GASTRORETENTIVE DRUG DELIVERY SYSTEM: AN OVERVIEW

B. Yamini¹, Karishma Rao¹, J. Naga Sri Lakshmi¹, K. Viswaja¹, T. Tejaswini¹,
P. Geethika¹, B. Hemalatha¹*, K. Padmalatha²

¹Department of Pharmaceutics, Vijaya Institute of Pharmaceutical Sciences for women,
Vijayawada.

²Department of Pharmacology, Vijaya Institute of Pharmaceutical Sciences for women,
Vijayawada.

1. ABSTRACT
The most popular route of administration for systemic action is oral route. It is probable that at least 90% of all the drugs given by oral route. There are different drug deliveries to give drug by oral route. Gastro retentive drug delivery system plays a vital role among novel drug delivery systems. The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability, and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance. Therefore, extended release drug delivery systems possessing gastric retention properties may be potentially useful.

1. INTRODUCTION
Advancement in drug delivery, oral route is the most common route to the systemic circulation due to easiest way of administration, low cost of drug, patient compliance and flexibility in formulation. About 90% of all drugs used are administered by oral route. Though the drugs are administered orally, solid oral dosage forms is the most common class of products. Tablets are the most common type of solid dosage form in use which is classified based on the drug release pattern, i.e. immediate release and modified release. The immediate release tablets have many drawbacks including non-site specific drug release. However, many drugs are absorbed from specific sites and they require release at that site only for better absorption.
Drug absorption in the GIT is a highly variable process and it is depending on the factors like gastric emptying process, gastrointestinal transit time of dosage forms, drug release from the dosage form, and site of absorption of drugs. Drugs that are absorbed easily from the GIT and have short half-lives are eliminated quickly from the systemic circulation. Frequent dose is required to achieve suitable therapeutic activity.

Gastro retentive drug delivery is one of those approaches to prolong gastric residence time, thereby targeting site specific drug release in the stomach for local or systemic effects. These dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time of the drugs. It will release the drug in stomach in a controlled manner, so that the drug could be supplied continuously to absorption site in GIT i.e., stomach (Uttam Kumar Mandal et al., 2016).

1.1 Merits of Gastroretentive Drug Delivery System (GRDDS)

The GRDDS has the following advantages.

- **Increased bioavailability:** The bioavailability of the drugs having absorption in the upper part of the GIT like riboflavin, levodopa has tremendously been increased than that of the normal dosage forms.

- Sustained drug release and reduced frequency of dosing. This improves patient compliance.

- Targeted delivery of the drug at the upper part of the GIT making it suitable for the local treatment of the disease of the region e.g., antacids, anti-ulcer drugs, antibacterial for H. pylori infection.

- Suitable for the drugs which have pH dependent absorption from stomach e.g., Furosemide, Captopril, Diazepam, Verapamil, Cefpodoxime proxetil.

- Suitable for the drugs which degrade in the intestine or column e.g., Ranitidine hydrochloride.

- Drug level fluctuation is not observed and maintains the optimal therapeutic plasma and tissue concentrations over prolonged time period. This avoids sub-therapeutics as well as toxic concentration and minimizes the risk of failure of the medical treatment and undesirable side effects.

1.2 Limitations of GRDDS

- It is not suitable for the drugs which are not stable in acidic environment.
• It is not suitable for the drugs which are absorbed better in the lower part of GIT.
• Difficulty to attain the desired outcome and problem of the dose dumping.
• Gastric retention is influenced by many factors like gastric motility, pH and presence of food. Hence, the dosage form must be able to withstand the grinding and churning force of peristaltic wave of stomach.
• Poor in vitro and in vivo correlation.
• Higher cost of formulation.
• Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reaction.

1.3 Probable candidates for GRDDS
Following are the probable candidates, but not limited to, for gastro retentive drug delivery system.
• Drugs required to exert local therapeutic action in the stomach: antacids, anti-H.pylori agents, misoprostol.
• Drugs that have narrow absorption window in stomach or upper parts of the small intestine, e.g., furosemide, riboflavine-5-phosphate, metformin hydrochloride, ciprofloxacin, alfuzosin hydrochloride, ofloxacin, norfloxacin, domperidone etc.
• Drugs that disturb normal colonic bacteria, e.g., amoxicillin tirhydrate.
• Drugs unstable in the lower part of GIT, e.g., captopril.
• Drugs insoluble in intestinal fluids, e.g., quinidine, diazepam.

2. FACTORS AFFECTING THE GRDDS:
Since many factors affects the gastric emptying process, which may seriously affect the release of a drug and its absorption, it is desirable to develop a drug delivery system that exhibits an extended gastric residence and a drug release profile independent of patient related variables (Vijay Chudiwal et al., 2018).

The factors that affect the gastric emptying and hence the gastric retention of the drugs includes.
1. Fasting or fed state of the stomach.
During the fasting state an inter-digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. In the fed state, this cycle is delayed and hence the gastric emptying rate is slowed.
2. Size, Density and shape of the dosage form.
3. Intake of food along with drugs: the nature of the food, calorie content and its frequency of intake have considerable effect on the retention of drugs in stomach.

4. Concomitant administration of drugs like anticholinergic agents e.g., atropine, propantheline and opiates delay the gastric emptying while the prokinetic agents like metoclopramide and cisapride enhance the gastric emptying process.

5. Biological factors such as gender, posture, age, sleep, body mass index, physical activity and disease states e.g. diabetes and Crohn’s disease.

3. DIFFERENT APPROACHES OF THE GRDDS:

Different approaches have been pursued to increase the retention of oral dosage forms in the stomach. Some are formulated as single component whereas others are formulated as multi-component dosage forms. GRDDS can be broadly categorized into floating and non-floating system.

3.1 Non-floating system

These GDDS do not float in the stomach however they remain retained there by different mechanisms. Non-floating system is further divided into.

a. High density (sinking) drug delivery system
b. Bioadhesive or mucoadhesive system
c. Magnetic system
d. Unfoldable system

3.2 Floating drug delivery system (FDDS)

In contrast to the high-density drug delivery system, floating systems have density less than the gastric content so the system remain in the stomach for a prolonged period of time without affecting the gastric contents. Floating drug delivery systems are also known as low density system.

Floating drug delivery system can be divided into

a. Effervescent system
b. Noneffervescent system
   i. Hydrodynamically balanced system
   ii. Microballoons or hollow microspheres
   iii. Alginate beads
   iv. Microporous compartment
3.1 Non-floating system

a. High Density (Sinking) Drug Delivery System

In this approach formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulfate, zinc oxide and titanium oxide so that the density of the formulation exceeds the density of the normal gastric content (Ankur Raj Sharma et al., 2014). These materials increase the density up to 1.5-2.4 gm/cm$^3$. Depending on density, the GI transit time of pellets can be extended from an average of 5.8 to 25 hours. But effectiveness of this system in human beings was not observed and no formulation has been marketed (Shaikh Siraj et al., 2013).

b. Bioadhesive or mucoadhesive system

The gastric retention time is extended by adhering the bioadhesive system to gastric mucosa membrane. The adherence of the delivery system to the gastric wall increases residence time thereby improving bioavailability. The chemicals used for the mucoadhesion purpose include polycarbophil, carbopol, lectin, chitosan, carboxy methyl cellulose, gliadin etc. Novel adhesive material derived from fimbriae of bacteria or its synthetic analogues have also been tried for the attachment to the gut (M. Sharath Chandra Goud et al., 2016).

However, gastric mucoadhesive force does not tend to be strong enough to resist the propulsion force of stomach wall. The continuous production of mucus and dilution of the gastric content is another limitation for such type of system. Many investigators have tried out a synergistic approach between floating and bioadhesion system.
c. Magnetic system
In this system, the dosage form contains a small magnet and another magnet is placed on the abdomen over the position of the stomach. The external magnet should be placed with a degree of precision which may decrease the patient compliance (Yadav S et al., 2016).

d. Unfoldable system
The drug delivery system unfolds and increases in size and it remains lodged at sphincter avoiding its exit from the stomach. For this the system, should be small enough to be swallowed but unfold itself when it comes in contact with gastric fluid, and after a certain period of time its size should become small so that it will be easily evacuated. The unfoldable systems are made up of different biodegradable polymers.

3.2 Floating Drug Delivery System
a. Effervescent System
This system consists of the swellable polymers like chitosan and effervescent substance like sodium bicarbonate, disodium glycine carbonate, cyroglycine, citric acid and tartaric acid. When the system comes in contact with gastric fluid, it releases carbon dioxide causing the formulation to float in the stomach. The optimal ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. This system is further divided as single unit matrix tablets or multiple unit pills. Single unit matrix tablet may be single or multilayer type. Floating system with ion exchange resins has also been reported. Effervescent system and drug release from such system.

b. Non-effervescent system
In this system, gel forming or highly swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene are used. After oral administration, this dosage form swells in contact with gastric fluids and attains a bulk density of less than 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass. Superporous hydrogels are an excellent example working in this approach. The dosage form swells significantly to several times of original volume upon contact with gastric fluid, the gastric contraction pushes the dosage form to the pylorus but due to larger size of the dosage form, the contractions slip over the surface of the system, due to which the dosage form pushes back into the stomach (Chirag Chugh et al., 2017).
Non-effervescent system can be further divided into: hydrodynamically balanced system, microballoons, alginate beads, and microporous compartment.

i. **Hydrodynamically balanced system**

The hydrodynamically balanced system (HBS) was first designed by Sheth and Tossounian. HBS contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This system contains one or more gel forming cellulose type hydrocolloid e.g., hydroxypropyl methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, agar, carrageen or alginic acid. It also contains matrix forming polymers such as polycarbophil, polyacrylate and polystyrene. When such system comes in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface (Shashikant Sudarshan Upadhye et al., 2015).

ii. **Microballoons or hollow microspheres**

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells, are prepared by emulsion-solvent diffusion method. The steps involved in this method are summarized in figure 9. The ethanol: dichloromethane solution (1:1) and an acrylic polymer are poured into an agitated aqueous solution of polyvinyl alcohol at 40°C. The gas phase generated in the dispersed polymer droplet by the evaporation of dichloromethane form an internal cavity in the microsphere of the polymer with the drug. The microballoons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours (Korlapati Venkateswara Rao et al., 2016).

iii. **Alginate beads**

Freeze dried calcium alginates have been used to develop multi-unit floating dosage forms. By dropping sodium alginate solution into aqueous solution of calcium chloride spherical beads of about 2.5 mm diameter can be prepared. These beads are separated and air dried. This results in the formation of aporous system which remains buoyant in the stomach (Harshil P. Shah et al., 2017).

iv. **Microporous compartment**

In this system, drug reservoir is encapsulated inside a microporous compartment having pores along its top and bottom walls. The floatation chamber containing entrapped 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 in stomach and proximal part of the small intestine for absorption (Ayesha Tariq et al., 2014).

4. EVALUATION PARAMETERS OF GRDDS
Evaluation parameters of GRDDS generally include
A). Drug-excipient interaction
It is done by using FTIR studies. Appearance of a new peak and/or disappearance of original drug or excipient peaks indicate the drug-excipient interaction.

B). Floating lag time
It is the time taken to emerge tablet onto the surface after it is kept in to the dissolution medium. It is measured in minutes or seconds (Hemali Soni et al., 2015).

C). In vitro drug release and duration of floating
It is determined by using USP II apparatus (paddle) stirring at a speed of 50 or 100 rpm at 37°C in simulated gastric fluid of pH 1.2. Aliquots of the samples are collected and analyzed for the drug content. The time for which the drug remains floating on the surface of the medium is the duration of the floating time (A. Badoni et al., 2012).

D). In vivo evaluation of gastric retention
Analysis of the position of the dosage form in the GIT involves an imaging technique such as γ-scintigraphy and X-ray.

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 (Meenakshi Jassal et al., 2015).

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 fibereoptic and video systems. Ultrasonograpohy 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.
E). Water uptake study
It is done by immersing the dosage form in simulated gastric fluid at 37°C 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.

\[ W_U = \frac{(W_t - W_0) \times 100}{W_0}; \]

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.

5. CONCLUSION
Gastro retentive drug delivery technologies have been extensively explored in recent years. Gastro retentive drug delivery systems are the most preferable systems in order to deliver the drugs which have a narrow absorption window near the gastric region. Now a day’s numbers of drug delivery devices are being developed which aim at releasing the drug at gastric region. Even though these drug delivery systems have several advantages, they also have disadvantages like their in-vitro in-vivo correlation is very less. It is necessary to take into consideration the physiological event in the GIT, selection of correct combinations of drugs and excipients and design appropriate formulation strategies.

6. REFERENCES


