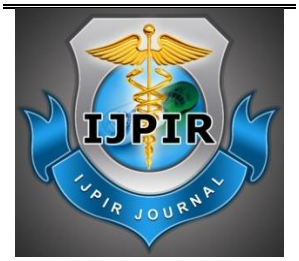
Review Article



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Gastro retentive drug delivery systems: a review

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ABSTRACT

In recent years, many efforts have been made in order to improve drug bioavailability after oral administration. Gastroretentive drug-delivery systems (GRDDS) provide a mean for controlled release of compounds that are absorbed by active transport in the upper intestine. They have the potential to prolong the gastric retention time and provide controlled/sustained release of a drug at the absorption site, thereby improving the bioavailability. Several approaches are used to increase the gastric residence time, namely bioadhesive or mucoadhesive systems, expandable systems, high-density systems, floating systems, superporous hydrogels and magnetic systems. The present review highlights some of the drugs that can benefit from gastroretentive strategies, such as the factors that influence gastric retention time and the mechanism of action of gastroretentive systems, as well as their classification into single and multiple unit systems. In the future, it is expected that they will become of significance in drug therapies.

Keywords: Bioavailability; Gastrorentive drug delivery systems (GRDDS); In vitro drug release; Hydrocolloids plasma concentration; Polymers; Therapeutic effect.

INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastro intestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent 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 gastrointestinal tract (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 a controlled manner, so that the drug could be supplied continuously to its absorption sites in the

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gastrointestinal tract (GIT)[1]. These drug delivery systems suffer from mainly two adversities, the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose[2]. To formulate a site-specific orally administered controlled release dosage form it is desirable to achieve prolong gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability ,increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment.

Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastro retentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs.

Over the last few decades, several gastro retentive drug delivery approaches wear designed and developed, including:

1. High density (sinking) systems that is retained in the bottom of the stomach,[3]
2. Low density (floating) systems that causes buoyancy in gastric fluid,[4]
3. Mucoadhesivesystems that causes bioadhesion to stomach mucosa, [5]
4. Unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach,[6]
5. Superporoushydrogel systems, [7]
6. Magnetic systems etc. [8]

The current review deals with various gastroretentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery systems.

Factors controlling gastric retention of dosage forms

The stomach anatomy and physiology contain parameters to be considered in the development of gastro retentive dosage forms. To pass through the pyloric valve in to the small intestine the particle size should be in the range of 1 to 2 mm.

The most important parameters controlling the gastric retention time (GRT) of oral dosage forms include:

1. Density,
2. Size and shape of the dosage form,
3. Food intake and its nature,
4. Effect of gender, posture, age.

Density of dosage forms

The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach [9]. Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm/ cm^3 is required to exhibit floating property.

Shape and size of the dosage form

Shape and size of the dosage forms are important in designing indigestible single unit solid dosage forms. The mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size, which may be large, medium and small units. In most cases, the larger the dosage form the greater will be the gastric retention time (GRT) due to the larger size of the dosage form would not allow this to quickly pass through the pyloric antrum into the intestine.

Dosage forms having a diameter of more than 7.5mm show a better gastric residence time compared with one having 9.9 mm. Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared with other shapes [10].

Food intake and its nature

Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms.

The presence or absence of food in the gastrointestinal tract (GIT) influences the gastric retention time (GRT) of the dosage form. Usually the presence of food in the gastrointestinal tract (GIT) improves the gastric retention time (GRT) of the dosage form and thus, the drugs absorption increases by allowing its stay at the absorption site

for a longer period. Again, increase in acidity and caloric value shows down gastric emptying time (GET), which can improve the gastric retention of dosage forms [11].

Effect of gender, posture and age

Generally females have slower gastric emptying rates than male. The effect of posture does not have any significant difference in the mean gastric retention time (GRT) for individuals in upright, ambulatory and supine state. In case of elderly persons, gastric emptying is slowed down [12].

Potential drugs for gastroretentive drug delivery systems

1. Drugs those are locally active in the stomach e.g. misroprostol, antacids etc.
1. Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. L-DOPA,
2. Para aminobenzoic acid, furosemide, riboflavin etc.
3. Drugs those are unstable in the intestinal or colonic environment e.g.captopril, ranitidineHCl ,Venlafaxine.
4. Drugs that disturb normal colonic microbes e. antibiotics against Helicobacter pylori.
5. Drugs that exhibit low solubility at high pH values e.g. diazepam,
6. chlordiazepoxide, verapamilHCl.

Drugs those are unsuitable for gastroretentive drug delivery systems

1. Drugs that have very limited acid solubility e.g. phenytoin etc.
2. Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
3. Drugs intended for selective release in the colon e.g. 5- amino salicylic acidand corticosteroids etc.

Approaches to achieve gastric retention

High density (sinking) system or non- floating drug delivery system:

This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content (~ 1.004 gm/cm^3). These formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulphate, zinc oxide and titanium oxide etc. The materials increase density by up to 1.5- 2.4 gm/cm^3. A density close to 2.5 gm/cm^3 seems necessary for significant prolongation of gastric residence time [13]. But effectiveness of this system in human beings was not observed and no system has been marketed.

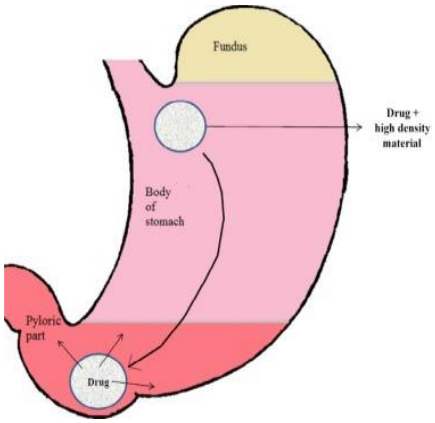

Figure 1: High density systems

Floating drug delivery systems

Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability. This delivery system is recommended for drugs with an absorption window in the stomach or in the upper small intestine [14]. This have a bulk density less then gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly as a desired rate from the system. After release of drug, the residual system is emptied from the stomach. This result in an increased gastric retention time (GRT) and a better control of the fluctuation in plasma drug concentration.

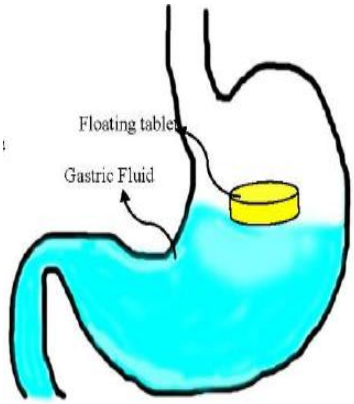

Figure 2: Floating drug delivery systems

The major requirements for floating drug delivery system are

- 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 (e.g. hollow chambers) or by the incorporation of low density materials (e.g. fatty materials or oils, or foam powder) [5]. These following approaches have been used for the design of floating dosage forms of single and multiple-unit systems. Recently a single-unit floating system was proposed consisting of polypropylene foam powder, matrix forming polymers, drug and filler [15].

The good floating behavior of these systems could be successfully combined with accurate control of the resulting drug release patterns. Single-unit dosage forms are associated with problems such as sticking together or being obstructed in the gastrointestinal tract (GIT) which may produce irritation. On the other hand multiple-unit floating systems may be an attractive alternative since they have been shown to reduce the inter- and intra- subject availabilities in drug absorption as well as to lower the possibility of dose dumping.

Various multiple-unit floating system like air compartment multiple-unit system [2], hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method ,microparticles based on low density foam powder, beads prepared by emulsion gelatin method etc. can be distributed widely throughout the GIT, providing the possibility of achieving a longer lasting and more reliable release of drugs. Based on the mechanism of buoyancy two distinctly different technologies, i.e. non-effervescent and effervescent systems have been utilized in the development of floating drug delivery system.

Non-effervescent Systems

Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment [16]. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methylcellulose (HPMC) polyacrylates, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

This system can be further divided into the sub-types

Hydrodynamically balanced systems

ShethandTossounian [17] first designated these ‘hydrodynamically balanced systems’. 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 [18].

The polymer is mixedwith drugs and usually administered in hydrodynamically balanced system capsule. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period. Because, continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form. Incorporation of fatty excipients gives low-density formulations reducing the erosion. Madopar LP®, based on the system was marketed during the 1980's. Effective drug deliveries depend on the balance of drug loading and the effect of polymer on its release profile. Several strategies have been tried and investigated to improve efficiencies of the floating hydrodynamically balanced systems [19].

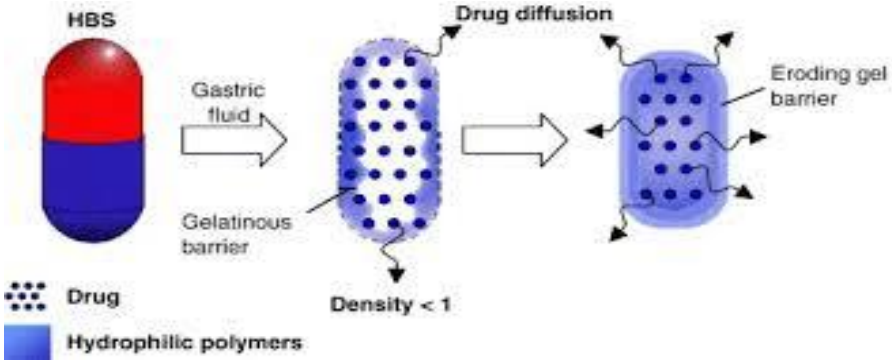

Figure 3: Hydrodynamically balanced systems

Microballoons / Hollow microspheres

Microballoons / hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion / evaporation methods [20] to prolong the gastric retention time (GRT) of the dosage form. Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer polymer ratio and the solvent used for formulation. The microballoons floated continuously over the surface of an acidic dissolution media containing surfactant for >12hours. At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good floating.

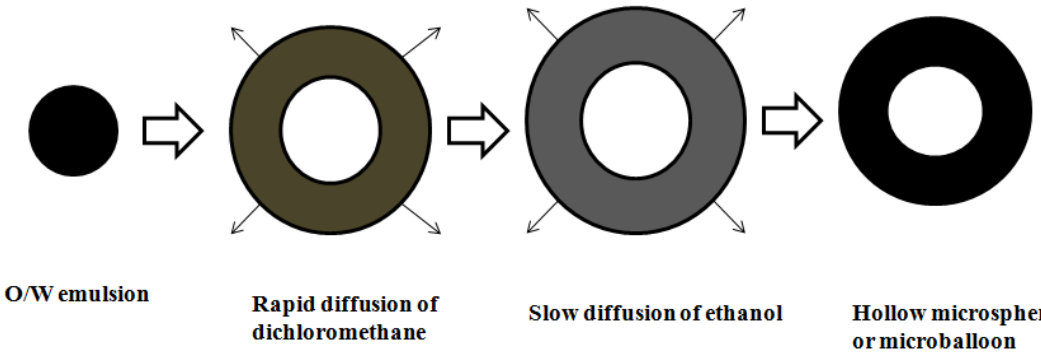

Figure 4: Formulation of floating hollow microsphere or micro balloon

Alginate beads

Talukdar and Fassihi recently developed a multiple-unit floating system based on cross-linked beads. They were made by using Ca2+ and low methoxylated pectin (anionic polysaccharide) or Ca2+ low methoxylated pectin and sodium alginate. In this approach, generally sodium alginate solution is dropped into aqueous solution of calcium chloride and causes the precipitation of calcium alginate. These beads are then separated and dried by air convection and freeze drying, leading to the formulation of a porous system, which can maintain a floating force for over 12 hrs. These beads improve gastric retention time (GRT) more than 5.5 hrs[21].

Microporous compartment system

This approachis based on the principle of the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls [22]. The peripheral walls of the device were completely sealed to present any direct contact of the gastric surface with the undissolved drug. In the stomach the floatation chamber containing entrapped air causes the delivery system to float in the gastric fluid. Gastric fluid enters through the aperture, dissolves the drug and causes the dissolved drug for continuous transport across the intestine for drug absorption.

Effervescent (gas generating) systems

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) [22]. The optimal stoicheometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1. In this system carbon dioxide is released and causes the formulation to float in the stomach (Figure 2). Other approaches and materials that havebeen reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating dosage forms that generate gas (carbon dioxide) when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone (PVP) coated with hydroxypropyl methylcellulose (HPMC), and floating system based on ion exchange resin technology etc. Bilayer or multilayer system has also been designed. Drugs and excipients can be formulated independently and the gas generating material can be incorporated in to any of the layers. Further modifications involve coating of the matrix with a polymer which is permeable to water, but not to carbon dioxide. The main difficulty of these formulations is finding a good compromise between elasticity, plasticity and permeability of polymers.

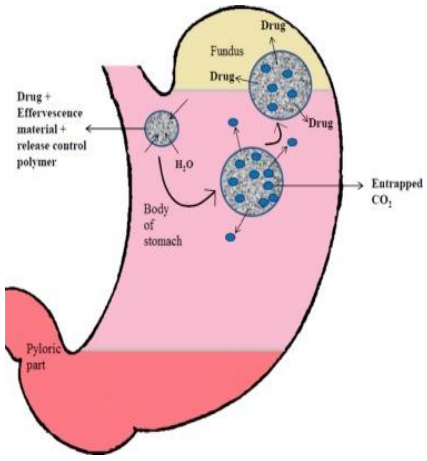

Figure 5: Gas generating systems

Bioadhesive or Mucoadhesive drug delivery systems

Bioadhesive drug delivery systems are used as a delivery device within the human to enhance drug absorption in a site-specific manner. In this approach, bio adhesive polymers are used and they can adhere to the epithelial surface in the stomach [23]. Thus, they improve the prolongation of gastric retention. The basis of adhesion is that a dosage form can stick to the mucosal surface by different mechanism.

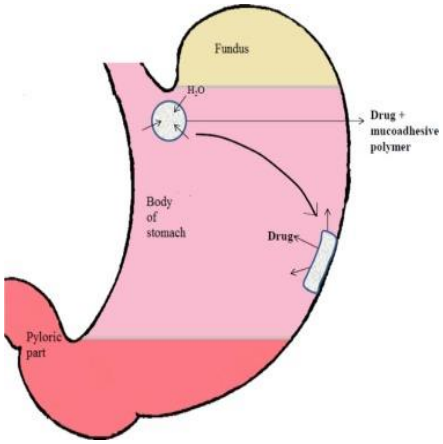

Figure 6: Bioadhesive systems

These mechanisms are [24]

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 mucinnetwork and the bio adhesive material.
5. Materials commonly used for bioadhesion are poly acrylic acid, chitosan, cholestyramine, sodium alginate, hydroxypropyl methylcellulose (HPMC), sucralfate, tragacanth, dextrin, polyethylene glycol (PEG) and polylactic acids etc. Even though some of these polymers are effective at producing bioadhesive, it is very difficult to maintain it effectively because of the rapid turnover of mucus in the gastrointestinal tract (GIT).

Expandable, unfoldable and swellable systems

A dosage form in the stomach will withstand gastric transit if it bigger than pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, their configurations [25] are required to develop an expandable system to prolong gastric retention time (GRT):

1. A small configuration for oral intake,
2. An expanded gastroretentive form, and
3. A final small form enabling evacuation following drug release from the device.

Thus, gastroretentivity is improved by the combination of substantial dimension with high rigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach. Unfoldable and swellable systems have been investigated and recently tried to develop an effective gastroretentive drug delivery. 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. Swellable systems are also retained in the gastro intestinal tract (GIT) due to

their mechanical properties. The swelling is usually results from osmotic absorption of water and the dosage form is small enough to be swallowed by the gastric fluid. 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. Again, permanent retention of rigid, large single-unit expandable drug delivery dosage forms may cause brief obstruction, intestinal adhesion and gastropathy.

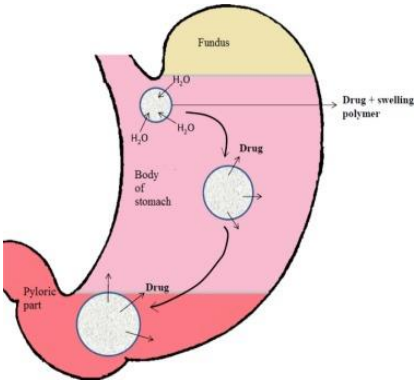

Figure 7: Swelling polymer

Super porous hydrogel systems

These swellable systems differ sufficiently from the conventional types to warrant separate classification. In this approach to improve gastric retention time (GRT) super porous hydrogels of average pore size >100 micro miter, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores. They swell to a large size (swelling ratio: 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is advised byco-formulation of hydrophilic particulate material [26].

Magnetic Systems

This approach to enhance the gastric retention time (GRT) is based on the simple principle that the dosage form contains a small internal magnet a magnet is placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance. Commonly used drugs in formulation of gastroretentive dosage forms and some gastroretentive products available in the market are listed in Table 1 respectively [27].

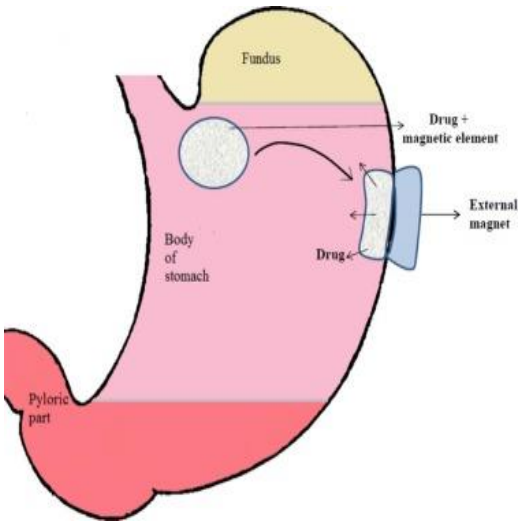

Figure 8: Magnetic systems

Table 1: Commonly used drugs in formulation of gastro retentive dosages form

Dosage forms	Drugs
Floating Tablets	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerzine, Chlorpheniramine maleate, Ciprofloxacin, Diltiazem, Fluorouracil, Isosorbidedinitrate, Isosorbidmononitrate, p-Aminobenzoic acid(PABA), Prednisolone, Nimodipine, Sotalol, Theophylline,Verapami
Floating Capsules	ChlordiazepoxideHCl, Diazepam, Furosemide, L-DOPA and Benserazide, Nicardipine, Misoprostol, Propranolol, Pepstatin
Microspheres	Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfenadine, Tranilast,Venlafaxine.
Floating Granules	Diclofenac sodium, Indomethacin, Prednisolone
Films	Cinnerzine

Anatomy of the gastro intestinal tract

The gastrointestinal tract can be divided intothree 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:9 The stomach is a Jshaped 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 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 [28].

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. From an engineering point of view, mucus is an outstanding water-based lubricant whose properties are extensively exploited within nature [29].

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%).

Themucin glycoprotein's form a highly entanglednetwork of macromolecules that associate withone another through non covalent bonds. Suchmolecular 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. 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 [30].

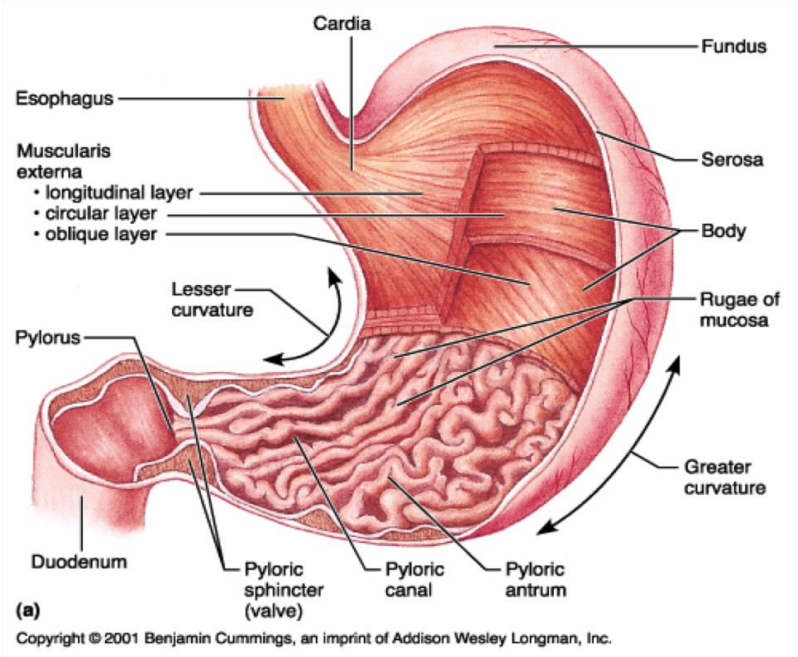

Figure 9: Anatomy of the gastro intestinal tract

Basic gastro intestinal tract physiology [31]

Anatomically the stomach is divided into 3regions:

1. Fundus,
2. Body,
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 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 interdigestivemyloelectric 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

Table 2: Four phases in migrating myoelectric complex (MMC): [32]

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 (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. Scintigraphy 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.

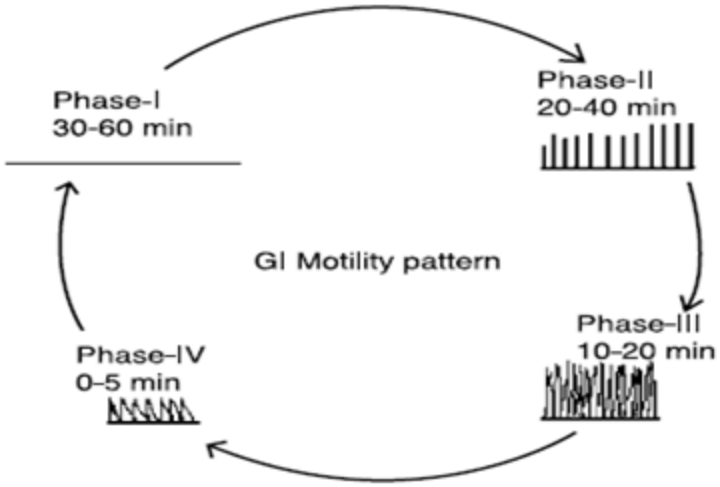

Figure 10: Schematic representation of the interdigestive motility pattern, frequency of contraction forces during each phase and average time Period for each period.

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,Venlafaxine.
- Exhibit low solubility at high pH values.

Advantages of gastro retentive drug delivery systems

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 [33].

Enhanced first-pass biotransformation

In a similar fashion to the increased efficiency 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 [34].

Sustained drug delivery/reduced frequency of dosing

For drugs with relatively short biological halflife, 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.

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 [35].

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.

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

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.

Extended time over critical (effective) concentration

For certain drugs that have non-concentration dependent pharmaco dynamics, 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 then pharmacological effects and improves the clinical outcomes.

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 pharmaco dynamic 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.

Site specific drug delivery

A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper small intestine [36]. 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 gastro retentive 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. Isosorbidedinitrate, Nifidiprine.
6. 6. Floating drug delivery systems require high fluid level in stomach to float and work effectively

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