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GASTRO RETENTIVE DRUG DELIVERY SYSTEMS – A REVIEW

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Abstract: In recent years several advancement has been made in research and development of oral drug delivery system. Gastro retentive drug delivery system is a topic of current interest in the design of controlled/sustained drug delivery systems. Oral route is most preferable route of administration, patient compliance and flexibility in the formulations but it has certain drawbacks of non-site specificity for those drugs which absorb from specific region of gastrointestinal tract. To overcome these limitations, gastric retentive drug delivery system is used. The bioavailability of drugs can be improved by increase their retention time in the stomach and several approaches are used to increase the gastric retention time of the dosage form are described. The success of controlled oral drug deliveries In order to understand various physiological difficulties like short gastric residence time and unpredictable gastric emptying time, we have summarized important factors controlling gastric retention time. Prolonged gastric residence increases duration of drug release, reduces drug waste, and improves drug solubility in gastric pH. We have reviewed various gastro retentive approaches designed and developed until now i.e. floating drug dosage systems (FDDS), swelling or expanding systems, mucoadhesive systems, high density system, Raft forming system, magnetic systems, super porous hydrogel system. Among these systems, FDDS have been most commonly used. Finally, Evaluation, advantages, disadvantages, future potential and marketed preparation of gastro retentive drug delivery systems were discuss.

Keywords: Gastro retentive drug delivery systems, factor affecting, different approaches, future prospects of GRDDS.

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INTRODUCTION

Historically, 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 predetermined and controlled rate.

Several approaches have been proposed to retain the dosage forms in the stomach. These methods include bioadhesive systems, swelling systems, expanding systems and floating systems. An oral sustained dosage form is particularly useful if the drug is absorbed throughout the GIT as the dosage form passes forward releasing drug in GIT. One of the major limiting factor in applicability of oral sustained drug delivery is the short tra nsit time which makes the drug to remain at the absorption site for too short time to get absorbed completely from the desired site and there is no or little control over release of drug and thus effective concentration has to be achieved by multiple dosing. These problems can be overcome by development of Gastroretentive drug delivery system (GRDDS)[1]. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH[2].

1.1. Need for Gastroretentive Drug Delivery Systems

Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous and controlled manner. Drugs delivered in this manner have a lower level of side effects and provide their therapeutic effects without the need for repeated dosages or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, which is where absorption occurs and contact time is limited. Under normal or average conditions, for example, material passes through the small intestine in as little as 1-3 hrs[1,3].

1.2. Ideal Drug Characteristics for GRDDS[4,5]

➢ Drugs acting locally in the stomach, e.g., Antacids and drugs for *Helicobacter pylori*, viz., Misoprostol, etc.

➢ Drugs that are primarily absorbed in the stomach and upper part of GIT, e.g., Amoxicillin, Calcium Supplements, Chlordiazepoxide and Cinnarazine, etc.

➢ 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, Furosemide, Levodopa etc.

➢ Drugs which are absorbed rapidly from the GI tract, e.g., Metronidazole, tetracycline etc.

➢ Drugs that degrade or unstable in the colon, e.g., Captopril, Ranitidine HCl, Metronidazole, Metformin HCl etc.

➢ Drugs that disturb normal colonic microbes, e.g., Amoxicillin Trihydrate, antibiotics against *Helicobacter pylori*.

1.2.3. Unsuitable Drugs for GRDDS[4,6]

➢ Drugs that have very limited acid solubility, e.g., Phenytoin etc.

➢ Drugs that suffer instability in the gastric environment, e.g., Erythromycin etc.

➢ Drugs intended for selective release in the colon, e.g., 5- amino salicylic acid and corticosteroids etc.

➢ Drugs which cause gastric irritation, e.g., several NSAIDs.

2. Factors Affecting Gastric Retention Time of the Dosage Form:

1. **Density:** GRT is a function of dosage form buoyancy that is dependent on thedensity. The density of a dosage form also affects the gastric emptying rate anddetermines the location of the system in the stomach. Dosage forms having adensity lower than the gastric contents can float to the surface, while high densitysystems sink to bottom of the stomach. Both positions may isolate the dosagesystem from the pylorus. A density of < 1.0 gm/ cm3 is required to exhibit floatingproperty.

2. **Size & Shape of dosage form:** These are importantin designing indigestible single unit solid dosage forms. The mean gastric residencetimes of non floating dosage forms are highly variable and greatly dependent ontheir size, which may be large, medium and small units. In most cases, the largerthe dosage form the greater will be the gastric.

3. **Single or multiple unit formulation:** Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failureof units allow co-administration of units with different release profiles or containingincompatible substances and permit a larger margin of safety against dosage formfailure compared with single unit dosage forms.

4. **Fed or unfed state: under fasting conditions:** GI motility is characterized byperiods of strong motor activity or the migrating myoelectric complex (MMC) thatoccurs every 1.5 to 2 hours. The MMC sweeps undigested material from thestomach and, if the timing of administration of the formulation coincides with that ofthe MMC, the GRT of the unit can be expected to be very short. However, in thefed state, MMC is delayed and GRT is considerably longer.

5. **Nature of meal:** Feeding of indigestible polymers or fatty acid salts can changethe motility pattern of the stomach, thus decreasing the gastricemptying rate and prolonging drug release.

6. **Caloric content:** GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats.

7. **Frequency of feed:** 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:** Male- 3.4±0.6hr to Female-4.6±1.2hr.

9. **Age:** Elderly people, especially those over 70, have a significantly longer GRT.

10. **Posture:** GRT can vary between supine and upright ambulatory states of the patient.

11. **Concomitant drug administration:** Anticholinergic like atropine, propentheline- increase GRT. Metoclopramide and cisapride- decrease GRT.

12. **Disease state:** Gastric ulcer, diabetes, hypothyroidism increase GRT. Hyperthyroidism, duodenal ulcers decrease GRT[1,7,8].

3. Gastrointestinal Tract:

Anatomy and Physiology of the gastrointestinal tract[9]

The gastrointestinal tract can be divided into three main regions namely:

1. Stomach

2. Small intestine- Duodenum, Jejunum and Ileum

3. Large intestine

The GIT is a continuous muscular tube, extending from the mouth to the anus, which functions to take in nutrients and eliminate waste by such physiological processes as secretion, motility, digestion, absorption and excretion. The main organization of stomach and different sites for gastro retentive drug delivery systems are shown in the **Figure 1.** The stomach is a J-shaped enlargement of the GIT which can be divided into four anatomical regions: cardiac, fundus,

body and antrum. The main function of the stomach is to store and mix food with gastric secretions before emptying its load (chyme) through the pyloric sphincter and into the small intestine at a controlled rate suitable for digestion and absorption.

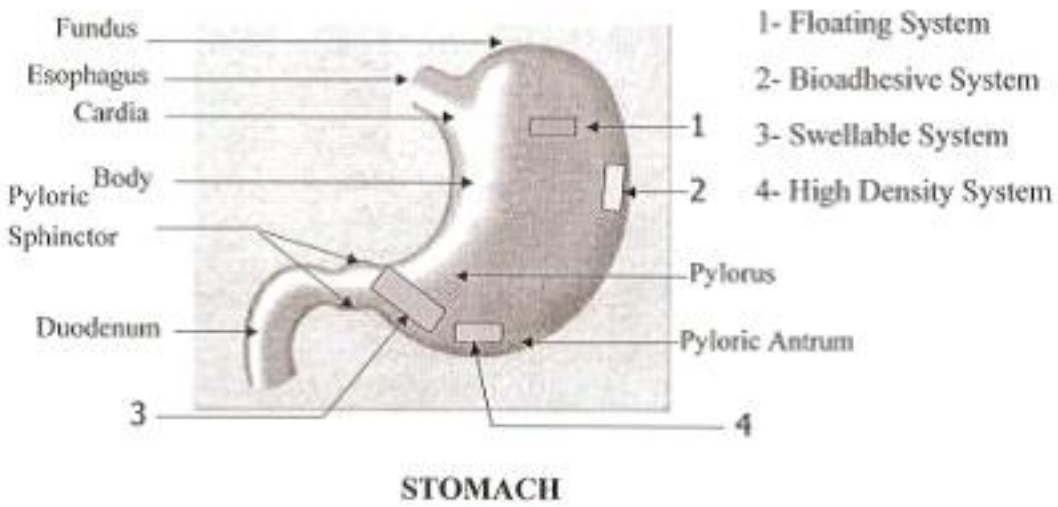

Figure 1: Structure of stomach and different sites for gastro retentive drug delivery systems.

When empty, the stomach occupies a volume of about 50 ml, but this may increase to as much as 1 liter when full. The walls of the GIT, from stomach to large intestine, have the same basic arrangement of tissues, the different layers, from outside to inside, comprising serosa, longitudinal muscle, intramuscular plane, circular muscle, sub mucosa, muscularis mucosa, lamina propria and epithelium. In addition to longitudinal and circular muscle, the stomach has a third muscle layer known as the "oblique muscle layer", which is situated in the proximal stomach, branching over the fundus and higher regions of the gastric body. The different smooth muscle layers are responsible for performing the motor functions of the GIT, i.e., gastric emptying and intestinal transit.

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an inter-digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hrs[10,11,12].

This is called the inter-digestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases[7,8,13,14, 15].

Phase I: It is a quiescent period lasting from 30 to 60 minutes with no contractions.

Phase II: It consists of intermittent contractions that gradually increase in intensity as the phase progresses, and it lasts about 20 to 40 minutes. Gastric discharge of fluid and very small particles begins later in this phase.

Phase III: This is a short period of intense distal and proximal gastric contractions (4–5 contractions per minute) lasting about 10 to 20 minutes; these contractions, also known as ''house-keeper wave,'' sweep gastric contents down the small intestine.

Phase IV: This is a short transitory period of about 0 to 5 minutes, and the contractions dissipate between the last part of phase III and quiescence of phase I.

4. Different Approaches of GRDDS: Several approaches have been proposed to retain the dosage forms in the stomach and release the drug for a longer period of time into gastrointestinal tract. Various approaches of GRDDS are as follows[16]:

- Low density (Floating) Systems
- Mucoadhesive (bioadhesive) Systems
- Raft Forming Systems
- High Density (sinking) Systems
- Expandable, Unfolding and Swelling Systems
- Magnetic Systems
- Super Porous Hydrogel Systems

A. Floating – A Low Density System:

Floating drug delivery systems (FDDS) or hydro-dynamically balanced systemshave a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time (3- 4 hours). While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the stomach. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the gastric retention time and a better control of fluctuations in the plasma drug concentration in some cases[17,18].

The major requirements for floating drug delivery systems[19]

• It should release contents slowly to serve as a reservoir.

• It must maintain specific gravity lower than gastric contents (1.004 – 1.01 gm/cm3).

• It must form a cohesive gel barrier.

The inherent low density can be provided by the entrapment of air (hollow chambers)[20]or by the incorporation of low density materials (e.g. fatty materials or oils, or foam powder)[21,22]. The good floating behavior of these systems could be successfully combined with accurate control of the resulting drug release patterns. The single-unit floating dosage forms are associated with problems such as sticking together or being obstructed in the GIT, which may produce gastric irritation. However, multiple-unit floating systems may be an attractive[23]. Based on the mechanism of buoyancy, two distinctly different technologies, i.e. non-effervescent and effervescent systems have been utilized in the development of FDDS[24].

- **Effervescent systems:** Effervescent systems utilize gas (CO_2) generating agents (e.g. sodium bicarbonate, citric acid or tartaric acid) to achieve floatability.

These effervescent systems further classified as gas generating systems and volatile liquid/vacuum systems.

a.Gas generating systems

b. Volatile liquid or vacuum containing systems

- **Non-effervescent systems:** Non-effervescent FDDS are normally prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene, polymethacrylate, carbopol, HPMC, sodium alginate, chitosan etc. These systems can be further divided into following sub-types[25]:

a. Hydrodynamically balanced systems (HBS)

b. Microballoons (Hollow microspheres)

c.Alginate beads

B. Bioadhesive Systems:

Bioadhesive drug delivery systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the Gastro retention of drug delivery system (DDS)in the stomach by increasing the intimacy and duration of contact of drug with the biological membrane. A bio/mucoadhesive substance is a natural or synthetic polymer capable of producingan adhesive interaction based on hydration mediated, bonding mediated or receptor mediated adhesion with a biological membrane or mucus lining of GI mucosa[26,27].

C. *Raft Systems Incorporating Alginate Gels:*

These have a carbonate component and upon reaction with gastric acid, bubbles form in the gel, enabling floating[28,29].

D. ***High Density Systems:***

They include coated pellets and have density greater than that of stomach content (1.004 gm/cm^3). This goal is achieved by coating the drug with a heavy inert material such as barium sulphate, ZnO, titanium dioxide. This formulation of high density pellet is based on assumption that heavy pellets might remain longer in the stomach, since they are positioned in the lower part of the antrum[4,19,30].

E. Expandable, Unfolding and Swelling Systems:

These types of products swell to an extent that prevents their exit from the stomach through the pylorus. This dosage form is retained in the stomach for a longer period of time. These systems may be referred as a "Plug type system" since they exhibit tendency to remain logged in the pyloric sphincters[28,31].

a. A small configuration for oral intake,

b. An expanded gastroretentive form, and

c. A final small form enabling evacuation following drug release from the device.

F. ***Magnetic Systems:***

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[32,33].

G. Super Porous Hydrogel Systems:

With pore size ranging, 10 nm to 10 µm, absorption window by conventional hydrogel is a very slow process and several hours may be needed to reach an equilibrium state during which, pre mature evacuation of the dosage form may occur[34]. Super porous hydrogels, average pore size less than 100 µm, swell to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores[35].

5. Advantages of Gastroretentive Drug Delivery Systems[36]

• Prolongs the residence time of the dosage form at the site of absorption which enhances absorption and the therapeutic efficacy of the drug.

• Excellent accessibility

• Rapid absorption because of enormous blood supply and good blood flow rates.

• Drug is protected from degradation in the alkaline environment in the GIT, e.g., Ranitidine, Captopril

• Improved patient compliance due to ease of drug administration.

• Reduced fluctuations of drug concentration in the blood.

• Targeted therapy for local acting drug in the upper GIT.

• Bioavailability of drugs enhanced by Gastro Retentive Dosage Forms. e.g. Furosemide

• Reduced frequency of dosing by sustained release drug delivery systems in the stomach.

• Minimized adverse effects of drug at the colon.

• Reduction of fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.

• Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics. e.g. Beta-lactam antibiotics (penicillin and cephalosporin).

• The sustained mode of drug release from Gastro retentive doses form enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes.

Gastro retentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency[1,4,9,25].

6. Limitations of GRDDS:

GRDDS have great potential in improving the bioavailability of drugs that exhibit an absorption window, but with certain limitations.

➢ Require a higher level of fluids in the stomach.

➢ Not suitable for Drugs that are unstable in acidic environment.

- Have solubility problems in gastric fluid.E.g. phenytoin
- Cause G.I irritation. E.g. NSAIDS.

➢ Drugs intended for selective release in the colon E.g. 5- amino salicylic acid and corticosteroids etc.

➢ The mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.

➢ In the case of bioadhesive systems, which form electrostatic and hydrogen bonds with the mucus, the acidic environment and the thick mucus prevent bond formation at the mucus–polymer interface.

➢ The high turnover rate of mucus may further aggravate the problem and localized high drug concentration could lead to irritation or ulceration.

7. CONCLUSION:

There is no doubt that the oral route is the most favored and probably most complex route of drug delivery system. Based on the literature surveyed, it may be concluded that gastroretentive drug delivery system showed the potential to enhance the gastric retention of drug and the bioavailability of drug with some limitations. These limitations can be reduced by formulating as multiple unit drug delivery system and by formulating the drug as bioadhesive. The idea of bioadhesive began with the clear need to localize a drug at a certain site in the GI tract. The increasing sophistication of these technologies will ensure the development of numerous gastroretentive drug delivery systems to optimize the delivery of drugs that exhibit absorption window, low bioavailability and extensive firstpass metabolism. Number of commercial product and patents issued in this field are the evidence of it. And hence, it can be concluded that these dosage forms serve the best in the treatment of diseases related to the GIT and for extracting a prolonged action from a drug with a short half-life.

8. Future Prospects for GRDDS:

The control of GI transit profiles could be the focus of the next two decades and might result in the availability of new products with new therapeutic possibilities and substantial benefits for patients. Soon, "once a day" formulations may be replaced by novel gastroretentive products. It is anticipated thatvarious novel products using gastroretentive drug delivery technologies may enhance this possibility. Further investigations may concentrate on the following concepts:

➢ Design of an array of gastroretentive drug delivery systems, each having narrow GRT for use according to the clinical need, e.g., dosage and state of diseases.

➢ Determination of minimal cut-off size above that dosage forms retained in the GIT for prolonged period of time.

➢ Design and development of gastroretentive drug delivery systems as a beneficial strategy for the treatment of gastric and duodenal cancers.

➢ Development of various anti-reflux formulation utilizing gastroretentive technologies.

➢ Design and development of gastroretentive drug delivery systems for drugs, which are potential to treat Parkinson's disease.

➢ Design and synthesis of novel polymers according to their clinical and pharmaceutical need.

➢ Design and synthesis of novel mucoadhesive agents to develop bioadhesive drug delivery systems for improved gastroretention.

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