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## Review Article

# A REVIEW ON GASTRORETENTIVE DRUG DELIVERY TO ENHANCE PROLONG DRUG RELEASE

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Gastro retentive dosage forms (GRDFs) are being used from a very long time to improve therapy with several important drugs. GRDFs greatly improves the pharmacotherapy of stomach by releasing the drug locally and thus results into high concentration of drug at the gastric mucosa which can be sustained over a longer duration of time. GRDFs enable prolonged and continuous release of the drug to the upper part of Gastro intestinal tract (GIT) and this significantly extend the duration of drug release and improve bioavailability of drugs that have narrow therapeutic window, by this way they prolong dosing interval and increase compliance of the patient. GRDDs are an approach to prolong gastric residence time, there by targeting site-specific drug release in the upper GIT for local or systemic effect. The purpose of this paper is to briefly describe the gastro retentive drug delivery (GRDD), factors related to GRDD, its advantages disadvantages, and emphasis is given over its significance over conventional form of drug deliveries

**Keywords:** gastric residence time, Gastroretention, hydrodynamically balanced system, effervescent, non- effervescent

## INTRODUCTION

Prolonged GRT enables the controlled delivery of drugs in stomach which can evade the repeated administration of dosage form of the drugs with short half-life. GRDDS is an approach to prolong the gastric residence time, thereby aiming site-specific drug release in the upper GIT for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Literature suggests that GRDDS has gained huge popularity in the field of oral drug delivery recently, as it can release the drug slowly that can combat many shortcomings allied with

conventional oral delivery, including poor bioavailability. Studies demonstrate that the drugs which have to be in the upper part of the GIT, have been prepared as gastroretentive dosage forms using various approaches. Such formulation improves the therapeutic efficacy of the drug and enhances the patient compliance.<sup>1,2</sup>

GRDFs have been researched for many antidiabetic drugs and studies revealed that the gastroretentive form of drug has led to better management of the disease status. Although, a lot of work has been done, but still there is tremendous scope to develop such dosage form



of antidiabetic drugs. Moreover, there are certain antidiabetic drugs which have a strong rationale for developing GRDDS, but no research has been reported to be performed on them.<sup>3</sup>

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<sup>4</sup>.

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

- 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.<sup>5</sup>

#### **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.<sup>6</sup>



Other limitations associated with specific types of GRDDS are given the table below<sup>7</sup>

Technology	Limitations
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

### FACTORS AFFECTING GASTRIC RETENTION<sup>8,9,10</sup>

- Density:** Density of dosage form should be in range of 1g/cm<sup>3</sup> to 2.5g/cm<sup>3</sup>.
- 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.
- 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.
- Single or multiple unit formulation:** Multiple unit formulations show a more

predictable release profile, co-administration of different units, larger safety margin.

- Fed or unfed state:** In the fed state, MMC is delayed and GRT is considerably longer.
- 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.
- 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. **Posture:** GRT can vary between supine and upright ambulatory states of the patient.

9. **Gender:** Mean ambulatory GRT in males ( $3.4 \pm 0.6$  hours) is less compared with their age and race matched female counter parts ( $4.6 \pm 1.2$  hours), regardless of the weight, height and body surface.

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

11. **Concomitant drug administration:** Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride.

12. **Other factors:** Diabetes and Crohn's disease, body mass index, physical activity.

#### 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) Bioadhesive / 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
  - Hydrodynamically balanced system
  - Microballoons or hollow microspheres
  - Alginate beads
  - Microporous compartment

##### A. Non Floating System

###### ➤ 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  $3\text{g}/\text{cm}^3$ ) 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, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to  $1.5\text{--}2.4\text{g}/\text{cm}^3$ .<sup>11</sup>

###### ➤ Bioadhesive or mucoadhesive system

Bioadhesive 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 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.<sup>12</sup>

The basis of adhesion in that a dosage form can stick to the mucosal surface by different mechanism. These mechanisms are<sup>13</sup>

- The wetting theory, which is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucous layers.
- 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.
- The absorption theory, suggests that bioadhesion is due to secondary forces such as Vander Waal forces and hydrogen bonding.
- The electron theory, which proposes attractive electrostatic forces between the glycoprotein mucin net work and the bio adhesive material.

➤ **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.<sup>14</sup>

➤ **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. 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.<sup>15</sup>

**B. Floating drug delivery system (FDDS):**

➤ **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). The optimal stoicheometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1. 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.<sup>16</sup>

➤ **Non effervescent system**

• **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.<sup>17</sup>

• **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.<sup>18</sup>

• **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.<sup>19</sup>

• **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 40°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.<sup>20</sup>

**SUITABLE DRUG CANDIDATES FOR GASTRO RETENTION**

- Narrow absorption window in GI tract, e.g., riboflavin and levodopa.<sup>21,22</sup>
- Drugs required to exert local therapeutic action in the stomach e.g., antacids and



misoprostol.<sup>23,24</sup>

- Drugs insoluble in intestinal fluids, e.g., quinidine, diazepam<sup>25,26</sup>
- Drugs that degrade in the colon, e.g., ranitidine HCl<sup>27,28</sup>
- Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.<sup>29,30</sup>

### 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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