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An Overview on Gastro-Retentive Drug Delivery System

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ABSTRACT

Gastro retentive drug delivery systems are an approach to prolong gastric residence time, there by targeting site-specific drug release in the upper GIT for local or systemic effect. Gastro retentive dosage forms (GRDFs) are being used from a very long time to improve therapy with several important drugs. Gastro-retentive drug delivery system (GRDDS) has gained immense popularity in the field of oral drug delivery. Oral formulations have earned a significant place among the various dosage forms developed so far for human administration. This review include information about GRDDS, its advantages, disadvantages, approaches for GRDDS, and its application.

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INTRODUCTION

GRDDS are convenient for drugs that have low absorption in the lower part of the GIT, are unstable and poorly soluble at alkaline pH, have a short half-life, and show local activity at the upper part of the intestine for eradication of Helicobacter pylori. Gastro retentive drug delivery system has gained immense popularity in the field of oral drug delivery recently. It is widely employed approach to retain dosage form in the stomach for extended period of time and release the drug slowly that can address many challenges associated with conventional oral delivery including poor bioavailability. Different innovative approaches like magnetic field assisted gastro retention, lock type swelling system, muco-adhesion technique, floating system with or without effervescence are being applied to fabricate GRDDS.

Various formulation-related factors such as polymer types (nonionic, cationic, and anionic polymers), polymer composition in dosage form, viscosity grade, molecular weight of the polymer, and drug solubility can affect the quality of the gastro retentive dosage form.

ANATOMY AND PHYSIOLOGY OF STOMACH

The stomach is a hollow organ that is part of the gastrointestinal system, and it is responsible for functions including the formation of chyme, synthesis of proteins necessary for vitamin absorption, microbial defenses, and propagates the peristaltic reflex. The main role of the stomach is to store the food temporarily, grind it, and then slowly release it into the duodenum. There are four main regions in the stomach: the cardia, fundus, body, and pylorus. The cardia (or cardiac region) is the point where the esophagus connects to the stomach and through which food passes into the stomach. Located inferior to the diaphragm, above and to the left of the cardia, is the dome-shaped fundus. Below the fundus is the body, the main part of the stomach. The funnel-shaped pylorus connects the stomach to the duodenum. The wider end of the funnel, the pyloric antrum, connects to the body of the stomach. The narrower end is called the pyloric canal, which connects to the duodenum. The smooth muscle pyloric sphincter is located at this latter point of connection and controls stomach emptying. In the absence of food, the stomach deflates inward, and its mucosa and submucosa fall into large folds called rugae. In the GRDDS, the stomach has a crucial role; therefore, a good understanding of the anatomy and physiology of the stomach is a prerequisite for successful development of the gastro-retentive dosage form.

FACTORS AFFECTING GRDDS

The stomach anatomy and physiology contain parameters to be considered in the development of gastro retentive dosage forms.

1. First density of dosage form: The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Density of dosage form should be in range of $1g/cm^3$ to $2.5g/cm^3$.

2. Size: Dosage form units 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.

3. Shape of dosage form: Tetrahedron and ring-shaped devices are reported to have better GRT and ~ 90% to 100% retention at 24 hours compared with other shapes.

4. Single or multiple unit formulation: Multiple unit formulations show a more predictable release profile, co-admiration of different units, larger safety margin.

5. Fed or unfed state: In the fed state, MMC is delayed and GRT is considerably longer.

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

7. Caloric content and Frequency of feed: GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats. The GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC.

8. Gender: Gender mean ambulatory GRT in male (3.4hrs) is less compared with the age and race matched female counterparts (4.6hrs) regardless of height, weight and body surface.

9. Age: People with age more than 70 have a significant longer GRT.

CLASSIFICATION OF GRDDS

They may be broadly classified into:

1. High density systems;
2. Floating systems;
3. Expandable systems;

4. Super porous hydrogels;
5. Mucoadhesive or bioadhesive systems;
6. Magnetic systems; and
7. Dual working systems.

1. High density system

These systems, which have a density of ~ 3 g/cm^3, 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/cm^3, such systems can be retained in the lower part of the stomach. Results of a clinical study showed that an enteric-coated sinking ursodeoxycholic acid (UDCA) tablet formulation gives better bioavailability in comparison to enteric-coated floating tablets and hard gelatin capsule formulations of UDCA in 12 healthy subjects. The area under the curve [AUC, μmol/1 (8 h)] following oral administration of enteric-coated, sinking UDCA (39.0 ± 8.5) was significantly higher than that obtained after both conventional UDCA (30.5 ± 4.9) and floating enteric-coated UDCA (29.3 ± 3.4).

2. Low-Density Systems/Floating system

Low-density/floating systems are the most practical and extensively studied gastroretentive dosage forms. The floating system was first introduced by Davis in 1968. In this system, the bulk density of the dosage form is lower than that of the gastric fluid (1.004 g/cm^3). This property allows the system to remain buoyant in the stomach for a prolonged period of time while the drug is released at the desired rate from the system during the GRT. Floating drug delivery system can be divided into (i) Non-effervescent and (ii) Gas-generating system.

i) Non-effervescent systems

This type of system, after swallowing, swells unrestrained via imbibition of gastric fluid to an extent that it prevents their exit from the stomach. One of the formulation methods of such dosage forms involves the mixing of the drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

ii) Gas-generating (effervescent) systems

These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). The system is so prepared that upon arrival in the stomach; carbon dioxide is released, causing the formulation to float in the stomach.

3. Expandable Systems

Expandable drug delivery systems are designed to have a longer GRT through an increase in their volume or shape. Initially, they were used for veterinary purposes and, subsequently, their applications were extended to humans. Expansion mechanism of this system is swelling to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as "plug type system", since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18mm in their expanded state.

4. Superporous hydrogel

A superporous hydrogel (SPH) is a 3-dimensional network of hydrophilic polymers that are not soluble and accommodate a large amount of water in a very short period of time due to the presence of interconnected microscopic pores. The hydrogel which having pore size of hundreds of micrometers is called as superporous hydrogel and it differs from other types of porous hydrogel such as macroporous and mesoporous. However, these systems can be highly sensitive to pH, and swelling can be reversible due to changes in pH and poor mechanical strength of the structure.

5. Bioadhsive or mucoadhesive system

Bio adhesive or mucoadhesive formulations were originally developed for increasing GRT and controlling drug delivery of all kinds of drugs. The technique involves coating of microcapsules with bio adhesive polymer, which enables them to adhere to intestinal mucosa and remain for longer time period in the GI while the active drug is released from the device matrix. The cationic chitosan polymers are pharmaceutically acceptable to be used in the preparation of bio adhesive formulations owing to their known ability to bind well to gastric mucosa.

6. Magnetic system

In magnetic systems, a dosage form consists of active pharmaceutical ingredient, excipients and also a small amount of internal magnet. An extracorporeal magnet is placed over the stomach to control the position of the dosage form containing internal magnet.

7. Dual working system

These systems are based on the two working principles of either floating and bioadhesion or swelling and bioadhesion. FDDS are formulated to persist floating on the gastric fluid when the stomach is full after a meal. However, as the stomach empties and the tablet reaches the pylorus, the buoyancy of the dosage form may be reduced. It may be that the dosage form will then pass through the pylorus into the small intestine. Thus, the buoyancy of an FDDS in the stomach may be limited to only 3–4 h. Furthermore, floating systems do not always release the drug at the intended site. In a bioadhesive drug delivery system, it is quite likely that the system becomes dislodged from the stomach mucosa wall when the system is full and the semi-liquid contents are churning around due to the effect of peristalsis.

MERITS OF GRDDS:

- Delivery of drugs with narrow absorption window in the small intestine region.
- 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.
- Improved bio-availability is expected for drugs that are absorbed readily upon release in the GI tract such as cyclosporine, ciprofloxacin, ranitidine, amoxycillin, captopril, etc.
- Patient compliance by making a once a day therapy.
- Improved therapeutic efficacy.
- Reduces frequency of dosing.
- Targeted therapy for local ailments in the upper GI tract.
- The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT by this gastroretentive drug delivery approach in comparison to the administration of non gastroretentive drug delivery.

- Gastro retentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for drug with a narrow therapeutic index.

DEMERITS OF GRDDS

- Unsuitable for drugs with limited acid solubilty e.g.: phenytoin
- Drugs undergo significant first pass metabolism. e.g.: Nifedipine
- These systems also require the presence of food to delay their gastric emptying.
- May lead to alter systemic bioavailability

APPLICATION OF FLOATING DRUG DELIVERY SYSTEM

1. Enhanced Bioavailability:

The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.

2. Sustained delivery of drugs:

Oral CR formulations experienced problems in the GIT like gastric residence time. HBS systems that can stay in the stomach for prolonged period of time and having a bulk density of less than 1 and can float on the gastric contents can usually overcome these problems.

3. Site specific drug delivery systems:

The controlled, gradual drug delivery to the stomach provides appropriate local therapeutic rates and reduces the system exposure of the drug. The dosing frequency can be decreased by extended gastric availability from a site driven drug delivery system. E.g. Furosemide and Riboflavin.

4. Reduced fluctuations of drug concentration:

Continuous input of the drug following GRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms.

CONCLUSION

Gastro-retentive drug delivery system has gained immense popularity in the field of oral drug delivery recently. Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. GRDDS promises to be a potential approach for gastric retention. GRDDS can be used as carriers for drugs which are absorbed from absorption windows in stomach. To design a successful GRDDS, it is necessary to take into consideration the physicochemical properties of the drug, physiological events in the GIT, formulation strategies, and correct combination of drug and excipients.

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