Gastroretentive Drug Delivery System

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Abstract

Gastroretentive dosage form (GRDF) has played an important role in the past few periods in improving the limitation of most predictable and oral controlled release drug delivery system related to fast gastric-emptying time. GRDF system can be defined as a system which remains in the stomach for an adequate time interval against all the physiological barriers, and releases active moiety in a well-ordered manner. This paper gives an overview of the parameters affecting gastric emptying as well as on the main thoughts used to design pharmaceutical dosage forms with prolonged gastric residence times. In particular, bioadhesive, size-increasing, and floating drug delivery systems are presented, and their major advantages and limitations are discussed. Both single and multiple-unit dosage forms with dual working arrangements are reviewed. Dual-working classifications are more efficient than the traditional systems.

Introduction

From the past many years, oral drug administration has been the main route for drug delivery. During the past two decades, many oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a prearranged and controlled rate. However, this route has some physiological problems, including an unpredictable gastric emptying rate that varies from person to person, a brief gastrointestinal transit time (8–12 h), and the presence of an absorption window in the upper small intestine for several drugs. To express a specific site orally administered controlled release dosage form, it is desirable to succeed a prolonged gastric residence time by the drug delivery. Prolonged gastric retention develops bioavailability, increases the duration of drug release, reduces drug unwanted, and improves the drug solubility that are less soluble in a high pH environment. Drugs that are simply absorbed from the gastrointestinal tract (GIT) and have short half-lives are removed fast from the systemic circulation. Frequent dosage of these drugs is mandatory to achieve suitable therapeutic activity. Also, the drugs which have a narrow absorption window (NAW) in the upper part of GIT are not proper for oral sustained release drug delivery system due to the brief gastric emptying time as tablets have 2.7±1.5 hours (h) stomach transit and 3.1±0.4 h intestinal transit time. Thus the bioavailability of such drugs having absorption window in stomach is generally restricted. Gastroretentive drug delivery is one of those methods to prolong gastric residence time, thereby targeting site-specific drug release in the stomach for local or systemic effects. These dosage forms can endure in the gastric region for long periods and hence significantly prolong the gastric preservation time of the drugs. It will release the drug in stomach in a well-ordered manner, so that the drug could be provided continuously to absorption site in GIT, i.e. stomach. Gastroretentive drug delivery is prepared with the purpose to retain drug in the gastric region for prolonged time and release incorporated drug candidates and thereby allow sustained and prolonged input of the drug to the upper part of the GIT, thus leading to its optimum bioavailability. Gastroretentive drug delivery got popularity from last two periods leading to its potential application to recover oral delivery of some important drugs, for which prolonged gastroretention can importantly

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improve their oral bioavailability. GRDDs not only prolong the dosing breaks, but also increase the patient compliance beyond the equal of existing controlled release dosage form.\(^5\)

**Physiology of the Stomach**

Physically, the stomach is divided into three regions: fundus, body and antrum (pylorus). The proximal part made one novel approach in this part is GRDDS (gastro retentive drug delivery system). Dosage forms that can be engaged in the stomach are called GRDDs. GRDDs can develop the controlled delivery of drugs that can be engaged in the stomach and which have an absorption window by continuously releasing the drug for a prolonged period before it reaches its absorption site.

Prolonging the gastric retention of the drugs is sometimes desired for succeeding therapeutic benefits of drugs that are absorbed from the proximal part of the GIT (gastro intestinal tract) or those are less soluble in or are degraded by alkaline pH or they happenstance at the lower part of the GIT. GRDDs are useful for such drugs by educating their:

- Bioavailability
- Therapeutics efficiency and possible reduction of the dose
- Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in the therapeutic levels
- Reduce drug wastage
- Improve solubility of drugs that are less soluble at high pH environment (e.g. weakly basic drug like domperidone, papaverine)

Of fundus and body acts as a reservoir for undigested materials, while the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions.\(^6,7\) Gastric emptying occurs in both the fasting and fed states. During the fasting state, an interdigestive chain of electrical events takes place which cycle both through stomach and intestine every 2–3 h, which is called as interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into four phases. After the ingestion of a mixed meal, the arrangement of contractions changes from fasted to that of fed state which is also termed as digestive motility configuration.\(^8,9\)

![Figure 1. Physiology of Stomach](image)

![Figure 2. Phase of Gastric Cycle](image)
Phase 1: (Basic phase) lasts from 30–60 minutes with rare contractions.
Phase 2: (Preburst phase) lasts for 20–40 minutes with intermittent action potential and contractions.
Phase 3: (Burst phase) lasts for 10–20 minutes which includes intense and regular contractions for a short period.
Phase 4: lasts for 0–5 minutes and occurs between phase 2 and 1 of two consecutive cycles.

Need for GRDDs

- Conventional oral delivery is commonly used in pharmaceutical field to treat diseases. However, conventional delivery had many problems and the major drawback is non-site specificity.
- Some drugs are absorbed at specific site. They need release at specific site or a release such that extreme amount of drug reaches the specific site.
- Pharmaceutical field is now focusing towards such drugs which require specific site.
- Gastroretentive delivery is a site-specific delivery for the delivery of drugs either at stomach or at intestine. It is obtained by retaining dosage form into stomach and the drug is released in a controlled manner to the specific site either in stomach, duodenum or intestine.\(^{11}\)

Merits

- Delivery of drugs with fine absorption window in the small intestine region.
- Longer residence time in the stomach could be advantageous for local action in the upper portion of the small intestine, for example, treatment of peptic ulcer disease.
- Better bio-availability is expected for drugs that are absorbed readily upon release in the GI tract such as cyclosporine, ciprofloxacin, amoxycillin, captopril, etc.
- Patient compliance by making once-a-day therapy.
- Therapeutic efficacy improved.
- Moderates frequency of dosing.
- Directed therapy for local ailments in the upper GI tract.
- Prolongs the residence period of the dosage form at the specific site.
- Avoids the first pass metabolism.
- Outstanding accessibility.
- Fast absorption because of enormous blood supply and good blood flow rates.
- Drug bioavailability increases due to first pass metabolism.
- Specific site for drug delivery.
- Decreasing mucosal irritation by drugs, by drug releasing slowly at a controlled rate.
- Reducing mucosal irritation by drugs, by drug releasing slowly at a controlled rate.\(^{12}\)

Demerits

- Floating systems have the limitation that they need high level of fluids in the stomach for floating and working efficiently. So more water drinking is prescribed with such dosage forms.
- In supine posture (like sleeping), floating dosage form may get cleared away (if not of larger size) by contractile waves. So patient must not take floating dosage form just before going to bed.
- Drugs having stability problem in high-acidic environment, having very small solubility in acidic environment, and drugs causing irritation to gastric mucosa cannot be incorporated into GRDDs.
- Swellable dosage form must be clever to swell fast before its exit from stomach and achieve size larger than pylorus aperture. It need be capable to resist the housekeeper waves of Phase III of MMC.
- Gastric retention is influenced by several factors such as gastric motility, \(pH\) and presence of food. These factors are never endless and hence the buoyancy cannot be predicted.
- The major trial for a bioadhesive system is the high turnover rate of gastric mucus.
- There is also probability of esophageal binding with bioadhesive drug delivery systems.
- Drugs which have stability and solubility problems in GIT are not appropriate candidates for these types of systems.\(^{12}\)

Approaches of Various Gastroretentive Drug Delivery Systems

Swelling and Expanding Systems

This method is based on the swelling properties of the polymers. As the size of the system is prolonged (due to swelling), the system is confined to the stomach, as (due to increased size) it cannot pass over the pyloric sphincters. So this method is also called as “Plug-type system”. In the system, polymers are used with a suitable molecular mass and swelling properties, which (in addition to imparting floatation) also result in controlled and sustained drug release. This system makes contact with gastric media; the polymer absorbs water and swells, developed swelling systems of Losartan tablets using sodium bicarbonate, sodium carboxy methyl cellulose (Na CMC), and hydroxyl ethyl cellulose (HEC). The improved formulation showed swelling to 2 cm in diameter within 3 h and floating time more than fabricated swelling systems of levofloxacin hemihydrates, using gel-forming polymers including: sodium alginate, gellan gum, pectin and xanthan gum. Effect of cross-linkers like aluminum and calcium chloride on the drug release was also studied.\(^{13}\)
Bioadhesive Systems

These methods usually contain a synthetic and natural polymer that are accomplished to tie on the mucus lining, gastric epithelial cell surface, and enlarge the GRT. These systems use the natural and synthetic polymers, i.e., hydrophilic gelling constituents by forming hydrogen bond with various groups, such as sulfate, hydroxyl, carboxyl and amide groups (e.g., cross-linked carrageenan, sodium alginate, Na CMC and polyacrylic acids) that can stick on the epithelial surface of the GIT, fabricated bioadhesive methods of Ofloxacin tablets using hydroxypropyl methyl cellulose (HPMC K100M), crospovidone and psyllium husk polymers. Optimized formulations showed the drug release for 24 h. Fabricated floating mucoadhesive systems of Dipyridamole tablets using HPMC K4M and carbopol 934P. The improved formulations showed 99.92% drug released at 12 h.

Floating Drug Delivery Systems

In 1968, Davis first described the FDDS. These methods are low-density systems. Due to low-density, it offers enough buoyancy to float the drug in gastric media in the stomach for a long time. The system floats in the gastric media and the drug is slowly delivered at the required rate that results in enlarged GRT along with reduced fluctuations in plasma drug concentration. It has three types, i.e., raft-forming systems, effervescent systems and non-effervescent systems. FDDS of Cefuroxime Axetil tablets using several grades of HPMC. In vivo radiographic studies of the improved formulations were also conducted in five healthy human volunteers, which showed 6 h gastroretention. Fabricated gastroretentive floating method of Ofloxacin tablets using HPMC K100M and sodium bicarbonate polymers utilizing Box Behnken designs. In vitro studies of the improved formulations showed the drug release above 12 h and excellent buoyancy properties: floating lag time less than 1 min, floating time more than 16 h. The prepared floating pellets of Theophylline by hot melt extrusion techniques using the ammonio-methacrylate (Eudragit RSPO) co-polymer. Improved formulation was showing the increased floating potency after 30 min due to matrix swelling in prepared floating bioadhesive systems of Ondansetron Hydrochloride tablets. These tablets were prepared using different concentrations of extending rate releasing polymer Na CMC and HPMC for the drug release in upper part of GIT. Optimized formulation showed well results for buoyancy and content uniformity.

Effervescent Systems

These systems are prepared with swellable polymers, for instance, polysaccharides (e.g., chitosan) or methocel and effervescent agents, e.g., citric acid or tartaric acid and sodium bicarbonate or matrices containing reservoirs of liquid which evaporate at the body temperature. The matrices are made so that upon connection with gastric fluid, carbon dioxide is released by the acidity of gastric content and entrapped in the gel hydrocolloid. This makes the upward motion and maintains the buoyancy prepared effervescent matrix tablets of water soluble drug Tapentadol Hydrochloride using xanthan gum and chitosan polymers utilizing the 32 packed factorial designs. Improved formulations showed sustained drug release pattern. X-ray studies of the improved formulations showed gastroretention for 6 h.

Non-effervescent Systems

These systems are made by using gel-forming or highly swellable cellulose-type hydrocolloids, polysaccharides and matrix-making polymers such as polystyrene, polymethacrylate, polyacrylate and polycarbonate. In the method, the dosage form swells when it comes in contact with gastric fluids and attains a bulk density of less than 1 g/mL. The air trapped within the swollen matrix imparts buoyancy to the dosage form. Developed non-effervescent
low density floating systems of Cefpodoxime Proxetil tablets by direct compression technique using Accurel® MP1000, gum dammar and HPMC K15M polymers. In vivo studies of the improved preparations in rabbit were carried out by using barium sulfate radio opaque marker.25

**Raft-Forming Systems**

These systems contain a gel-forming solution (e.g., sodium alginate solution containing bicarbonates or carbonates) which swell and form a sticky cohesive gel containing trapped CO2 bubbles in contact with gastric fluid. These methods are used in the antacid formulation because a cover produce sat the top of gastric fluids in the raft forming systems. Therefore, such systems are useful in for gastroesophageal reflux treatment. In vitro studies of the improved formulation exhibited the drug release of 98.86% in 12 h and showed the maximum raft strength.26

**High-density Systems**

This system is made by covering the drug or mixed with heavy inert material such as titanium dioxide, barium sulfate, iron and zinc oxide powder. In the system, the formulation density exceeds the common stomach content (1.004 g/mL). The resulting tablets can be coated with a suitable polymer in order to obtain desired release profile.27 In vitro studies the FDDS offers a capable drug delivery system for development of bioavailability of Diltiazem Hydrochloride.28

**Magnetic Systems**

In these systems, a slight internal magnet in the system and a magnet located on the abdomen above the position of the stomach, is employed. In this system, an extracorporeal magnet is used which enlarges the GRT of the dosage form27 investigated a magnetic system of acetaminophen tablets. These tablets were prepared by direct compression process using ultrafine ferrite, microcrystalline cellulose and hydroxypropyl cellulose-H polymers. The authors studied the result of gastric residence of acetaminophen magnetic tablets on drug bioavailability; a stable magnet (neodymium iron-boron magnet) was applied to the stomach of beagle dogs for 8 h after administration of the magnetic tablets.30

**Ion-Exchange Resins**

Ion-exchange resins are complete with bicarbonate and bound to a negative charge drug. The resulting beads are encapsulated in a semipermeable membrane to overcome the fast loss of carbon dioxide. After arriving in the stomach, an interchange of bicarbonate and chloride ion takes place. As a result of this reaction, carbon dioxide is released and is entrapped in the membrane carrying the beads towards the gastric media and producing a floating sheet of resin to distinguish the uncoated beads, which will be sunk rapidly.22 It produced an ion exchange resin system of Samarium-152 (III) chloride hexahydrate pill. It was covered with biocompatible polymer Eudragit TM L100. In vitro breakdown studies of optimized formulations showed that all the capsules remained intact in the simulated gastric fluid for 72 h and started to disintegrate in less than 15 min when in the simulated intestinal fluid.31

**Factors Controlling Gastric Retention of Dosage Forms**

**Density of Dosage Forms**

The density of a dosage form also affects the gastric emptying rate and controls the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high-density systems drop to bottom of the stomach.27 Both locations may isolate the dosage system from the pylorus. A density of <1.0 gm/cm3 is necessary to exhibit floating property.33

**Shape and Size of the Dosage Form**

Size and shape of the dosage forms are important in designing indigestible single-unit solid-dosage forms. The mean gastric residence times of non-floating dosage forms are extremely variable and greatly dependent on their size, which may be large, medium or small units. In most cases, the larger the dosage form the better will be the gastric retention time (GRT) due to the larger size of the dosage form would not permit this to quickly pass through the pyloric antrum into the intestine.34 Dosage forms having a diameter of more than 7.5 mm show an improved gastric residence time compared with one having 9.9 mm. Ring-shaped devices have a well gastric residence time as compared with other shapes.35

**Food Intake and Its Nature**

Food ingestion, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the gastrointestinal tract (GIT) effects the gastric retention time (GRT) of the dosage form. Usually the
presence of food in the gastrointestinal tract (GIT) increases the gastric retention time (GRT) of the dosage form and thus, the drug 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 time (GET), which can increase the gastric retention of dosage forms.²⁶

Effect of Gender, Posture and Age

Generally, females have slow gastric emptying rates than males. The effect of posture does not have any significant alteration in the mean gastric retention time (GRT) for individuals in vertical, ambulatory and supine state. In case of elderly people, gastric emptying is slowed down.²⁷

Conclusion

Based on the literature surveyed, it may be concluded that gastroretentive drug delivery offers several potential advantages for drug with poor bioavailability due their absorption is controlled to the upper gastrointestinal tract (GIT) and they can be delivered powerfully thereby maximizing their absorption and enhancing absolute bioavailability. Another promising area of investigation for gastroretentive drug delivery system is eradication of Helicobacter pylori, which is now understood to be causative bacterium of chronic gastritis and peptic ulcers. Although, this microorganism is highly sensitive to many antibiotics, its complete eradication needs high concentration of antibiotics to be maintained within gastric mucosa for a prolonged time period. An important feature to take into reason is the stomach physiology. The time when the drug is taken (during or apart from the meal) is the main parameter. All these gastroretentive drug delivery systems (high-density, floating, expandable or unfoldable or enlargement, superporous, bioadhesive, magnetic systems, etc.) are interesting and existing their advantages and disadvantages. In the future, it is predictable that they will become of increasing importance, ultimately leading to improved efficiencies of several types of pharmacotherapies.

Conflict of Interest: None

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