide HCl, Diazepam and Furosemide,
Gastroretentive floating microspheres	Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfenadine, Tranilast
Gastroretentive floating granules	Diclofenac sodium, Indomethacin, Prednisolone
Gastroretentive floating powders	Several basic powder drugs
Gastroretentive floating films	Cinnnerazine

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).

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

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).

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: Metoprolol 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: Nifidepine etc.).
3. Drugs which cause very low acidic solubility example: phenytoin 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/cm^3).
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 time. 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.

Patent Number	Patent Title	Field of Invention	Inventors Name	Priority Date
US9125803B2	Gastric release pulse system for drug delivery (Flanner *et al.*, 2015)	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.	Henry H. Flanner, Donald Treacy, Sanna Tolle-Sander Scott Ibrahim, Marcus Schestopol, Beth A. Burnside	08-09-2015
US6207197	Gastroretentive controlled release microspheres for improved drug delivery (Illum *et al.*, 2001)	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.	Illum; Lisbeth (Nottingham, GB), Ping; He (Miami, FL)	27-03-2001
US5972389	Gastric-retentive, oral drug dosage forms for the controlled-release of sparingly soluble drugs and insoluble matter (Shell *et al.*, 1999)	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.	Shell; John W. (Hillsborough, CA), Louie-Helm; Jenny (Union City, CA)	19-09-1996
US5443843	Gastric retention system for controlled drug release (Curatolo *et al.*, 1995)	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.	Curatolo; William J. (Niantic, CT), Lo; Jeelin (Old Lyme, CT)	22-08-1995
US5232704	Sustained release, bilayer buoyant dosage form (Franz *et al.*, 1993)	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.	Franz; Michel R. (Brussels, BE), Oth; Marianne P. (Brussels, BE)	19-12-1990

Table 6 Continued

US5169638	Buoyant controlled release powder formulation (Dennis *et al.*, 1992)	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
US4814179	Floating sustained release therapeutic compositions (Bolton *et al.*, 1989)	Non-compressed sustained release tablets which will float on gastric fluid are described. The tablets comprise a hydrocolloid gelling agent, therapeutically acceptable inert oil, the selected therapeutic agent and water.	Bolton; Sanford (Cresskill, NJ), Desai; Subhash (Plainsboro, NJ)	21-03-1989
US4767627	Drug delivery device which can be retained in the stomach for a controlled period of time (Caldwell *et al.* 1988)	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
US4167558	Novel sustained release tablet formulations (Sheth *et al.*, 1979)	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
US4126672	Sustained release pharmaceutical capsules (Sheth *et al.*, 1978)	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 R. (Pearl River, NY), Tossounian; Jacques L. (Pine Brook, NJ)	21-11-1978

Table 7: Marketed products for gastroretentive drug delivery system available in market (Nayak *et al.*, 2010).

Brand Name ®	Delivery system	Drug	Company and country
Madopar	Floating	Delayed Release (DR) capsules Levadopa (10 mg), Benserazide (25 mg)	Rovhe Products, USA
Valrelease	Floating Capsules	Diazepam (15 mg)	Hoffmann- LaRoche, USA
Liquid Gaviscon	Effervescent floating liquid alginate preparation	Aluminium Hydroxide (95 mg)	GlaxoSmithKline, India
Topalkan	Floating liquid alginate preparation	Aluminium - Magnessium Antacid	Peerre Fabre Drug, France
Almagate Float Coat	Floating dosage form	Aluminium - Magnessium Antacid	--------
Conviron	Colloidal gel forming FDDS	Ferrous sulphate	Ranbxy, India
Cifran OD	Gas-generating floating form	Ciprofloxacin (1mg)	Ranbaxy, India
Cytotech	Bilayer Floating Capsules	Misoprostol (100 µg)	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.

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CONFLICTS OF INTEREST

None.

REFERENCES

Ali, J. H. S., & Ali, M. (2006). Formulation and development of gastroretentive drug delivery system for ofloxacin. *Methods and findings in experimental and clinical pharmacology*, *28*(7), 433-440. [DOI]

Andrews, G. P., Laverty, T. P., & Jones, D. S. (2009). Mucoadhesive polymeric platforms for controlled drug delivery. *European Journal of Pharmaceutics and Biopharmaceutics*, *71*(3), 505-518. [DOI]

Arora, S., Ali, J., Ahuja, A., Khar, R. K., & Baboota, S. (2005). Floating drug delivery systems: a review. *AAPS PharmSciTech*, *6*(3), E372-E390.

Awasthi, R., & Kulkarni, G. T. (2016). Decades of research in drug targeting to the upper gastrointestinal tract using gastroretention technologies: where do we stand? *Drug delivery*, *23*(2), 378-394. [DOI]

Bardonnet, P. L., Faivre, V., Pugh, W. J., Piffaretti, J. C., & Falson, F. (2006). Gastroretentive dosage forms: Overview and special case of Helicobacter pylori. *Journal of controlled release*, *111*(1-2), 1-18. [DOI]

Bolton, S., Izevbehai, P. H., & Desai, S. (1989). *U.S. Patent No. 4,814,178*. Washington, DC: U.S. Patent and Trademark Office.

Caldwell, L. J., Gardner, C. R., & Cargill, R. C. (1988). *U.S. Patent No. 4,767,627*. Washington, DC: U.S. Patent and Trademark Office.

Chawla, G., & Bansal, A. (2003). A means to address regional variability in intestinal drug absorption. *Pharm Technol*, *27*(6), 50-68.

Chen, R. N., Ho, H. O., Yu, C. Y., & Sheu, M. T. (2010). Development of swelling/floating gastroretentive drug delivery system based on a combination of hydroxyethyl cellulose and sodium carboxymethyl cellulose for Losartan and its clinical relevance in healthy volunteers with CYP2C9 polymorphism. *European Journal of Pharmaceutical Sciences*, *39*(1-3), 82-89. [DOI]

Curatolo, W. J., & Lo, J. (1995). *U.S. Patent No. 5,443,843*. Washington, DC: U.S. Patent and Trademark Office.

Dennis, A., Timmins, P., & Lee, K. (1992). *U.S. Patent No. 5,169,638*. Washington, DC: U.S. Patent and Trademark Office.

DeSesso, J. M., & Jacobson, C. F. (2001). Anatomical and physiological parameters affecting gastrointestinal absorption in humans and rats. *Food and Chemical Toxicology*, *39*(3), 209-228. [DOI]

Flanner, H. H., Treacy, D., Tolle-Sander, S., Ibrahim, S., Schestopol, M., & Burnside, B. A. (2015). *U.S. Patent No. 9,125,803*. Washington, DC: U.S. Patent and Trademark Office.

Franz, M. R., & Oth, M. P. (1993). *U.S. Patent No. 5,232,704*. Washington, DC: U.S. Patent and Trademark Office.

Garg, R., & Gupta, G. D. (2008). Progress in controlled gastroretentive delivery systems. *Tropical Journal of Pharmaceutical Research*, *7*(3), 1055-1066.

Hörter, D., & Dressman, J. B. (2001). Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract1. *Advanced drug delivery reviews*, *46*(1-3), 75-87. [DOI]

Illum, L., & Ping, H. (2001). *U.S. Patent No. 6,207,197*. Washington, DC: U.S. Patent and Trademark Office.

Kumar, V., Ahmad, S., & Singh, R. B. (2014). *U.S. Patent Application No. 14/350,615*.

Mandal, U. K., Chatterjee, B., & Senjoti, F. G. (2016). Gastro-retentive drug delivery systems and their *in vivo* success: A recent update. *asian journal of pharmaceutical sciences*, *11*(5), 575-584. [DOI]

Mayur, C., Senthilkumaran, K., & Hemant, G. (2013). Super porous hydrogels: a recent advancement in gastroretentive drug delivery system. *Indonesian Journal of Pharmacy*, *24*(1), 1-13.

Mojaverian, P., Vlasses, P. H., Kellner, P. E., & Rocci, M. L. (1988). Effects of gender, posture, and age on gastric residence time of an indigestible solid: pharmaceutical considerations. *Pharmaceutical research*, *5*(10), 639-644.

Mouzam, M. I., Dehghan, M. H. G., Asif, S., Sahuji, T., & Chudiwal, P. (2011). Preparation of a novel floating ring capsule-type dosage form for stomach specific delivery. *Saudi Pharmaceutical Journal*, *19*(2), 85-93. [DOI]

Murphy, C. S., Pillay, V., Choonara, Y. E., & du Toit, L. C. (2009). Gastroretentive drug delivery systems: current developments in novel system design and evaluation. *Current drug delivery*, *6*(5), 451-460. [PMID: 19751198]

Nayak, A. K., Malakar, J., & Sen, K. K. (2010). Gastroretentive drug delivery technologies: Current approaches and future potential. *Journal of Pharmaceutical Education and Research*, *1*(2), 1.

Nayak, K. P., Upadhyay, P., Valera, J. D. A. R., & Chauhan, N. P. (2012). Gastroretentive drug delivery systems and recent approaches: A review. *Journal of Research and Opinion*, *2*(1).

Prajapati, V. D., Jani, G. K., Khutliwala, T. A., & Zala, B. S. (2013). Raft forming system—an upcoming approach of gastroretentive drug delivery system. *Journal of controlled release*, *168*(2), 151-165.

Prinderre, P., Sauzet, C., & Fuxen, C. (2011). Advances in gastro retentive drug-delivery systems. *Expert opinion on drug delivery*, *8*(9), 1189-1203. [DOI]

Rocca, J. G., Omidian, H., & Shah, K. (2003). Progresses in gastroretentive drug delivery systems. *Business briefing. Pharma Tech*, *5*, 152-6.

Rosenzweig, O., Lavy, E., Gati, I., Kohen, R., & Friedman, M. (2013). Development and *in vitro* characterization of floating sustained-release drug delivery systems of polyphenols. *Drug delivery*, *20*(3-4), 180-189. [DOI]

Rossi, A., Conti, C., Colombo, G., Castrati, L., Scarpignato, C., Barata, P., & Colombo, P. (2016). Floating modular drug delivery systems with buoyancy independent of release mechanisms to sustain amoxicillin and clarithromycin intra-gastric concentrations. *Drug development and industrial pharmacy*, *42*(2), 332-339. [DOI]

Sastry, S. V., Nyshadham, J. R., & Fix, J. A. (2000). Recent technological advances in oral drug delivery–a review. *Pharmaceutical science & technology today*, *3*(4), 138-145. [PMID: 10754543]

Sharma, R., & Ahuja, M. (2011). Thiolated pectin: Synthesis, characterization and evaluation as a mucoadhesive polymer. *Carbohydrate Polymers*, *85*(3), 658-663. [DOI]

Shell, J. W., & Louie-Helm, J. (1999). *U.S. Patent No. 5,972,389*. Washington, DC: U.S. Patent and Trademark Office.

Sheth, P. R., & Tossounian, J. L. (1978). *U.S. Patent No. 4,126,672*. Washington, DC: U.S. Patent and Trademark Office.

Sheth PR, Tossounian JL, inventors; Hoffmann-La Roche Inc, assignee. (1979) Novel sustained release tablet formulations. United States patent US 4,167,558.

Sheth, P. R., & Tossounian, J. L. (1979). *U.S. Patent No. 4,167,558*. Washington, DC: U.S. Patent and Trademark Office.

Sheth, P. R., & Tossounian, J. L. (1978). *U.S. Patent No. 4,126,672*. Washington, DC: U.S. Patent and Trademark Office.

Singh, B. N., & Kim, K. H. (2000). Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. *Journal of Controlled release*, *63*(3), 235-259. [PMID:10601721]

Soni, S., Ram, V., & Verma, A. (2017). Crushed Puffed Rice-HPMC-Chitosan based Single-Unit Hydro-dynamically Balanced System for the Sustained Stomach Specific Delivery of Metoprolol Succinate. *Journal of Applied Pharmaceutical Science Vol*, *7*(12), 047-057. [DOI]

Soni, S., Verma, A., & Ram, V. (2016). Evaluation of Chitosan-Hydroxy Propyl Methyl Cellulose as a Single Unit Hydrodynamically Balanced Sustained Release Matrices for Stomach Specific Delivery of Piroxicam. *MOJ Bioequiv Availab*, *2*(1), 00014. [DOI]

Streubel, A., Siepmann, J., & Bodmeier, R. (2006). Gastroretentive drug delivery systems. *Expert opinion on drug delivery*, *3*(2), 217-233. [DOI]

Talukder, R., & Fassihi, R. (2004). Gastroretentive delivery systems: a mini review. *Drug development and industrial pharmacy*, *30*(10), 1019-1028. [DOI]

Tiwari, P., Soni, S., Ram, V., & Verma, A. (2015). Raft forming buoyant pH dependent thixotropic gelling systems incorporated with gelucire 43/01 as a potential stomach specific drug delivery system for famotidine. *Journal of Applied Pharmacy*, *7*(3), 183-202. [DOI]

Vantrappen, G., Janssens, J., Peeters, T. L., Bloom, S. R., Christofides, N. D., & Hellemans, J. (1979). Motilin and the interdigestive migrating motor complex in man. *Digestive diseases and sciences*, *24*(7), 497-500. [PMID: 45623]

Verma, A., Dubey, J., Hegde, R. R., Rastogi, V., & Pandit, J. K. (2016). Helicobacter pylori: past, current and future treatment strategies with gastroretentive drug delivery systems. *Journal of drug targeting*, *24*(10), 897-915. [DOI]

Xu, W. L., Tu, X. D., & Lu, Z. D. (1991). Development of Gentamicin sulfate sustained release tablet remaining-floating in stomach. *Acta pharmaceutica Sinica*, *26*(7), 541-545. [PMID:1805513]

Zhang, H., Zhang, J., & Streisand, J. B. (2002). Oral mucosal drug delivery. *Clinical pharmacokinetics*, *41*(9), 661-680.