

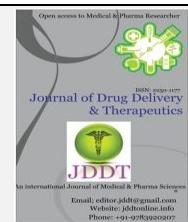


Available online on 15.07.2018 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

© 2011-18, publisher and licensee JDDT, This is an Open Access article which permits unrestricted non-commercial use, provided the original work is properly cited



Open Access

Review Article

GASTRORETENTIVE DRUG DELIVERY SYSTEM

Swapnil More* Kaustubh Gavali, Onkar Doke, Prasad Kasgawade

Department of Pharmaceutics, Sahyadri College of Pharmacy, Methwade, Sangola, 413307, Solapur, Maharashtra, India

ABSTRACT

Oral route of drug administration is the most preferable route because of its flexibility in formulation, ease of administration, and patient compliance. But this route has certain limitations like limited gastric residence time (GRT) for sustained drug delivery system and for the drugs which are absorb from specific region of gastrointestinal tract (GIT). To overcome these limitations, various approaches have been proposed to increase the gastric retention time of the delivery system in the upper part of gastrointestinal tract. Gastroretentive dosage form (GRDF) prolongs the GRT by targeting site-specific drug release in upper part of GIT. GRDFs enable continuous and the extended duration of drug release and improve bioavailability of drugs that have narrow therapeutic window, by this way they prolong dosing interval and increase compliance of the patient. The purpose of this article is to compile the various gastroretentive approaches. In order to understand various physiological difficulties to achieve gastric retention, we have summarized important factors controlling gastric retention. Finally the evaluation parameters of gastroretentive drug delivery systems are covered. The present review addresses briefly about the current status of various leading gastroretentive drug delivery technologies, developed until now, i.e. high density (sinking), floating, bio- or mucoadhesive, expandable, unfoldable, super porous hydrogel, magnetic systems etc. In addition, important factors controlling gastroretention, advantages and finally, future potential are discussed.

Keywords: Floating Delivery, Gastro retentive system.

Article Info: Received 19 May, 2018; Review Completed 31 May 2018; Accepted 01 June 2018; Available online 15 July 2018



Cite this article as:

More S Gavali K, Doke O, Kasgawade P, Gastroretentive drug delivery system, Journal of Drug Delivery and Therapeutics. 2018; 8(4):24-35 DOI: <http://dx.doi.org/10.22270/jddt.v8i4.1788>

*Address for Correspondence:

Mr. Swapnil More, Asst. Professor, Department of Pharmaceutics, Sahyadri College of Pharmacy, Methwade-413307, Maharashtra, India

INTRODUCTION

Oral sustained drug delivery system is complicated by limited gastric residence time. Rapid gastrointestinal transit can prevent complete drug release in the absorption zone and reduce the efficacy of administered dose, since the majority of drugs are absorbed in stomach or the upper part of small intestine. Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability.¹

Need for GRDDS²

- Conventional oral delivery is widely used in pharmaceutical field to treat diseases. However,

conventional delivery had many drawbacks and major draw-back is non-site specificity.

- Some drugs are absorbed at specific site only. They require release at specific site or a release such that maximum amount of drug reaches to the specific site.
- Pharmaceutical field is now focusing towards such drugs which require site specificity.
- Gastro-retentive delivery is one of the site specific delivery for the delivery of drugs either at stomach or at intestine. It is obtained by retaining dosage form into stomach and drug is being released at controlled manner to specific site either in stomach, duodenum and intestine

Potential candidates for gastroretentive drug delivery system

1. Drugs that are primarily absorbed in the stomach e.g. Amoxicillin.
2. Drugs that are poorly soluble in alkaline pH e.g. Furosemide, Diazepam.
3. Drugs that have narrow absorption window e.g. Levodopa, Methotrexate.
4. Drugs that degrade in the colon e.g. Ranitidine, Metformin HCL.
5. Drugs that disturb normal colonic microbes e.g. Antibiotics against Helicobacter pylori.
6. Drugs rapidly absorbed from the GI tract e.g. Tetracycline.
7. Drugs acting locally in the stomach.³

Drug delivery systems are used for maximizing therapeutic index of the drug and also for reduction in the side effects. The most preferred route is the oral route especially for the administration of therapeutic drugs because low cost of therapy and ease of administration leads to higher level of patient compliance. More than 50% of the drug delivery systems available are to be administered through oral route. Reasons behind using oral route are that it is the most promising route of the drug delivery and effective oral drug delivery may depend upon many factors such as gastric emptying process, gastrointestinal transit time of the dosage form, drug release from the dosage form and site of absorption of drug. High level of patient compliance is the major advantage of using the oral route. To modify the GI transit time is one of the main challenge in the development of oral controlled drug delivery system. Gastric emptying of pharmaceuticals is highly variable and dependent on the dosage form and the fed/fasted state of the stomach. Normal gastric residence time usually ranges between 5 minutes to 2 hours. In the fasted state the electrical activity in the stomach – the interdigestive myoelectric cycle or migrating myoelectric complex (MMC) governs the activity and the transit of dosage forms. It is characterized by four Phases.⁴

❖ Anatomy of the stomach

The gastro intestinal tract can be divided into three main regions

- a) Stomach
- b) Small intestine- duodenum, jejunum, and ileum
- c) Large intestine

The GIT is a muscular tube of about 9m which extends from mouth to anus. Its function is to take nutrients and eliminate out waste product by physiological processes such as digestion, absorption, secretion, motility and excretion. The stomach has three muscle layers called oblique muscles and it is situated in the proximal part of the stomach, branching over the fundus and higher regions of the gastric body. The stomach is divided into fundus, body and pylorus^[8]. The stomach is a shaped

organ located in the upper left hand portion of the abdomen. The main function of the stomach is to store the food temporarily, grind it and releases slowly in to the duodenum.

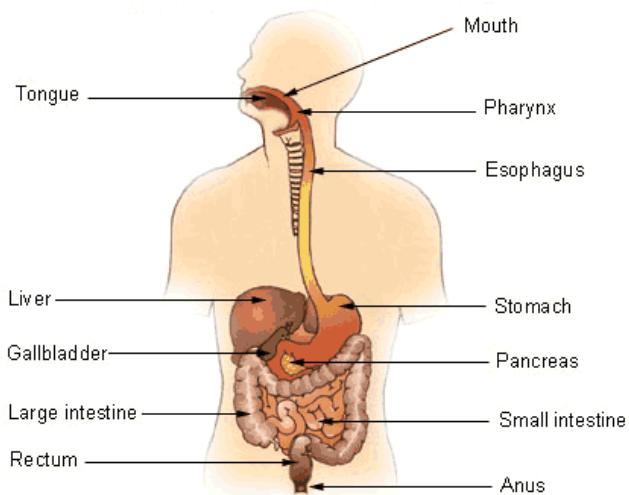


Figure 1: General Gastrointestinal tract³³

Physiology of the stomach

The stomach is an expanded section of the digestive tube between the esophagus and small intestine. In the empty state the stomach is contracted and its mucosa and sub mucosa are thrown up into folds called rugae. There are 4 major types of secretory epithelial cell that covers the stomach and extends into gastric pits and glands.

1. Mucous cells- secrete alkaline mucus
2. Parietal cells – secrete HCL
3. Chief cells- secrete pepsin
4. G cells- secrete hormone gastrin.⁵

Gastric motility and gastric empty rate

Two distinct patterns of gastrointestinal motility and secretion exist to the fasted and fed state.

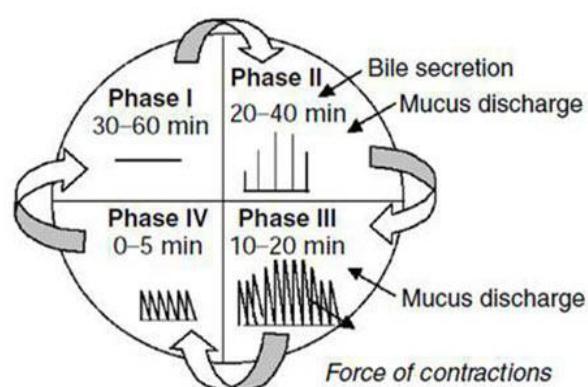


Figure 2: Phases of Gastric motility and gastric emptying rate³⁴

The bioavailability of the orally administered drug depend upon the state of feeding. In the fasted state, it is characterized by an interdigestive series of electric event called inter digestive myoelectric cycle or migrating motor complex. It is divided into 4 phases^[5].

- a) Phase I (basal phase) it lasts from 40-60 min with rare contractions
- b) Phase II (preburst phase) last from 40-60 min with intermittent potential and contractions.
- c) Phase III (burst phase) last for 4-6 min. in this intense and regular contraction occur for short periods. Due to these contractions the undigested food is swept from stomach to intestine. These are known as house keeper waves.

- d) Phase IV it lasts for 0-5 min and occurs between phases III and I for two consecutive cycles.

After the ingestion of the mixed meal the pattern of contraction changes from fed to that of fasted state, this is known as digestive motility pattern, these contractions reduces the size of the food particles to less than 1 mm after that it is propelled to the pylorus in the suspension form. During fed state the onset of MMC is delayed which result in slow down of gastric emptying rate.⁶

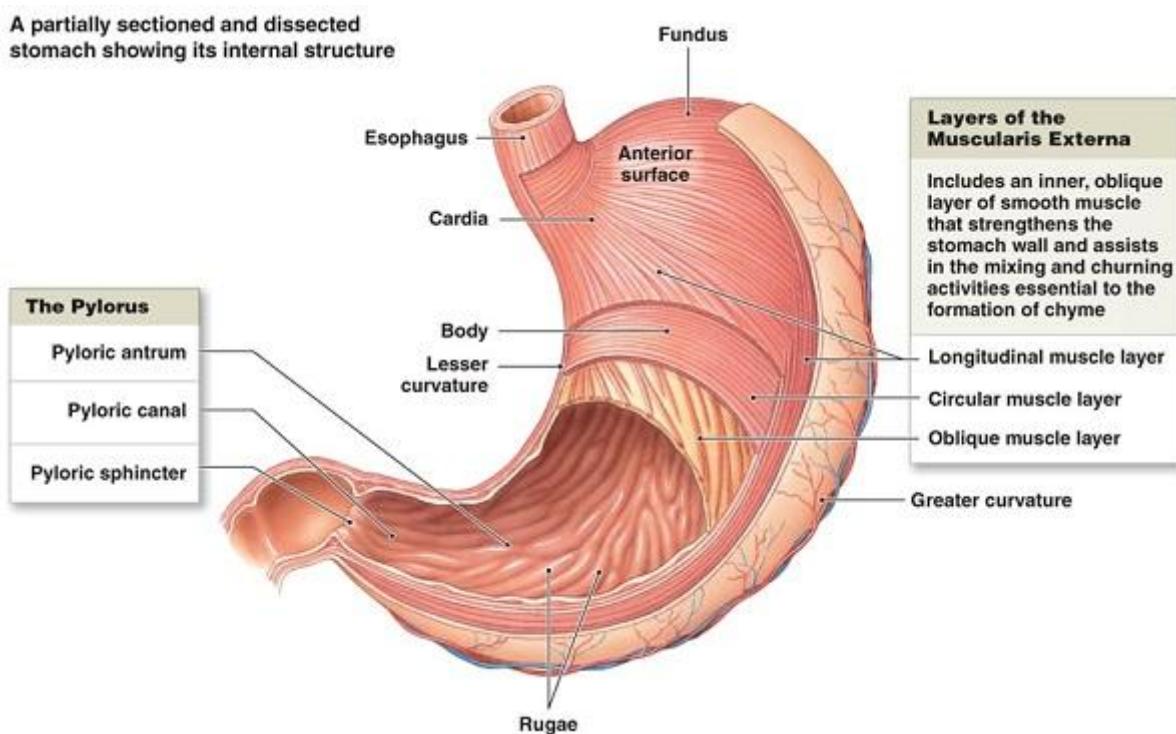


Figure 3: Shows Physiology of stomach³⁵

Advantages of gastroretentive drug delivery system^{6,7}

1. It increases patient compliance by reducing dosing frequency
2. Buoyancy increases gastric residence time
3. Better therapeutic effect of short half-life drugs
4. Site specific drug delivery to stomach can be achieved
5. Gastric irritation can be avoided by designing sustained release.
6. No risk of dose dumping by making single unit floating unit such as microspheres releases drug uniformly.^[7]
8. Delivery of drugs with narrow absorption window in the small intestine region.
9. Longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease.
10. Improved bio-availability is expected for drugs that are absorbed readily upon release in the GI tract such as cyclosporine, ciprofloxacin, ranitidine, amoxicillin, captopril, etc.

11. Targeted therapy for local ailments in the upper GI tract.⁸

Disadvantages of gastroretentive drug delivery system⁹

- 1) Floating systems has limitation, that they require high level of fluids in stomach for floating and working efficiently. So more water intake is prescribed with such dosage form.
- 2) In supine posture (like sleeping), floating dosage form may swept away (if not of larger size) by contractile waves. So patient should not take floating dosage form just before going to bed.
- 3) Drugs having stability problem in high acidic environment, having very low solubility in acidic environment and drugs causing irritation to gastric mucosa cannot be incorporated into GRDDS.
- 4) Bio/mucoadhesives systems have problem of high turnover rate of mucus layer, thick mucus layer & soluble mucus related limitations.
- 5) Swellable dosage form must be capable to swell fast before its exit from stomach and achieve size larger than

pylorus aperture. It must be capable to resist the housekeeper waves of Phase III of MMC.

6) Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.

7) The major challenge for a bio adhesive system is the high turnover rate of gastric mucus.

8) There is also possibility of esophageal binding with bio adhesive drug delivery systems.

9) Drugs which have stability and solubility problems in GIT are not suitable candidates for these types of systems.

Gastroretentive Techniques

Several techniques, including floating, swelling, inflation, and adhesion have been explored to increase the gastro retention of dosage forms³

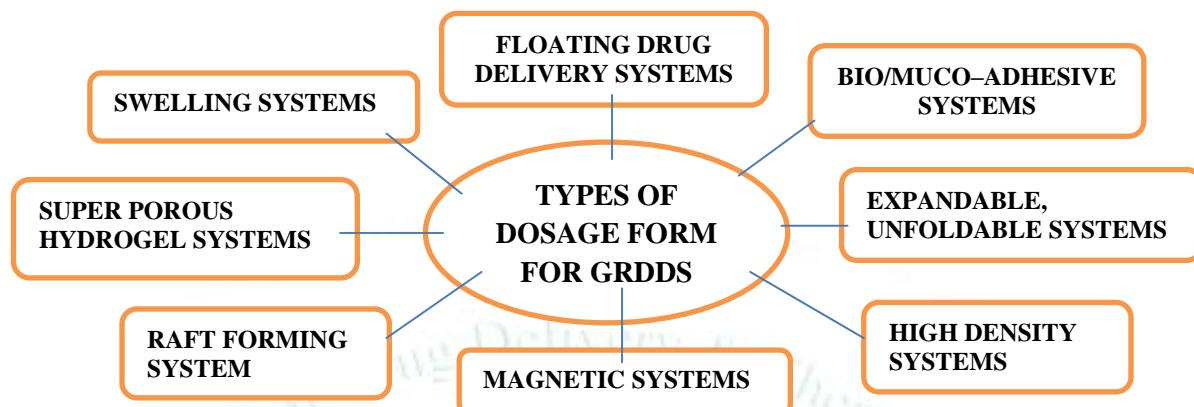


Figure 4: Gastroretentive Techniques

TYPES OF GASTRORETENTIVE DOSAGE FORM

A) Floating systems¹⁰

Floating systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate which results

in increased GRT and reduces fluctuation in plasma drug concentration. The floating drug delivery system and bio adhesive drug delivery are widely used technique for gastro retention and floating systems in particular has been extensively researched, mainly because the floating system does not adversely affect the motility of GI tract. Floating systems can also be classified as effervescent and noneffervescent systems.

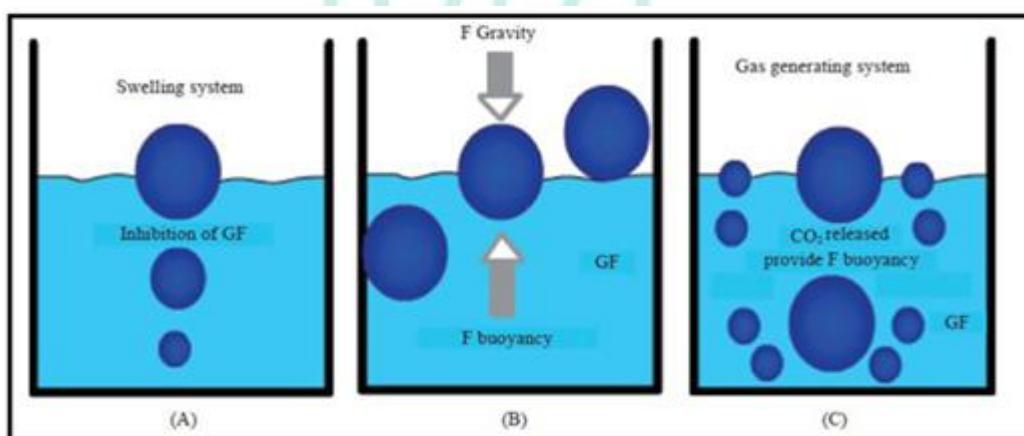


Figure 5: Mechanism of floating systems³⁶

I) Effervescent systems

Flootation of a drug delivery system in the stomach filled with vacuum, air, or an inert gas. Gas can be introduced into the floating chamber by the volatilization of an organic solvent (e.g., ether or cyclopentane) or by the CO₂ produced as a result of an effervescent reaction

between organic acids and carbonate–bicarbonate salts. These devices contain a hollow deformable unit that converts from a collapsed to an expanded position and returns to the collapsed position after a pre determined amount of time to permit the spontaneous ejection of thin floatable system from the stomach.

a) Volatile liquid containing systems

This type of system consists of two chambers separated by an impermeable, pressure-responsive, movable bladder. The first chamber contains the drug and the second chamber contains the volatile liquid. The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. The device may also consist of a bio erodible plug made up of Poly vinyl alcohol, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach. The device inflates, and the drug is continuously released from the reservoir into the gastric fluid.¹¹

b) Gas generating system

Floatability can also be achieved by generation of gas bubbles. CO₂ can be generated *in situ* by the incorporation of carbonates or bicarbonates, which react with acid- either the natural gastric acid or coformulated as citric or tartaric acid. The optimum stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. An alternative is to incorporate a matrix with entrapped of liquids, which forms a gas at body temperature. These approaches have been used for single and multiple unit system.

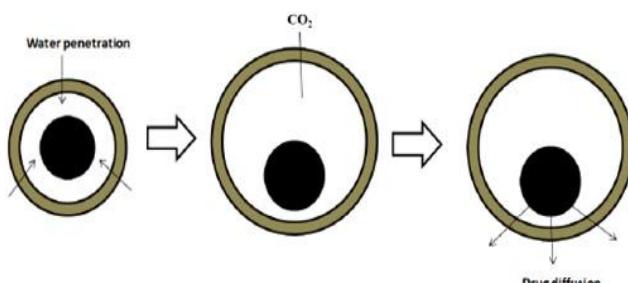


Figure 6: Gas generating system³⁷

II.) Non effervescent systems¹²

Noneffervescent systems incorporate a high level (20–75 % w/w) of one or more gel-forming, highly swellable, cellulosic hydrocolloids (e.g., hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose (HPMC), and sodium carboxymethyl cellulose), polysaccharides, or matrix-forming polymers (e.g., polycarbophil, polyacrylates, and polystyrene) into tablets or capsules. Upon coming into contact with gastric fluid, these gel formers, polysaccharides and polymers hydrate and form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the dosage form. The following approaches used in designing intragastric floating systems:

a) Hydrodynamically balanced systems OR Colloidal Gel Barrier System:

These are single unit dosage form, containing one or more gel forming hydrophilic polymers, HPMC is the most commonly used excipient, although HEC, HPC, NaCMC, agar and alginic acid are also used. The polymer is mixed with drug and usually administered in a gelatin capsule. The capsules rapidly dissolve in the gastric fluid, and hydration and swelling of the surface polymer produce a floating mass. Drug release is controlled by the formation of hydrated boundary at the surface. Continuous erosion of the surface allows water penetration to the inner layer, maintaining surface hydration and buoyancy. Incorporation of fatty excipients gives low density formulations and reduces penetration of water, reducing the erosion. The main drawback is the passivity of operation. It depends on the air sealed in the dry mass centre following hydration of gelatinous surface layer and hence the characteristics and amount of polymer. Effective drug delivery depends on the balance of drug loading and effect of polymer on its release profile.

b.) Microporous compartment system

This technology is based on the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber contains trapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption

c. Alginate beads

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40°C for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hours.¹³

d. Micro balloons or Hollow Microspheres¹⁴

Micro balloons / hollow microspheres loaded with drugs in their other polymer shell were prepared by simple solvent evaporation or solvent diffusion method to prolong the GRT of the dosage form. Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer/polymer ratio and the solvent used for formulation. These micro balloons floated continuously over the surface of an acidic dissolution media containing surfactant for >12 hours. At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good floating.

B) Bio/mucoadhesive systems

Bio adhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a site specific manner. This approach involves the use of bio adhesive polymers, which can adhere to the epithelial cell surface or mucin in the stomach. It increases the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membrane. The adherence to the gastric wall increases residence time at a particular site, thereby improving bioavailability. Gastric mucoadhesion

does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastro retentive force. Some of the most promising excipients that have been used are polycarbophil, carbopol, lections, chitosan and gliadin, etc. BDDS are used as a delivery device within the human to enhance drug absorption in a site-specific manner.¹⁵

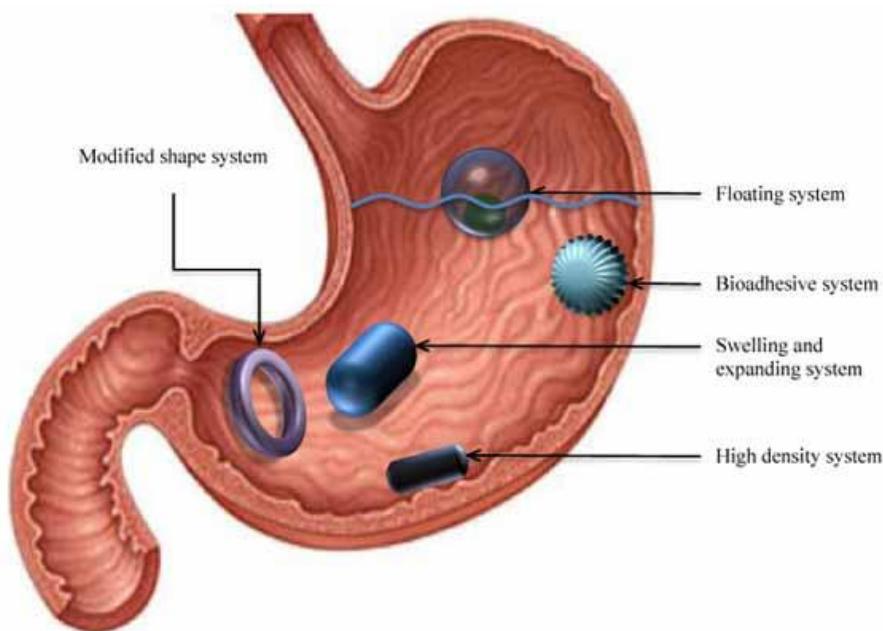


Figure 7: Bio-adhesion System³⁸

The basis of adhesion is that a dosage form can stick to the mucosal surface by different mechanism. These mechanisms are:

- 1) The wetting theory, which is based on the ability of bio adhesive polymers to spread and develop intimate contact with the mucous layers.
- 2) The diffusion theory which proposes physical entanglement of mucin strands the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate.
- 3) The absorption theory, suggests that bio adhesion due to secondary forces such as Vander Waal forces and hydrogen bonding.
- 4) The electron theory, which proposes attractive electrostatic forces between the glycoprotein mucin network and the bio adhesive material.

Binding of polymers to the mucin/epithelial surface can be divided into three categories:

a. Hydration – mediated adhesion-

Certain hydrophilic polymers have the tendency to imbibe large amount of water and become sticky, thereby acquiring bio adhesive properties. The prolonged gastro retention of the bio/muco-adhesive

delivery system is further controlled by the dissolution rate of the polymer.

b. Bonding – mediated adhesion

The adhesion of polymers to a mucus or epithelial cell surface involves various bonding mechanisms including physical, mechanical and chemical bonding. Physical or mechanical bonds can result from deposition and inclusion of the adhesive material in the crevices of the mucosa. Chemical bonds may be either covalent (primary) or ionic (secondary) in nature. Secondary chemical bonds consist of dispersive interactions (i.e. Vander Waals interactions) and stronger specific interactions such as hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl and carboxylic groups.¹⁶

c. Receptor – mediated adhesion-

Certain polymers have the ability to bind to specific receptor sites on the cell surface. The receptor mediated events serves as a potential approach in bio/muco-adhesion, hence enhancing the gastric retention of dosage forms. Certain plant lections, like tomato lections, interact specifically with the sugar groups present in mucus or on the glycocalyx.¹⁷

C) Expandable, unfoldable and swellable systems^{18, 19}

A dosage form in the stomach will withstand gastric transit if it bigger than pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, their configurations are required to develop an expandable system to prolong GRT:

- 1) A small configuration for oral intake,
- 2) An expanded gastro retentive form, and
- 3) A final small form enabling evacuation following drug release from the device.

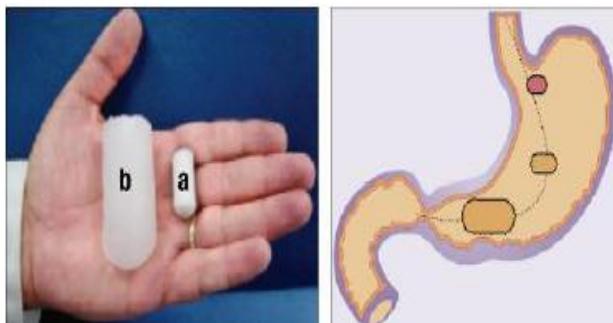


Figure 8: Unfoldable and swellable systems³⁹

Thus, gastro-retention is improved by the combination of substantial dimension with high rigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach. Unfoldable and Swellable systems have been investigated and recently tried to develop an effective GRDDS. Unfoldable systems are made of biodegradable polymers. They are available in different geometric forms like tetrahedron, ring or planar membrane (4 - label disc or 4 - limbed cross form) of bio erodible polymer compressed within capsule which extends in the stomach. Swellable systems are also retained in the GIT due to their mechanical properties. The swelling is usually results from osmotic absorption of water. Expandable systems have some drawbacks like problematical storage of much easily hydrolysable, biodegradable polymers relatively short-lived mechanical shape memory for the unfolding system most difficult to industrialize and not cost effective. Again, permanent retention of rigid, large single-unit expandable drug delivery dosage forms may cause brief obstruction, intestinal adhesion and gastropathy.

D) High-density systems

These systems, which have a density of ~3 g/cm³, are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. Above a threshold density of 2.4–2.8 g/cm³, such systems can be retained in the lower part of the stomach. The only major drawbacks with such systems is that it is technically difficult to manufacture them with a large amount of drug (>50 %) and to achieve the required density of 2.4–2.8 g/cm³. Diluents such as barium sulphate (density = 4.9), zinc oxide, titanium dioxide, and iron powder may be used to manufacture such high-density formulations.

E. Magnetic Systems

This approach to enhance the GRT is based on the simple principle that the 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. The technological approach in rabbits with bio adhesive granules containing ultra-fine ferrite. They guided them to esophagus with an external magnet for the initial 2 minutes and almost all the granules were retained in the region after 2 hours²⁰

F) Raft-forming System

Raft System incorporate alginic gels these have a carbonate component and, upon reaction with gastric acid, bubbles form in the gel, enabling floating. Raft forming systems have received much attention for the drug delivery for GI infections and disorders. The mechanism includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO₂. Usually, the system ingredients includes age forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO₂ to make the system less dense and float on the gastric fluids. An antacid raft forming floating system contains a gel forming agent (e.g. sodium alginate), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft), which when comes in contact with gastric fluids, the raft floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as barrier between the stomach and esophagus.²¹

G) Super porous Hydrogels²²

Although these are swellable systems, they differ sufficiently from the conventional type to warrant separate classification. With pore size ranging between 10nm and 10 μ m, absorption of water by conventional hydrogels is very slow process and several hours may be needed to reach an equilibrium state during which premature evacuation of dosage form may occur. Superporous hydrogels, average pore size > 100 μ m, swell to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores.

H) Swelling systems²³

After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems are sometimes referred to as plug type systems because they tend to remain lodged at the pyloric sphincter. These polymeric matrices remain in the gastric cavity for several hours even in the fed state. Sustained and controlled drug release may be achieved by selecting a polymer with the proper molecular weight and swelling properties. Upon coming in contact with gastric fluid, the polymer

imbibes water and swells. The extensive swelling of these polymers is a result of the presence of physical-chemical crosslinks in the hydrophilic polymer network.

These crosslink's prevent the dissolution of the polymer and thus maintain the physical integrity of the dosage form. A balance between the extent and duration of swelling is maintained by the degree of cross linking between the polymeric chains. A high degree of cross linking retards the swelling ability of the system and maintains its physical integrity for a prolonged period. On the other hand, a low degree of cross linking results in extensive swelling followed by the rapid dissolution of the polymer. An optimum amount of cross linking is required to maintain a balance between swelling and dissolution. The swollen system eventually will lose its integrity because of a loss of mechanical strength caused by abrasion or erosion or will burst into small fragments when the membrane ruptures because of continuous expansion. These systems also may erode in the presence of gastric juices so that after a predetermined time the device no longer can attain or retain the expanded configuration.

FACTORS AFFECTING GASTRIC RESIDENCE TIME OF GRDDS²⁴

Gastric retention time (GRT) is depends upon the dosage form buoyancy which is further dependent on the density. Density of the dosage form that is used for GRDDS should be less than the gastric contents (1.004gm/ml).

1) Size and Shape

Dosage form unit with a diameter of more than 7.5 mm are more suitable candidate as compared to those which have a diameter of 9.9 mm because they have an increased GRT. Similarly the dosage form having a tetrahedron shape and ring shape devises with a flexural modulus of 48 and 22.5 kilopond per square inch (KSI) are reported to have better GIT for 90 to 100% retention and hence more suitable for GRDDS as compared with other shapes.

2) Viscosity of polymer

Viscosity of polymer and their interaction greatly affect the drug release and rafting properties of GRDDS. Low viscosity polymers (e.g., HPMC K100LV) were found to be more suitable candidates for GRDDS than high viscosity polymers (e.g., HPMC K4M) because they improve rafting properties. Also, with an increase in polymer viscosity a decrease in the release rate was observed.

3) Fed or Unfed State

Under fasting conditions, the GRT of the unit is expected to be very short because of the periods of strong motor activity or the migrating myoelectric complexes (MMC) that occurs every 1.5to 2 hours. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC then obviously GRT of the dosage form expected to be very short. But, in the fed state, GRT is considerably longer because MMC is delayed.

4) Nature of meal

Motility pattern of the stomach can change to fed state when indigestible polymers or fatty acid salts are fed and because of this the gastric emptying rate is decreased and drug release is prolonged.

5) Frequency of feed

When successive meals are given, the GRT can increase by over 40 minutes compared with a single meal because of the low frequency of MMC.

6) Gender

Mean GRT of a male in meals (3.4±0.4 hours) is less compared to the female of the same age and race (4.6±1.2 ours), regardless of the height, weight, and body surface of the two.

7) Age

Elderly people have a significantly longer GRT, especially those who are over 70 years of age.

8) Posture

Rafting forms are protected by an upright position against postprandial emptying because at this position, the rafting form remains above the gastric contents irrespective of its size. While the conventional dosage form sink to the lower part of the distal stomach at this position from where they are expelled by astral peristaltic movements through the pylorus. But supine position offers no such protection against early and erratic emptying of rafting dosage forms. Only large dosage forms (both conventional and rafting) experience prolonged retention when they are anywhere between the lesser and greater curvature of the stomach. On moving distally, these units show significant reduction in GRT compared with upright subjects because of peristaltic movement.

9) Gastro retentive dosage form

Gastro retentive dosage forms are the systems that can stay in the gastric region for several hours and thus, prolong the gastric residence time of the drugs. After oral administration, such a dosage form is retained in the stomach and releases the drug in a controlled and sustained manner so that the drug can be supplied continuously in the upper GIT. This prolonged gastric retention improves bioavailability, decreases drug wastage, and improves solubility of drugs that are less soluble in a high pH environment.

10) Other factors:-

- Diseased states of the individual (chronic disease, diabetes etc.)
- Body mass index
- Physical activity
- Molecular weight and lipophilicity of the drug depending on its ionization state.²⁵

Criteria for selection of drug²⁶

For Gastro retentive drug delivery system

- Drugs those are locally active in the stomach (e.g. misoprostol, antacids)
- Drugs that have narrow absorption window in GIT (e.g. L-DOPA, paminobenzoic acid, furosemide, riboflavin).
- Drugs those are locally active in the stomach (e.g. misoprostol, antacids).
- Drugs exhibit low solubility at high pH values (e.g. diazepam, chlordiazepoxide, verapamil).
- Drugs that disturb normal colonic microbes such as tetracycline, clarithromycin, amoxicillin
- Drugs those are unstable

Ideal Characteristics ²⁷

- Drugs acting locally in the stomach, e.g. Antacids and drugs for H. Pylori viz., Misoprostol

- Drugs that are primarily absorbed in the stomach and upper part of GI, e.g. Amoxicillin, Calcium Supplements, Chlordiazepoxide and Cinnarazine
- Drugs that is poorly soluble at alkaline pH, e.g. Furosemide, Diazepam, Verapamil HCL, Chlordiazepoxide etc.
- Drugs with a narrow window of absorption in GIT, e.g. Riboflavin, ParaAminobenzoic Acid, Cyclosporine, Methotrexate, Levodopa etc.
- Drugs which are absorbed rapidly from the GI tract. e.g. Metronidazole, tetracycline.
- Drugs that degrade or unstable in the colon. e.g. Captopril, Ranitidine HCL, Metronidazole, Metformin HCl.
- Drugs that disturb normal colonic microbes, e.g. Amoxicillin Trihydrate, antibiotics against Helicobacter pylori.

Table 1: List of Drugs Formulated in Multiple Unit Forms of Floating Drug Delivery Systems

Drug Dosage form	Drug Dosage form
Verapamil Hydrochloride	Floating Micro particles
Ketoprofen Floating	Micro particles
Ranitidine Hydrochloride Floating Granules	Ranitidine Hydrochloride Floating Granules
Metronidazole Floating Beads	Metronidazole Floating Beads
Lansoprazole Floating Micro pellets	Lansoprazole Floating Micro pellets
Meloxicam	Low density multiparticulate system
Diltiazem Hydrochloride, Theophylline & Verapamil Hydrochloride	Theophylline and Micro particles
Nifedipine Hollow Microsphere	Acetohydroxamic Acid Floating Microsphere
Nifedipine Hollow Microsphere	Acetohydroxamic Acid Floating Microsphere
Piroxicam Floating Microsphere	Residronate Sodium Granules
Diltiazem Hydrochloride Granules	
Piroxicam Floating Microsphere	Residronate Sodium Granules

Approaches for gastro retention:

To improve the retention of an oral dosage form in the stomach various approaches have been developed, it includes floating systems and non-floating systems. Floating systems includes effervescent systems and non-effervescent systems, these systems have the bulk

density lower than the gastric fluid and remain floating and releases the drug slowly in a desired rate. Non floating systems include bio adhesive systems, swelling systems, high density systems expandable systems, raft forming systems, magnetic systems which utilize different mechanisms to prevent the exit of drugs through pyloric sphincters.²⁸

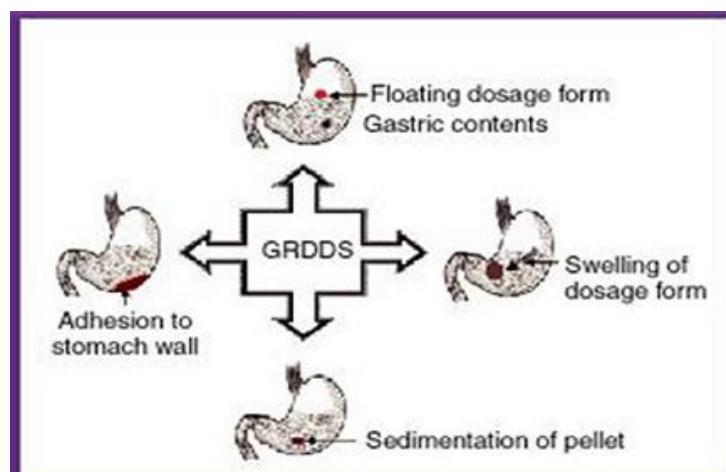


Figure 9: Approaches for gastro retention⁴⁰

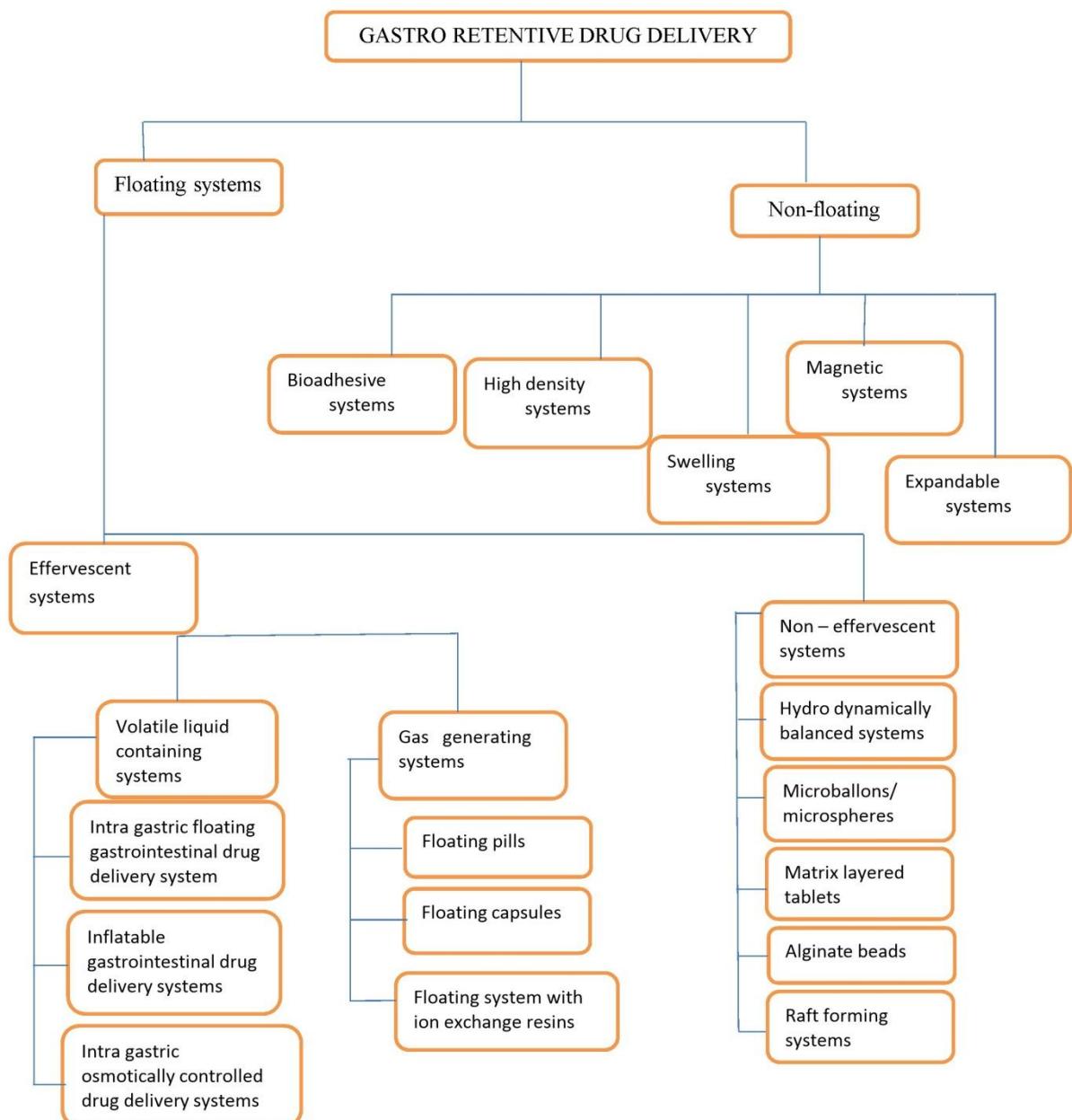


Figure 10: Flowchart showing different approaches for gastro retentive drug delivery systems⁴¹

EVALUATION PARAMETERS OF GASTRORETENTIVE DOSAGE FORMS:^{29,30}

A) In- Vitro Evaluation

1) **General tests:** These tests include appearance, hardness, friability, drug content, weight

Variation, uniformity of content.

2) Floating systems

a) Buoyancy Lag Time:

Buoyancy lag time is determined to assess the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test.

b) Floating Time:

The time for which the dosage form continuously floats on the dissolution media is termed as floating time. It is usually performed in Simulated Gastric Fluid maintained at 370°C.

c) Specific Gravity / Density:

Density can be determined by the displacement method using Benzenes displacement medium.

3) Swelling systems

a) Swelling Index:

After immersion of swelling dosage form into Simulated Gastric Fluid at 370°C, dosage form is removed out at regular interval and dimensional changes are measured in terms of increase in tablet thickness / diameter with time.

B) In-Vivo Evaluation

1) Radiology:

Barium Sulphate is widely used as Radio Opaque Marker. X-ray is used for examination of internal body systems. So, BaSO₄ is incorporated inside dosage form and X-ray images are taken at various intervals to view gastric retention.

2) Gastroscopy: Gastroscopy is used to inspect visually the effect of prolongation in stomach.

3) Scintigraphy: Similar to X-ray, emitting materials are incorporated into dosage form and then images are taken by scintigraphy. Widely used emitting material is 99 Tc.

4) Ultrasonography: It is not used generally because it is not traceable at intestine.

5) Magnetic Marker Monitoring: This technique is radiation less and so not hazardous. In this technique, dosage form is magnetically marked by incorporating iron powder inside, and images can be taken by very sensitive bio-magnetic measurement equipment.

In vivo evaluation of gastric retention ^{31, 32}

Analysis of the position of the dosage form in the GIT involves an imaging technique such as γ -scintigraphy and X-ray. 1) In γ -scintigraphy, a small amount of stable isotope is compounded in the dosage forms during its preparation. The inclusion of a γ -emitting radio-nuclide in a formulation allows indirect external observation using a γ -camera or scinti scanner. For x-ray, barium sulfate is used as a contrast medium. It helps to locate dosage form in the GIT by which one can predict and

correlate the gastric emptying time and the passage of dosage form. In addition, gastroscopy and ultrasonography studies can be included in the in vivo evaluation of GRDDS. Gastroscopy comprises of per-oral endoscopy, used with a fiber optic and video systems. Ultrasonography is not routinely used in the evaluation of GRDDS. In vivo plasma profile can also be obtained by performing the study in suitable animal model.

Water uptake study: It is done by immersing the dosage form in simulated gastric fluid at 37OC and determining the dimensional changes, such as diameter and thickness, at regular interval of time. After the stipulated time the swollen tablets are weighed and water uptake is measured in the terms of percentage weight gain, as given:

$$WU = (W_t - W_0) \times 100/W_0$$

In which, W_t and W_0 are the weight of the tablet after time t and initially, respectively. The tablets are also evaluated for hardness, friability, weight variation etc. which are applicable for conventional instant release tablets. For the multiple unit dosage forms like microsphere following tests are also essential apart from the above tests:

- 1) Morphological and dimensional analysis: It is done with the aid of scanning electron microscopy and optical microscope.
- 2) Percentage yield of microsphere.
- 3) Entrapment efficiency: The drug is extracted by suitable method and analyzed to find out the amount of drug present.

Patents on Grdds ⁴¹

Sr.No	Patents	
1	Gastrorentevive dosage form systems and process of preparation thereof.	US20140271871846
2	Gastrorentevive sustained and pulsatile drug delivery systems	W02013051036 A1
3	GRDDS and their dosage form their method of preparation using calcium carbonate.	W02014057086 A1
4	A novel gastro retentive drug delivery of macrolide.	W02011125075 A3
5	Gastrorentevive controlled release microsphere for improved drug delivery	US6207197 B1
6	Extended release gastro retentive oral drug delivery systems for valsartan	EP2061438 A1
7	GRDDS.	W02009089665 A2
8	GRDDS comprising an extruded hydratable polymer.	US8586083 B2

CONCLUSION

Gastro retentive drug delivery system offers a potential advantage of enhanced bioavailability and controlled delivery of drug. Gastro retentive drug delivery system showed the potential to increase the gastric retention of drug. Growing understanding of impact of GIT physiology on drug delivery will ensure development of an increasing number of drug delivery system to optimize drug delivery of molecules exhibiting regional variability in drug absorption. The increasing sophistication of delivery technology will ensure the

development of increase number of gastro retentive drug delivery to optimize the delivery of molecules that exhibit absorption window, low bioavailability and extensive first pass metabolism. Based on the literature surveyed, we concluded that Gastro retentive drug delivery offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper gastrointestinal tract and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability. Gastro retentive drug delivery system gives maximum benefit to patient.

REFERENCES

- Pawar H A, Dhavale R. Development and evaluation of gastroretentive floating tablets of an antidepressant drug by thermoplastic granulation technique. beni-suef university journal of basic and applied sciences. 2014; 3:122-132.
- Subhramanyam CVS, Setty JT. Laboratory manual of physical pharmaceutics. Vallabh prakashan 2002; page no 21.
- Mathur P, Saroha K, Syan N, Verma S and Kumar V. Floating drug delivery system: An innovative acceptable approach in gastro retentive drug delivery. Scholars research library 2010; 2:257-270
- Dixit N. Floating drug delivery system. Journal of Current Pharmaceutical Research, 2011; 7(1):6-20.
- Vyas SP, Khar RK. Controlled drug delivery: concept and advances. Vallabh Prakashan Delhi, 2002; 1:123-231.
- Streubel A, Siepmann J, Bodmeier R. Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. European Journal of Pharmaceutical Sciences, 2003; 18:37-45.
- Khan R. Gastro retentive Drug Delivery System – A Review. Int J Pharm Bio Sci, 2013; 4(2):630-646.
- Joseph R, Robinson, Lee V. Controlled Drug Delivery, Fundamentals and Applications. 2nd Edition, Revised and Expanded, Marcell. Dekker Inc., New York (2009).
- Sharma S and Pawar A. Low density multiparticulate system for pulsatile release of meloxicam. Int J Pharm. 2006; 313:150-158.
- Sangekar, S., Evaluation of effect of food and specific gravity of the tablets on gastric retention time. Int.J.Pharm, 1985; 35:34-53.
- Bardonnet PL, Faivre V, Pugh WJ, Piffaretti JC and Falson F. Gastroretentive dosage forms: overview and special case of helicobactor pylori. J Control Release. 2006; 111:1-18.
- Whitehead L, Fell JT and Collett JH. Development of a gastroretentive dosage form. Eur J Pharm Sci. 1996;4:182
- Kawashima Y, Niwa T, Takenchi H, Hino T, Itoh Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. J Pharm Sci 1992; 81:135- 40
- Moes AJ. Gastroretentive Dosage forms. Crit. Rev, Ther Drug Carrier Syst. 1993; 10:143- 195.
- Chien YW. "Oral drug delivery system." In: Chien, Y.W. (Ed.), Novel drug delivery system, Marcel Dekker, New York, 1992; 139.
- Jorgen F, Toftkjar H. Antacid composition.US Patent 50681095.14:815
- Klusner EA, Lavy E, Friedman M, Hoffman A. Expandable gasrtroretentive dosage forms. J Control Release 2003; 90(2):143-62.
- Klusner EA, Lavy E, Stepensley D, Friedman M, Hoffman A. Novel gasrtroretentive dosage form: evaluation of gastroretentivity and its effect on riboflavin absorption in dogs. Pharm Res 2002; 19:1516-23.
- Abubakar O, Nur Jun S, Zhang. Recent progress in sustained: controlled oral delivery of captopril: an overview. Int J Pharm. 2000;139-146.
- Jorgen F, Toftkjar H. Antacid composition.US Patent 50681095.14:815.
- Chen J, Blevins WE, Park H, Park K. Gastric retention of superporous hydrogel composites. J Control Release 2000; 64(1-3):39-51.
- Klusner EA, Lavy E, Friedman M, Hoffman A. Expandable gasrtroretentive dosage forms. J Control Release 2003; 90(2):143-62.
- Nayal AS, Pandey S, Gnanarajan G, et al. Review: An Overview on Gastroretentive Floating Tablet. International Journal of Pharmaceutical and Chemical Sciences, 2013; 2(3):1357-1365.
- Larhed AW, Artursson P, Grasjo J, Bjork K. Diffusion of drugs in native and purified gastrointestinal mucus. J Pharm Sci 1997; 86(6): 660-665.
- Nayak AK, Malakar J, Sen KK, Gastroretentive drugdelivery technologies: Current approaches and future potential. J Pharm Educ Res, 2010; 1(2):1-10.
- Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems. Trop. J Pharm Res 2008; 7(3):1055-66.
- Sandinaswetha., et al; A review on gastroretentive drug delivery systems. International journal of research in Pharmaceutical and biomedical sciences, 2012; 3(3):1285-1293.
- Soni RP, Patel AV, Patel RB, Patel MR, Patel KR, Patel NM. Gastro-retentive Drug Delivery systems: A Review. International Journal of Pharma World Research, 2011; 2(1):1-22.
- Kshirsagar SJ, Wadekar SB, Bhalekar MR, Ughade PB, Madgulkar AR. Gastroretentive Drug Delivery System of Hydrochlorothiazide: Formulation, Optimization and *In Vivo* Evaluation. Asian Journal of Pharmaceutical Sciences, 2011; 6(3-4): 166-174.
- Khan AD, Bajpal M. Floating Drug Delivery System: An Overview, Int. J. Pharm Tech Res.2010; 2:2497.
- Nagigot J, Shayed, Floating Drug Delivery System, Int. J. Pharm. Scien. Nano.2009; 2:595.
- <http://pediatricfeeding.com/gi-anatomy-and-disease/>
- Rathod HJ, Mehta DP, Yadav JS; A review on Gastroretentive Drug Delivery Systems; PharmaTutor; 2016; 4(7):29-40
- <http://unmasadalha.blogspot.in/2016/01/stomach-diagram.html>
- Maheta H, Patel MR, Patel KR, Patel MS, Review: An Overview on Floating Drug Delivery System, PharmaTutor, 2014; 2(3):61-71
- Nayak AK, Maji R, Das B. Gastroretentive Drug Delivery systems: a review. Asian Journal of Pharmaceutical and Clinical Research. 2010;3(1):2-10.
- Alzaher W, Shaw J, Al-kassas. Gastroretentive Formulations for Improving Oral Bioavailability of Drugs-Focus on Microspheres and their Production. Current Drug Delivery.2016; 13(5):646-651.
- Sravya K, Kavitha K, Rupesh Kumar M, Jagdeesh Singh SD. Gastroretentive Drug Delivery Systems: A Review. Research Journal of Pharmaceutical, Biological and Chemical Sciences 2012; 3(3):966-980.
- <http://www.pharmamirror.com/wp-content/uploads/2013/11/Floating-drug-delivery-system-FDDS.pdf>
- Parmar, G. Formulation And Evaluation Of Floating Microspheres Of Venlafaxine Hydrochloride. Pharma Science Monitor - An International Journal of Pharmaceutical Sciences. 2014; 5:10-22.
- Chugh C, Nanda A. Gastroretentive Drug Delivery Systems - A Review. International Journal of Pharma and Bio Sciences. 2017; 8(1):62 – 68.