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Review on Gastro Retentive Drug Delivery System

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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.

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. 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.

Keyword: Gastroretention, conventional drug delivery, Anatomy of GIT, GIT's physiology.

INTRODUCTION: Oral route of drug administration is the most convenient and commonly used method of drug delivery. However, this route has several physiological problems.

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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.[1]

These difficulties have prompted researchers to design a drug delivery system which can stay in the stomach for prolonged and predictable period. Attempts are being made to develop a drug delivery system which can provide therapeutically effective plasma drug concentration for a longer period, thereby

reducing the dosing frequency and minimizing fluctuation in plasma drug concentration at steady state by delivering the drug in a controlled and reproducible manner.[2]

One novel approach in this area is GRDDSs (gastro retentive drug delivery system).
Dosage forms that can be retained in the stomach are called GRDDs.
GRDDSs can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site. [3]
Prolonging the gastric retention of the drugs is sometimes desirable for achieving therapeutic benefits of drug 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 encounter at the lower part of the GIT. GRDDS are beneficial for such drugs by improving their [4]

- Bioavailability
- Therapeutics efficiency and
- Possible reduction of the dose.
- Apart from these advantages, these systems offer various pharmacokinetic advantages like, maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in the therapeutic levels

Drugs that are easily absorbed from GIT and have short half-lives are eliminated quickly from the systemic circulation. Frequently dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained controlled release formulations is an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the systemic circulation for a long time.
After oral administration, such a drug delivery would be retained in the stomach and release the drug in controlled manner, so that the drug could be supplied continuously to its absorption sites in the GIT. [5]

GRDD Devices are primarily site specific drug delivery systems, which gets retained in the stomach for longer period of time, thus helping in absorption of drug for the intended duration of time. This in turn improves:-

- Bioavailability
- Reduce drug wastage
- Improves solubility of drugs that are less soluble at high pH environment (e.g. weakly basic drug like domperidone, papaverine)
- Also helps in achieving local delivery of drug to the stomach and proximal small intestine.

To formulate a site specific orally administered controlled release dosage form, it is desirable to achieve a prolong gastro residence time by the drug delivery.

In addition, for local and sustained drug delivery to the stomach and proximal part of the small intestine, to treat certain conditions, prolonged gastric retention of the therapeutic moiety may offer numerous advantages including [4]

- Improved bioavailability
- Improved therapeutic efficacy
- Possible reduction of dose size
- Improves the drug solubility that is less soluble in high pH environment. E.g. weakly basic drugs like Domperidone, papaverine etc.
- Decrease drug wastage
- Also helps in achieving local delivery of drug to the stomach and proximal part of small intestine.

Prolonged gastric retention time in the stomach could be advantageous for local action in the upper part of the small intestine e.g. treatment of peptic ulcer. [6]
In recent year, oral dosage forms for gastric retention have drown more and more attention for their therapeutic advantage in permitting command over the time and site of drug release.
Many drugs categorized as once a day delivery have demonstrated on transit time of dosage

form. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in small intestine. [7]

The controlled gastric retention of solid dosage forms may be achieved by the mechanism of

- Mucoadhesion
- Flotation
- Sedimentation
- Expansion
- Modified shape systems OR
- By the simultaneous administration of pharmacological agents that delay gastric emptying.

GASTRORETENTIVE DRUG DELIVERY SYSTEMS vs. CONVENTIONAL DRUG DELIVERY SYSTEMS

S.No		Conventional DDs	GRDDs
1.	Toxicity	High risk of toxicity	Low risk of toxicity
2.	Patient compliance	Less	Improves patient compliance
3.	Drug with narrow absorption window in small intestine	Not suitable	Suitable
4.	Drugs having rapid absorption through GIT	Not much advantageous	Very much advantageous
5.	Drug which degrades in the colon	Not much advantageous	Very much advantageous
6.	Drugs acting locally in the stomach	Not much advantageous	Very much advantageous
7.	Drugs which are poorly soluble at an alkaline pH	Not much advantageous	Very much advantageous
8.	Dose dumping	High risk of dose dumping	No risk of dose dumping

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 [8].

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, intermuscular plane, circular muscle, submucosa, muscularis mucosae, 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 [9].

MUCUS: STRUCTURE, FUNCTION AND COMPOSITION:

Mucus is a complex viscous adherent secretion which is synthesized by specialized goblet cells. These goblet cells are glandular columnar epithelium cells and line all organs that are exposed to the external environment. Mucus is found to serve many functions within these locations such as lubrication for the passage of objects, maintenance of a hydrated epithelium layer, a barrier function with regard to pathogens and noxious substances and as a permeable gel layer allowing for the exchange of gases and nutrients to and from underlying epithelium[10].

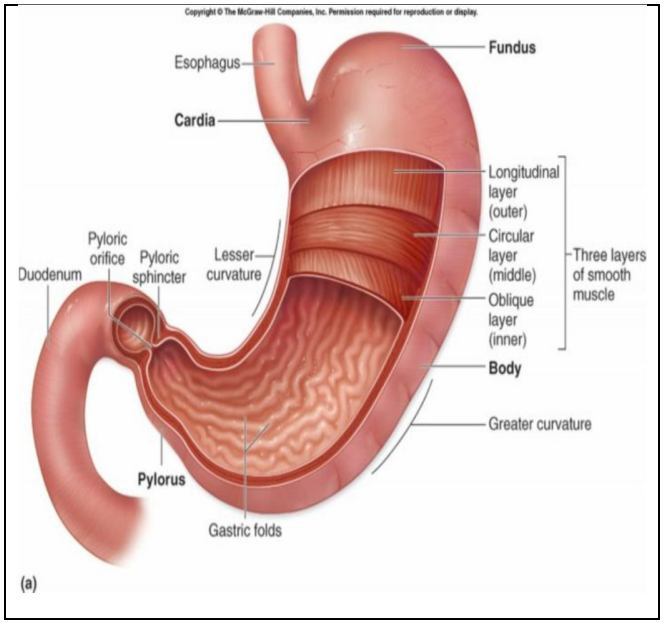

Figure 1: Anatomy of the gastrointestinal tract

From an engineering point of view, mucus is an outstanding water-based lubricant whose properties are extensively exploited within nature[11].

Mucus is composed mainly of water (>95%) and mucin, which are glycoprotein's of exceptionally high molecular weight (2–14 X106 g/mol). Also found within this ''viscoelastic soup" are proteins, lipids and mucopolysaccharides, which are found in smaller proportions (<1%). The mucin glycoprotein's form a highly entangled network of macromolecules that associate with one another through non covalent bonds. Such molecular association is central to the structure of mucus and is responsible for its rheological properties. Furthermore, pendant sialic acid (pKa = 2.6) and sulphate groups located on the glycoprotein molecules result in mucin behaving as an anionic polyelectrolyte at neutral pH[12]. Other nonmucin components of mucus include secretory IgA, lysozyme, lactoferrin, lipids, polysaccharides, and various other ionic species. Some of these non-mucin components are believed to be responsible for the bacteriostatic action observed in mucus[13].

BASIC GASTROINTESTINAL TRACT PHYSIOLOGY[14]

Anatomically the stomach is divided into 3 regions:

- Fundus,
- Body, and
- 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 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.
This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases.

1. Phase I (basal phase)
2. Phase II (preburst phase)
3. Phase III (burst phase)
4. Phase IV

Table1: Four phases in migrating myoelectric complex (MMC):[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.

Phase l: (basal phase) Period of no contraction
Phase ll: (preburst phase) Period of intermittent contraction
Phase lll: (burst phase) Period of regular contraction at the maximal frequency that migrate distally.
Phase lV: Period of transition between phase lll and phase l

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase 2 of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled towards the pylorus in a suspension from. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.13 Scintigraphic studies determining gastric emptying rate revealed that orally administered controlled released dosage forms are subjected to complications that of short gastric residence time and unpredictable gastric emptying rate.

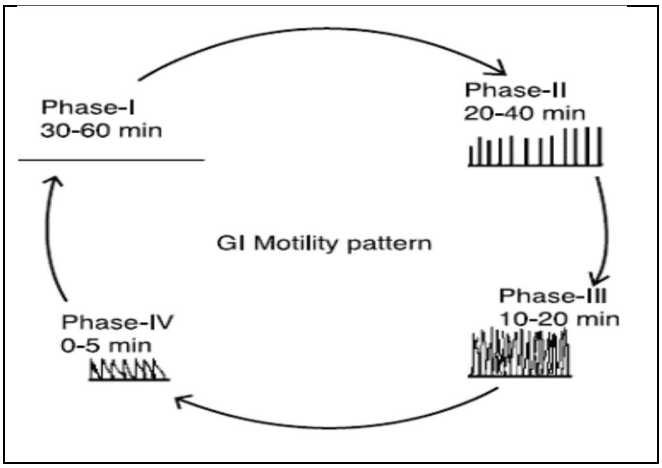

Figure. 2. A simplified schematic representation of the interdigestive motility pattern, frequency of contraction forces during each phase, and average time Period for each period.

FACTORS CONTROLLING GASTRIC RETENTION OF DOSAGE FORMS

There are many parameters related to stomach’s anatomy and physiology that are needed to be considered in the development of gastroretention dosage forms.

1. **Particle size**
   Should be in the range of 1-2 mm to pass through the pyloric valves into the small intestine. [17]

2. **Density**
   Density of dosage form should be in range of 1g/cm^3 to 2.5g/cm^3

3. **Size**
   Size should be greater than 7.5 mm in diameter. [18]

4. **Shape of dosage forms**
   Ring and tetrahedron devices with flexural modulus of 22.5-48 KSI (keto pound/ inch^2 show 90-100 % gastric retention times (GRT).

5. **Single unit/multiple unit**
Multiple units are preferable because of predictable release profile, co-administration of different units, larger safety margins.

6. **Food intake**
GRT is longer in fed states.

7. **Nature, calorie content**
Indigestible polymers, fatty acid salts, increase calorie content, increase acidity increases GRT, Fat and protein meal increases GRT.

8. **Frequency of intake**
GRT increases 400 times due to low frequency of **MMC**

9. **Posture**
Varies between spine and upright ambulatory states.

10. **Gender**
Females have shorter GRT than males. [19]

11. **Age**
Age > 70 shows longer GRT. [19]

12. **Nature of drug**
Drugs with impact on gastro intestinal transit time e.g. Codeine and pharmacokinetic agents e.g. metclopramide, cisapride increases GRT. [20]

13. **Other factors**
- Diseased states of the individual (chronic disease, diabetes etc.)
- Body mass index
- Physical activity
- Molecular weight and lipophilicity of the drug depending on its ionization state.[21]

CERTAIN TYPES OF DRUGS CAN BENEFIT FROM USING GASTRIC RETENTION DEVICES.

These include drugs that:

- Are acting locally in the stomach e.g. Antacids and drugs for H.pylori viz. Misoprostol
- Primarily absorbed in the stomach. e.g. Amoxicillin
- Have an absorption window in the stomach or in the upper small intestine,
- Drugs with narrow window of absorption, e.g. Cyclosporine, Methotrexate, Levodopa
- Are unstable in the intestinal or colonic environment, e.g. Ranitidine, Metformin Hcl
- Exhibit low solubility at high pH values.

DRUGS THOSE ARE UNSUITABLE FOR GRDFs

1. Drugs that have very limited acid solubility e.g. Phenytoin etc.
2. Drugs that suffers instability in the gastric environment e.g. Erythromycin, Rabeprazole, Clarithromycin, Esomeprazole etc.
3. Drugs intended for selective release in the colon e.g. 5-amino salicylic acid and corticosteroids etc.

ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

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[22].

2. Enhanced first-pass biotransformation

In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input[23].

3. Sustained drug delivery/reduced frequency of dosing

For drugs with relatively short biological half-life, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.

4. Targeted therapy for local ailments in the upper GIT

The prolonged and sustained administration of the drug from GRDF to the stomach may be advantageous for local therapy in the stomach and small intestine. By this mode of administration, therapeutic drug concentrations may be attained locally while systemic concentrations, following drug absorption and distribution, are minimal.

5. Reduced fluctuations of drug concentration

Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index[24].

6. Minimization of fluctuations in drug concentration

It makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

7. Reduced counter-activity of the body

In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

8. Extended time over critical (effective) concentration

For certain drugs that have non-concentration dependent pharmacodynamics, such as etalactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration. The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.

9. Minimized adverse activity at the colon

Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

10. Site specific drug delivery

A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper small intestine[25]. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency.

DISADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

1. Unsuitable for drugs with limited acid solubility. E.g. Phenytoin
2. Unsuitable for drugs that are unstable in acidic environment. E.g. Erythromycin
3. Drugs that irritates or causes gastric lesions on slow release. E.g. Aspirin & NSAID's
4. Drugs that absorb selectively in colon. E.g. Corticosteroid
5. Drugs that absorb equally well through GIT. E.g. Isosorbide dinitrate, Nifidipine
6. Floating drug delivery systems require high fluid level in stomach to float and work effectively.

OVER THE LAST FEW DECADES, SEVERAL GRDD APPROACHES BEING DESIGNED AND DEVELOPED INCLUDING,

1. High density (sinking systems that retained at the bottom of the stomach.[26]
2. Low density floating systems that causes buoyancy in gastric fluid.[27,28]
3. Mucoadhesive systems that causes bioadhesion to stomach mucosa[29]
4. Unfoldable, extendible or swellable systems that limits emptying of the dosage forms through the pyloric sphincters of stomach.[30, 31]
5. Super porous hydrogel systems.[32]
6. Magnetic systems.[33]

HIGH DENSITY SINKING SYSTEM [34, 35]

These systems with a density of about 3 g/cm3 are retained in the antrum part of the stomach and are capable of withstanding its peristaltic movements. The only major drawbacks with such systems is that it is technically difficult to manufacture such formulations with high amount of drug (>50%) and to achieve a density of about 2.8 g/cm3.

LOW DENSITY FLOATING SYSTEM

Floating drug delivery systems (FDDS) or hydro-dynamically balanced systems have 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. 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.

HIGH DENSITY SINKING SYSTEM vs. LOW DENSITY FLOATING SYSTEM

S.No	High density sinking systems	Low density floating system
1.	Density of pellets/tablets > density of stomach fluid.	Density of pellets/tablets < density of stomach fluid.
2.	Density of pellet or tablet should be at least 150 g/ml	Density of pellet/tablet should be < 1g/ml
3.	Drug can be coated or mixed with heavy non toxic materials. e.g. barium sulphate, titanium dioxide etc.	Low bulk density systems, designed in such a manner that it floats in gastric fluid and release the drug slowly for a longer period of time.
4.	High density systems	Also called Hydrodynamic balanced system.

MUCOADHESIVE SYSTEM

These are developed to perform drug absorption in a site specific manner. In this approach, bioadhesive polymers are used that adhere to mucosal epithelial surface in stomach, thereby increase gastric retention time.

Various mechanisms of adhesion are:-

1. Wetting theory, ability of bioadhesive polymers to spread and cause intimate contact with mucin layers.
2. Diffusion theory, physical entanglement of mucin strand with soluble polymer or interpenetration of mucin strand into structure of polymer.

Absorption theory, bioadhesion is due to secondary forces such as vanderwalls forces and hydrogen binding.

Electronic theory, proposes attractive electrostatic forces between glycoprotein mucin network and bioadhesive material.

Bioadhesive polymers used are: - PAA, Chitosan, Sodium alginate, HPMC, Sucralfate, Tragacanth, Dextrin, PEG.

Limitation: - Bioadhesion is difficult to maintain due to rapid turnover of mucin in GIT

SWELLING SYSTEM

These are the dosage forms, which after swallowing, swells to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a longer period of time. These systems may be named as 'plug type systems', 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. The balance between the extent and duration of swelling is maintained by the degree of cross linking between the polymeric chains. A high degree of cross – linking retards the swelling ability of the system maintaining its physical integrity for prolonged period.

SUPER POROUS HYDROGEL SYSTEM

These swellable systems differ significantly from the conventional types to hold a separate classification. In this approach to improve the GRT super porous hydrogels of average pore size > 100 micrometer, swell to equilibrium size within a minute due to the rapid water uptake by capillary wetting through numerous interconnected open pores. They swell to large size (swelling ratio: 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is advised by co-formulation of hydrophilic particulate material.[36, 37]

MAGNETIC SYSTEM

Dosage forms contain a small internal magnet and a magnet is placed in abdomen over the position of stomach that retains dosage form in gastric region.

Disadvantage: -

- External magnet needs to be positioned with degree of precision.
- Patient non compliance
- Not very used

CONCLUSION

Based on the literature survey, it can be concluded that GRDDs offers various potential advantages for drugs with poor bioavailability. Drug absorption in the gastro intestinal tract is a highly variable process and prolonging gastric retention of the dosage form extends the time for drug absorption.

The control of gastro intestinal transit of orally administered dosage forms using GRDD systems can improve the bioavailability of drugs that exhibit site specific absorption. GRDFs also provide an additional advantage for drugs that are absorbed primarily in the upper segment of GIT, i.e., stomach, duodenum and jejunum.

Different approaches for GRDD are studied each having their own advantages and disadvantages. Due to unpredictability of human GIT development of efficient GRDFs is a real challenge to pharmaceutical technology as the drug delivery system must remain for a sufficient time in the stomach which is not compatible with normal physiology.

In the future it is can be easily assumed that GRDD systems will become more popular in terms of delivering drug to the systemic circulation with improving efficiency of various type of pharmacotherapy's.

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