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Review Article

Gastroretentive drug delivery system: a concise review

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ABSTRACT

An ideal dosage regimen in the drug therapy of any disease is the one which immediately attains the desired concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment. 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. Dosage forms with a prolonged GRT (gastric residence time), i.e. gastro-remaining or gastro retentive dosage forms (GRDF) or Intestinal Retentive dosage form will bring about new and important therapeutic options such as they significantly extend the period of time over which drugs may be released, and thus prolong dosing intervals and increase patient compliance and it will greatly improve the local drug release leading to high drug concentrations at the mucosa which are sustained over a long period of time. The purpose of this paper is to briefly describe the gastro retentive drug delivery (GRDD), classification, formulation consideration for GRDDS, factors related to GRDD, its advantages disadvantages, and emphasis is given over its significance over conventional form of drug deliveries. This review also summarizes various strategies for gastric retention such as floating system, swelling and expanding system, bio/mucoadhesive system, high density system and other delayed gastric emptying devices.

Key words: *Gastroretentive drug delivery system; Floating system; Swelling; Expanding system; Bio/mucoadhesive system; High density system*

INTRODUCTION

Oral route of drug administration is the most convenient and commonly used method of drug delivery. About 90% of all drugs used to produce systemic effects are administered by oral route. Of the drugs that are administered orally, solid oral dosage forms represent the preferred class of products.[1] this route has several physiological problems. Including an unpredictable gastric emptying rate that varies from person to person, a brief gastrointestinal transit time (80-12h), and the existence of an absorption window in the upper small intestine for several drugs.[2] An ideal dosage regimen in the drug therapy of any disease is the one which immediately attains the desired concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment. This is possible through the administration of conventional dosage form in a particular dose and at a particular frequency. [3]

The conventional instant 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.[4] Drug absorption in the gastrointestinal tract is a highly variable procedure and it depends upon the factors such as gastric emptying process, gastrointestinal transit time of dosage forms, drug release from the dosage form, and site of absorption of drugs. [5, 6]

The development of oral controlled release systems has been a challenge to formulation scientists due to their inability to restrain and localise the system at targeted areas of the gastrointestinal (GI) tract. Controlled drug delivery systems aim to maintain plasma concentration of drugs within the therapeutic window for a longer period of time, thereby to ensure sustained therapeutic action and for that reason an increasing interest in their development exist. Moreover, many of new therapeutics under development are large molecules such as peptides, proteins, oligonucleotides, and vaccines [7].

Gastroretentive drug delivery systems are designed to prolong the gastric retention time of the drugs which are:

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- Locally active in the stomach.
- Unstable in the intestinal environment.
- Have narrow absorption window in the git.
- Have low solubility at the high pH regions.[8]

Advantages of Gastro/Intestinal retentive Delivery Systems

- Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose.
- Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels.
- Retention of drug delivery systems in the stomach prolongs overall Gastrointestinal transit time there by increasing bioavailability of sustained release delivery systems intended for once-a-day administration.
- For drugs that have low bioavailability in acidic pH, and are well absorbed in intestinal pH, Intestinal retentive delivery system is advantageous.

Limitations of the Techniques of Gastro/Intestinal retention

- Not suitable for drugs that may cause gastric lesions e.g. Non-steroidal anti inflammatory drugs.
- More predictable and reproducible floating properties should be achieved in all the extreme gastric conditions
- For Intestinal retention, dosage form has to cross gastric conditions intact, which is not easily achievable.
- Not suitable for drugs that are unstable in the strong acidic or basic environment.
- These systems do not offer significant advantages over the conventional dosage forms for drugs that are absorbed throughout the gastro intestinal tract. [9]

Other drawbacks associated with specific types of GRDDS are given the table below [10]

Technology	Drawbacks
High density system	Very difficult to incorporate large amount of drugs. No such systems are available in the market till date
Floating system	Floating highly depends on the fed state of the stomach and higher level of fluid is required in gastric region
Expandable system	Chocking problem; storage problem due to hydrolysable and biodegradable polymers; difficult to manufacture and not economical
Mucoadhesive system	Can be detached from gastric mucosa due to rapid turnover of mucus and peristaltic wave of stomach. It may also attach to the mucus of oesophagus
Magnetic system	Problem with patient compliance

Functional Anatomy of the Gastrointestinal Tract

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 organization of the GIT, from stomach to large intestine, is shown in Fig.1. The stomach is a J shaped enlargement of the GIT which can be divided into four anatomical regions: cardia, 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. When empty, the stomach occupies a volume of about 50 ml, but this may increase to as much as 1 litre when full.[11]

MUCUS LAYER

The tissue layer responsible for the formation of the adhesive interface is mucus. Mucus is a translucent and viscid secretion which forms a thin, continuous gel blanket adherent to the mucosal epithelial surface. The mean thickness of this layer varies from about 50 to 450 µm in humans.

The composition of the mucus varies widely depending on animal species, anatomical location and the normal or pathological state of the organism. It is secreted by the goblet cells lining the epithelia or by special exocrine glands with mucus cells acini. The lubrication properties of mucus secretions are a result of their viscous and gel forming properties and general stickiness.

It has following general composition;

1.	Water	95%
2.	Glycoproteins and lipids	0.5-5%
3.	Mineral salts	1%
4.	Free proteins	0.5-1%

Mucus glycoproteins are high molecular proteins possessing attached oligosaccharide units. These units contain an average of about 8-10 mono saccharide residues of five different types namely, L-Fucose,D-Galactose, N-Acetyl-D-Galactosamine, N-Acetyl-D-Glucosamine, Sialic acid. In humans, the only important sialic acid is N-acetylneuramic acid. Amino acids are principally serine, threonine and proline.[12]

Basic gastrointestinal tract Physiology

Anatomically the stomach is divided into 3 Regions:

1. fundus,
2. body, and
3. antrum pylorus.

The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for

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mixing motions And acts as a pump for gastric emptying by Propelling actions. 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 interdigestive series of Electrical events take place, which cycle through both stomach and intestine every 2 to 3 hours and is called inter digestive myoelectric cycle or migrating motor complex.[13]

It is divided into 4 phases

- phase I (basal phase) it lasts from 40-60 min with rare contractions
- phase II (preburust phase) last from 40-60min with intermittent potential and contractions.
- Phase III (burst phase) last for 4-6 min. in this intense and regular contraction occur for short periods. Due to these contractions the undigestive food is swept from stomach to intestine. These are known as house keeper waves.
- Phase IV it lasts for 0-5 min and occurs between phases III and I for two consecutive cycles.[14]

Different Features of Stomach

Gastric pH:	Fasted healthy subject 1.1 ± 0.15 Fed healthy subject 3.6 ± 0.4
Volume:	Resting volume is about 25-50 mL
Intestinal pH:	In the duodenum, the section closest to the pyloric sphincter of the stomach may be acidic (due to the HCl). However, the acidic chime from the stomach is quickly neutralized through the release of secretin which targets the pancrease to release an alkalinic solution, bringing the pH back up to around 7
Gastric secretion:	Acid, pepsin, gastrin, mucus and some enzymes about 60 ml with approximately 4 mmol of hydrogen ions per hour.
Intestinal secretion:	Pancreatic secretion: trypsin, chymotrypsin and carboxypolypeptidase, pancreatic amylase, pancreatic lipase
Intestinal Enzymes:	Peptidase, disaccharidase, intestinal lipase, intestinal amylase.
Effect of food on Gastric secretion:	About 3 liters of secretions are added to the food. [15]

FACTORS AFFECTING GASTRIC RETENTION

1. **Density**
   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-admistration 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 increasedby4 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. **Posture**
   GRT can vary between supine and upright ambulatory states of the patient.[16]
9. **Gender**
   Mean ambulatory GRT in males (3.4±0.6hours) is less compared with their age and race matched female counter parts (4.6 ± 1.2hours), regardless of the weight, height and body surface.
10. **Age**
    Elderly people, especially those over 70, have a significantly longer GRT.[17]
11. **Concomitant drug administration**
    Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride.[18]
12. **Other factors**
    Diabetes and Crohn's disease, body mass index, physical activity.[19]

DIFFERENT APPROACHES OF THE GRDDS

GRDDS are categorized as

A. Non-floating system:

These systems are retained in stomach by many mechanisms but not by floating.

Non-floating system is again divided into:

a) Sinking (High density) drug delivery system
b) Bioadhsive / mucoadhesive system
c) Magnetic system
d) Unfoldable system

B. Floating drug delivery system (FDDS):

These systems are known as low density system as their density is less than the gastric contents thus they float in stomach.

Floating drug delivery systems are classified as:

a) Effervescent system
b) Non effervescent system
   i. Hydrodynamically balanced system
   ii. Microbaloons or hollow microspheres
   iii. Alginate beads
   iv. Microporous compartment [20]

A. Non Floating System

a) High density (sinking) drug delivery system

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the folds of the stomach body near the pyloric region. Dense pellets (approximately 3g /cm3) trapped in fold also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on diameter of the pellets. Commonly used excipients are Barium sulphate, zincoxide, titaniumdioxide and iron powder, etc. These materials increase density by up to 1.5–2.4g/cm^3.[21]

b) Bioadhsive or mucoadhesive system

Bioadhesive or mucoadhesive formulations were originally developed for increasing GRT and controlling drug delivery of all kinds of drugs.[22]The technique involves coating of microcapsules with bioadhesive 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 bioadhesive formulations owing to their known ability to bind well to gastric mucosa.[23]

The basis of adhesion in that a dosage form can stick to the mucosal surface by different mechanism. These mechanisms are.[24, 25]

1) The wetting theory, which is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucous layers.

2) The diffusion theory, which proposes physical entanglement of mucin strands the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate.

3) The absorption theory, suggests that bioadhesion is due to secondary forces such as Vander Waal forces and hydrogen bonding.

4) The electron theory, which proposes attractive electrostatic forces between the glycoprotein mucin net work and the bio adhesive material.

c) Magnetic system

This system is based on the simple idea that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Using a extracorporeal magnet, gastric residence time of the dosage form can be enhanced for a prolonged period of time. [26]

d) Unfoldable system

Unfoldable systems are made of biodegradable polymers. They are available in different geometric forms like tetrahedron, ring or planner membrane (4 - label disc or 4 - limbed cross form) of bioerodible polymer compressed within a capsule which extends in the stomach.[27] Expandable systems have some drawbacks like problematical storage of much easily hydrolysable, biodegradable polymers relatively short-lived mechanical shape memory for the unfolding system most difficult to industrialize and not cost effective.[28]

B. Floating drug delivery system (FDDS):

a) Effervescent system

Floatability can be achieved by generation of gas bubbles. These buoyant systems utilize matrices prepared with swellable polymers such as polysaccharides (e.g. chitosan), effervescent components (e.g. sodium bicarbonate, citric acid or tartaric acid) [29]. The optimal stoicheometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1 [30]. 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 is shown in figure 5 and 6 respectively. [30]

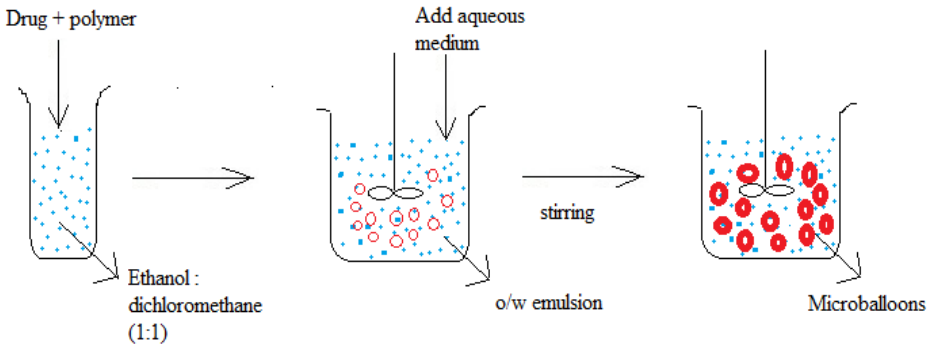
b) Non effervescent system

i. Hydrodynamically balanced system

These systems contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. These are single-unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxypropyl methylcellulose (HPMC), hydroxethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans or alginic acid are commonly used excipients to develop these systems. [31, 32]

ii. Microbaloons or hollow microspheres

These systems contain outer polymer shell loaded with drug. The outer polymer shell is made up of polymers like polycarbonate, cellulose acetate, calcium alginate, agar, etc. Buoyancy lag time and drug release from the system is dependent on the quantity of polymers used in the formulation. These are prepared by emulsion-solvent diffusion method. The steps involved are summarized in Figure.[33]



iii. Alginate beads

Multi-unit floating dosage forms have been developed from freeze-dried calcium-alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate leading to formation of a porous system, when compared with solid beads, which gave a short residence, time of 1 hr, and these floating beads gave a prolonged residence time of more than 5.5 hr. [34]

iv. Microporous compartment

Hollow Microspheres: Hollow microspheres (microballoons), loaded with ibuprofen in their outer polymer shells were prepared by novel emulsion solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer were poured into an agitated aqueous solution of PVA that was thermally controlled at 400 C. The gas phase was generated in dispersed polymer droplet by evaporation of dichloromethane and formed an internal cavity in microsphere of polymer with drug.[35]

SUITABLE DRUG CANDIDATES FOR GASTRO RETENTION

(i) Narrow absorption window in GI tract, e.g., riboflavin and levodopa .[36,37]

(ii) Drugs required to exert local therapeutic action in the stomach e.g., antacids and misoprostol. [38]

(iii) Drugs insoluble in intestinal fluids, e.g., quinidine, diazepam [39]

(iv) Drugs that degrade in the colon, e.g., ranitidine HCl [40]

(v) Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.[41]

Future Prospects

GRDDS's have a future of not only increasing bioavailability and overcoming other drawbacks related to delivering drug to systemic circulation, instead GRDDS may prove to be an important perspective regarding controlled timed profile of certain drugs which have been found to distribute in certain non targeted tissues because of fast release. By making GRDDS many drug profiles have been found to be distributed in targeted desired tissue. Along with advantage it is a challenge to design such formulations due to unpredictability of GIT and retaining formulation for long time is not compatible with normal physiology.

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