



Review on Gastro Retentive Drug Delivery System (GRDDS)

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ABSTRACT

In the recent years, various technological and scientific researchers have been committed to the development of rate-controlled oral drug delivery systems to overcome physiological problems, various dosage forms came in existence. Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Dosage form with prolonged GRT i.e. Gastro Retentive Dosage Forms (GRDFs) will offer new and important therapeutic options. Gastro retentive dosage forms through local drug release will greatly improve the pharmacotherapy of the stomach leading to high drug concentrations at the gastric mucosa. In conventional sustained release dosage forms they pass the absorption window although they still contain a large fraction of the drug which is consequently lost and not available for absorption. Various factors influence on drug retention such as density, Size, Shape, Fed or Unfed State, Single or multiple unit formulation, Caloric Content, Frequency of feed, Gender, Age, Posture, Concomitant drug administration, Diseased state of the individual etc. Current Approaches to GRDDS are floating drug delivery systems, Swelling system, Bioadhesive system, High density system.

Keywords: Floating drug delivery systems (FDDS), Gastro Retentive Dosage Forms (GRDFs), Gastro Retentive Drug Delivery system (GRDDS), Gastric residence time (GRT), Gastrointestinal tract (GIT), Hydro dynamically balanced systems (HBS).

INTRODUCTION

In the recent years, a great deal of technological and scientific research has been committed to the development of rate-controlled oral drug delivery systems to overcome physiological problems, such as short gastric residence time (GRT) and unpredictable gastric emptying times (GET), in order to be able to prepare gastro-retentive dosage forms, which will allow the delivery of restricted 'absorption window' drugs which are absorbed in a particular portion of the GI tract. Several approaches are currently being used to prolong the GRT, including floating drug delivery systems (FDDS), also known as hydro dynamically balanced systems (HBS), swelling and expanding systems, high-density systems, and other delayed gastric emptying devices.¹

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic effects, such as simplicity of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug possibly will be

supplied continuously to its absorption sites in the gastrointestinal tract (GIT).²

The problem frequently encountered with sustained release dosage forms is the failure to increase the residence time of the dosage form in the stomach and proximal portion of the small intestine. Therefore it would be beneficial to develop sustained release formulations which remain at the absorption site for an extensive period of time. One of the possible approaches for achieving delayed and expected drug delivery profile in GIT is to control Gastric Retention time (GRT) of the formulation. Dosage form with prolonged GRT i.e. Gastro Retentive Dosage Forms (GRDFs) will offer new and important therapeutic options.³

GASTRO RETENTIVE DRUG DELIVERY SYSTEMS

The relatively short gastric emptying time in humans, which normally averages 2-3 hrs through the major absorption zone (stomach or upper part of the intestine), can result in incomplete drug release from the drug delivery system leading to diminished efficiency of the administered dose. Thus, localization of a drug delivery system in an exact region of the GIT offers numerous advantages, especially for drugs having narrow absorption window. The intimate contact of the dosage form with the absorbing membrane has the potential to maximize drug absorption and may also influence the rate of drug absorption. These considerations have lead to the development of oral sustained release dosage forms possessing gastric retention potential. The primary concern in the development of once daily oral sustained release dosage form is not just to prolong the delivery of drugs for 24hrs but also to prolong the presence of



dosage forms in the stomach or somewhere in the upper small intestine. Gastro retentive dosage forms through local drug release will greatly improve the pharmacotherapy of the stomach leading to high drug concentrations at the gastric mucosa, which are sustained over a long period of time. This is mainly useful for suppression of *Helicobacter pylori*, which requires the administration of various drugs. Conventional sustained release dosage forms pass the absorption window although they still contain a large fraction of the drug which is consequently lost and not available for absorption. In contrast, an appropriate gastro retentive dosage form would slowly release Gastro retentive dosage forms through local drug release will greatly enhance the pharmacotherapy the complete dose over its defined GRT and thus make it continuously available at the site of absorption.^{4,5}

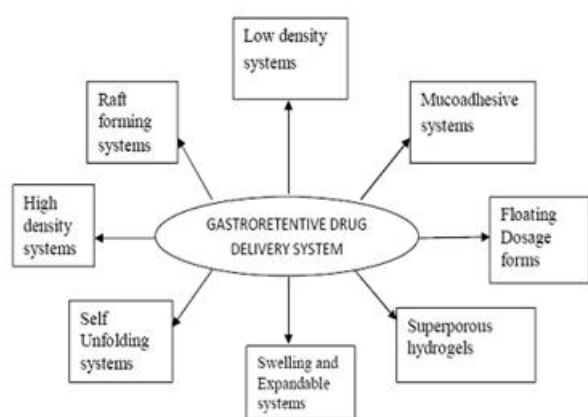


Figure 1: Approaches for GDDS

Advantages of Gastro retentive Drug Delivery System⁶

1. Improves patient compliance by decreasing dosing frequency.
2. Bioavailability enhances first pass effect because fluctuations in plasma drug concentration are avoided; a desirable plasma drug concentration is maintained by continuous drug release.
3. Gastric retention time is increased because of buoyancy.
4. Enhanced absorption of drugs which solubilize only in stomach.
5. Drug releases in controlled manner for prolonged period.
6. Site-specific drug delivery to stomach can be achieved.
7. Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
8. Avoidance of gastric irritation, because of sustained release effect.

9. Better therapeutic effect of short half-life drugs can be achieved.

Limitations of the Techniques of Gastroretention⁷

More conventional and reproducible floating properties should be achieved in all the extreme gastric conditions.

1. The floating systems in patients with achlorhydria can be questionable in case of swellable systems, faster swelling properties are required and complete swelling of the system should be achieved well before the gastric emptying time.
2. Bioadhesion in the acidic environment and high turnover of mucus may raise questions about the effectiveness of this technique.
3. Not suitable for drugs that may cause gastric lesions e.g. Non-steroidal anti-inflammatory drugs. Drugs that are unstable in the strong acidic environment, these systems do not offer significant advantages over the conventional dosage forms for drugs that are absorbed throughout the gastrointestinal tract.
4. The mucus on the walls of the stomach is in a state of constant renewal, resulting in erratic adherence.
5. In all the above systems the physical integrity of the system is very important and primary requirement for the success of these systems.

Basic Gastro-Intestinal Tract Physiology

The GI tract is essentially a tube about nine meters long that runs through the middle of the body from the mouth to the anus. The wall of the GI tract has the same general structure throughout most of its length, with some local variations for each region. The stomach is an organ with a capacity for storage and mixing. Anatomically the stomach is divided into 3 regions: fundus, body, and pylorus. Under fasting conditions, the stomach is a collapsed bag with a residual volume of approximately 50 ml and contains a small amount of gastric fluid and air. Gastric emptying occurs during fasting as well as fed states. The GI tract is in a state of continuous motility consisting of two modes: inter-digestive motility pattern and digestive motility pattern. The former is dominant in the fasted state with a primary function of cleaning up the residual content of the upper GI tract, which cycle both through stomach and intestine every 2 to 3 hours. This is called inter digestive myoelectric cycle or migrating myoelectric cycle (MMC) and is organized in cycles of activity and quiescence. Each cycle lasts 90–120 minutes and consists of four phases. The concentration of the hormone motilin in the blood controls the duration of the phases.⁸

The various phases are as below⁸

Phase I (basal phase)-Period of no contraction (40-60 minutes),

Phase II (preburst phase)-Period of intermittent contractions (20-40 minutes),

Phase III (burst phase)-Period of regular contractions at the maximal frequency that travel distally also known as housekeeper wave; includes intense and regular contractions for short period. It is due to this wave that all the un-digested material is swept out of the stomach down to the small intestine (10-20 minutes),

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

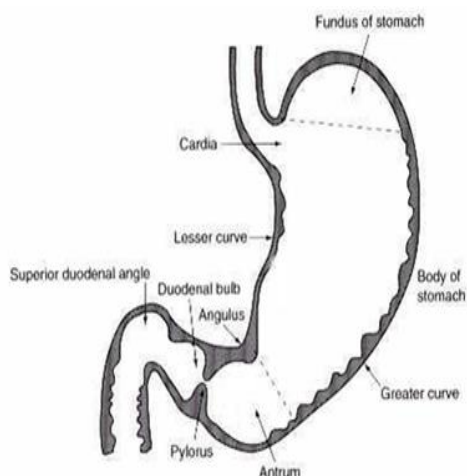


Figure 2: Anatomy of stomach

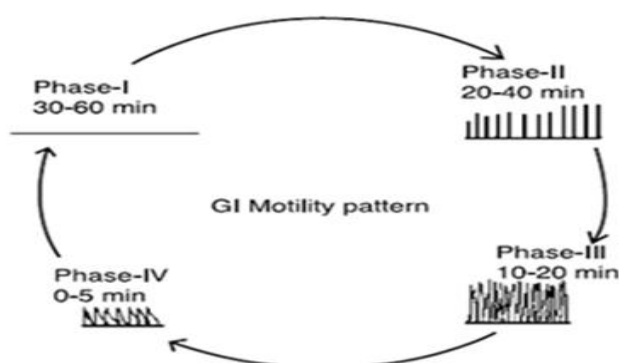


Figure 3: A simplified schematic representation of the inter digestive motility pattern, frequency of contraction forces during each phase, and average time Period for each period.

Factors affecting gastric retention⁹

Density

Density of the dosage form should be less than the gastric contents (1.004gm/ml).

Size

Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.

Shape

The dosage form with a shape tetrahedron and ring shape devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better

GRT, 90 to 100% retention at 24 hours compared with other shapes.

Fed or Unfed State

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (MMC) that occurs every 1.5 to 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, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

Single or multiple unit formulation

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

Nature of the meal

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

Caloric Content

GRT can be increased between 4 to 10 hours with a meal that is high in proteins and fats.

Frequency of feed

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

Gender

Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down.

Age

Elderly people, especially those over 70 years have a significantly longer GRT.

Posture

GRT can vary between supine and upright ambulatory states of the patients.

Diseased state of the individual

Biological factors also affect the gastric retention e.g. Crohn's disease, gastrointestinal diseases and diabetes.

Concomitant drug administration

Anti-cholinergics like atropine and propentheline opiates like codeine and prokinetic agents like metoclopramide and cisapride.

CURRENT APPROACHES TO GRDDS**Floating drug delivery systems (FDDS)¹⁰**

Floating systems was first described by Davis in 1968. FDDS is an effective technology to prolong the gastric residence time in order to increase the bioavailability of the drug. FDDS are low-density systems that have enough buoyancy to float over the gastric contents and remain in the stomach for a prolonged period.

Floating systems can be classified as

- i) Effervescent and
- ii) Non effervescent systems

i) Effervescent systems¹⁰

These buoyant delivery systems utilize matrices prepared with swellable polymers such as Methocel or polysaccharides, e.g., chitosan, and effervescent components, e.g., sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature. Flotation of a drug delivery system in the stomach can be achieved by incorporating a floating chamber filled with vacuum, air, or an inert gas. Gas can be introduced or by the CO₂ produced as a result of an effervescent reaction between organic acids and carbonate–bicarbonate salts. So that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the jellified hydrocolloid. This produces an upward motion of the dosage form and maintains its optimism.

Recently a multiple-unit type of floating pill, which generates carbon dioxide gas, has been developed. The system consisted of sustained- release pills as seeds surrounded by double layers. The inner layer was made up of effervescent layer containing both sodium bicarbonate and tartaric acid. The outer layer was made up of swellable membrane layer containing mainly polyvinyl acetate and purified shellac. The effervescent layer was divided into two sub layers to avoid direct contact between sodium bicarbonate and tartaric acid. Sodium bicarbonate was contained in the inner sub layer and tartaric acid was in the outer layer. When the system was immersed in a buffer solution at 37°C, it sank at once in the solution and formed swollen pills, like balloons, with a density much lower than 1 g/ ml. The reaction was due to carbon dioxide generated by neutralization in the inner effervescent layers with the diffusion of water through the outer swellable membrane layers. The system was found to float completely within 10 min and approximately 80% remained floating over a period of 5 hr irrespective of pH and viscosity of the test medium. While the system was floating, a drug was released. A variation of this approach utilizing citric acid and sodium bicarbonate as effervescing agents and HPC-H grade as a release controlling agent has also been reported.

ii) Non effervescent systems¹¹

Non effervescent systems incorporate a high level (20–75% w/w) of one or more gel-forming, highly swellable, cellulosic hydrocolloids (e.g., Hydroxy ethyl cellulose, Hydroxy Propyl cellulose, Hydroxy Propyl methylcellulose [HPMC], and sodium carboxy methyl cellulose), polysaccharides, or matrix-forming polymers (e.g., polycarbophil, polyacrylates, and polystyrene) into tablet or capsules. When comes in 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 nearby hydrocolloid layer. The air trapped by the swollen polymer lowers the density of and confers optimism to the dosage form.

Bio/Mucoadhesive systems¹²

Bio/mucoadhesive systems bind to the gastric epithelial cell surface, or mucin, and increase the GRT by increasing the connection and duration of contact between the dosage form and the biological membrane. The concept is based on the self-protecting mechanism of the GIT. Mucus secreted continuously by the specialized goblet cells located throughout the GIT plays a cytoprotective role. Mucus is a viscoelastic, gel-like, stringy slime comprised mainly of glycoproteins. The primary function of mucus is to protect the surface mucosal cells from acid and peptidases. In addition, it serves as a lubricant for the passage of solids and as a barrier to antigens, bacteria, and viruses. The epithelial adhesive properties of mucin are well known and have been applied to the development of GRDDS through the use of bio/mucoadhesive polymers. The adherence of the delivery system to the gastric wall increases residence time at a particular site, thereby improving bioavailability. The characteristics of these polymers are molecular flexibility, hydrophilic functional groups, and specific molecular weight, chain length, and conformation. They must be nontoxic and non absorbable, form non covalent bonds with the mucin–epithelial surfaces, have quick adherence to moist surfaces, easily include the drug and offer no obstruction to drug release, have a specific site of attachment, and be economical. The binding of polymers to the mucin-epithelial surface can be subdivided into three broad categories.

- A. Hydration-mediated adhesion
- B. Bonding-mediated adhesion
- C. Receptor-mediated adhesion

A. Hydration-mediated adhesion

Certain hydrophilic polymers tend to swallow large amount of water and become sticky, thereby acquiring bioadhesive properties.



B. Bonding-mediated adhesion

The adhesion of polymers to a mucus or epithelial cell surface involves various bonding mechanisms, including physical-mechanical bonding and chemical bonding. Physical-mechanical bonds can result from the insertion of the adhesive material into the crevices or folds of the mucosa.

Chemical bonds may be either covalent (primary) or ionic (secondary) in nature. Secondary chemical bonds consist of dispersive interactions and stronger specific interactions such as hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl and carboxylic groups.

C. Receptor-mediated adhesion

Certain polymers can bind to specific receptor sites on the surface of cells, thereby enhancing the gastric retention of dosage forms. Certain plant lectins such as tomato lectins interact specifically with the sugar groups present in mucus or on the glycocalyx.

Swelling/ Expanding Systems¹³

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 stuck 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. As dosage form 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 cross-links in the hydrophilic polymer network. These cross-links 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 essential 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.

High-density systems¹⁴

Gastric contents have a density close to water (1.004 g/cm³). When high density pellets is given to the patient, it will sink to the bottom of the stomach and are entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall 40, 41. Sedimentation has been employed as a retention mechanism for high density systems. A density ~3 g/cm³ seems necessary for significant prolongation of gastric residence time. Barium sulphate, zinc oxide, iron powder, titanium dioxide may be used to formulate such high density systems due to their high density. The only major drawbacks with this 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.

Magnetic systems¹⁵

This system is based on a simple idea that the dosage form contains a small internal magnet and a magnet placed on the abdomen over the position of the stomach. They guided them to the esophagus with an external magnet (1700 G) for the initial 2 min and almost all the granules were retained in the region after 2 h. Although these systems seem to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance.

CONCLUSION

Gastro retentive Drug Delivery system have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. It provides several advantages including greater flexibility and adaptability gives clinicians and those engaged in product development powerful new tools to optimize therapy. The increasing sophistication of delivery technology will ensure the development of increasing number of gastro retentive drug delivery systems to optimize the delivery of molecules that exhibit narrow absorption window, low bioavailability and extensive first pass metabolism. The control of gastro intestinal transit could be the focus of the next decade and may result in new therapeutic possibilities with substantial benefits for patient.

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