

Pharmacophore

(An International Research Journal)

Available online at <http://www.pharmacophorejournal.com/>

Review Article

GASTRORETENTION: A MEANS TO ADDRESS LOCAL TARGETTING IN THE GASTRIC REGION

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ABSTRACT

The purpose of writing this review on gastroretention was to compile the recent literature on the development of gastroretentive drug delivery system (GRDDS). Prolonged gastric retention can be achieved by using floating, bio/mucoadhesive, swelling or high-density systems. GRDDS extend significantly the period of time over which the drugs may be released to most efficient site of absorption. By prolonging the gastric residence time of dosage forms, it is possible to target the gastrointestinal tract (GIT), mainly the stomach and the small intestine. This is of great importance for drugs for which absorption is limited to certain sites along the GIT or having local action in the certain sites of GIT. Thus these systems not only prolong dosing interval but also increase patient compliance beyond the level of existing controlled release dosage forms.

Keywords: Gastroretention, Floating, Gastrointestinal tract, Local targeting, Bioavailability.

INTRODUCTION

The idealized objective of any drug delivery pinpoints two critical aspects of utmost importance i.e. spatial placement and temporal delivery. Scientific advancement and technological sophistication have made possible for alteration and modulation of drug release characteristics so as to suit the need of a patient. Despite tremendous advancements in drug delivery, the oral route remains the preferred route for the administration of therapeutic agents because the cost of therapy and ease of administration lead to high level of patient compliance.^{1,2} Along with this, the controlled drug administration has been the most popular one, though brief gastrointestinal (GI) transit time in human, estimated to be 8-10 hours from mouth to colon, is a significant impediment in preparing

once a day dosage form for most drugs.³ An important requisite for the successful performance of oral controlled release drug delivery system (CRDDS) is that the drug should have good absorption throughout the gastrointestinal tract (GIT) to ensure continuous absorption of the released drug. However, the development process is precluded by several physiological difficulties, such as an inability to restrain and localize the delivery system within desired regions of the GIT and the highly variable nature of gastric emptying process.⁴ It can be anticipated that, depending upon the physiological state of the subject and the design of pharmaceutical formulation, the emptying process can last from a few minutes to 12 hours. This variability, in turn, may lead to unpredictable bioavailability and times to achieve peak plasma levels, since the majority of drugs are preferentially absorbed in the upper part of the

small intestine. Furthermore, the relatively brief gastric emptying time (GET) in humans, which normally averages 2-3 hours through the major absorption zone (stomach or upper part of the

intestine), can result in incomplete drug release from the delivery system, although slight variation exist among various dosage forms (see table 1)

Table 1: Transit time of various dosage forms across the segments of the GIT

Dosage forms	Transit time (hours)		
	Stomach	Small intestine	Total
Tablets	2.7±1.5	3.1±0.4	5.8
Pellets	1.2±1.3	3.4±1.0	4.6
Capsules	0.8±1.2	3.2±0.8	4.0
Solutions	0.3±0.07	4.1±0.5	4.4

Thus, control of placement of a drug delivery system in a specific region of the GIT i.e. gastroretention, a means to address local targeting in the gastric region⁴, offers numerous advantages^{1,5}, such as

- Prolongation of gastric residence time leads to better drug absorption.
- Improvement of bioavailability.
- Reducing frequency of dosing.
- Reducing the adverse effects in other body sites.
- Overall reduction in the health care cost.

Gastroretentive drug delivery system (GRDDS) has been desirable especially for drugs⁶

- Those are locally active in the stomach.
- Those have absorption window in the stomach.
- Those are unstable in the intestinal or colonic environment.
- Those have low solubility at high pH value.

Examples of drugs evaluated when incorporated into GRDDS: (see table 2)

Anatomical and Physiological Considerations

To comprehend the considerations taken in the design of GRDDS and to evaluate their performance the relevant anatomy and physiology of the gastrointestinal tract must be fully understood. The stomach is situated in the left upper part of the abdominal cavity immediately under the diaphragm. Its size varies according to the amount of distention: up to 1500ml following a meal; after food has emptied, a collapsed state is obtained with a resting volume of only 25-50ml.³⁰ Anatomically the stomach is divided into 3

regions: fundus, above the opening of the esophagus into the stomach; body, the central part; and antrum. The pylorus is an anatomical sphincter situated between the most terminal antrum and the duodenum. The proximal part, made of fundus and body, acts as a reservoir for undigested material temporarily, secrete digestive juices and propulse chyme, a milky mixture of food with gastric juices, to the antrum. The antrum is the main site for mixing motions grinds and triturates food particles and regulates the secretion of hydrochloric acid as well as act as a pump for gastric emptying by propelling actions.^{6,31,32} The pyloric sphincter has a diameter of 12.8±7 mm in humans and acts as a sieve as well as a mechanical structure to the passage of large particles.³³ The small intestine, comprising the duodenum, jejunum and ileum, is the principal site for the absorption of digestive products from the gastrointestinal tract. Extending from the stomach to the cecum of the large intestine, it is about 2.5-5.0 cm in diameter and approximately 6.0 meters in length. The first 25 cm of the small intestine is the duodenum, the main function of which is to neutralize gastric acid and pepsin and to initiate further digestive processes. The next segment of the small intestine, the jejunum, is the major part for food absorption. In addition to the great length of the small intestine, the available surface area is further enhanced by^{33,34}

- Circularly arranged folds of the mucosa and submucosa, called plica circulars, or valves of Kerckring (the plica are particularly numerous in the jejunum);

- Finger like projection, or villi, in the mucosa;
- Extensive microvilli (brush-border) on the surface of each intestinal lining cell;
- Invaginations of the mucosa between the bases of the villi into crypts, called the crypts of lieberkuhn.

These features boost the total surface area of the small intestine in humans approximately 463 m² which is comparable to the area of a basket ball court. This is the main reason it is the primary absorption site of water, ions, vitamins and nutrients such as amino acids, fats and sugars.

The ileum links the jejunum to the large intestine via the ileocaecal junction.

The large intestine (colon) is approximately 5cm. in diameter and 150cm. in length and extends from ileum of the small intestine to the anus. The large intestine has two main functions^{35,36}

- To absorb water and electrolytes.
- To store and eliminate fecal matter.

Factors such as pH, enzymes, nature and volume of secretions, residence time, and effective absorbing surface area of the site of delivery play an important role in drug liberation and absorption (see table 3).

Table 2: Anatomical and physiological features of GIT

Section	Average length(cm)	Diameter (cm)	Absorption mechanism	pH	Major constituents	Transit time(h)
Oral cavity	15-20	10	Passive diffusion	5.2-6.8	Amylase, maltase, mucin	Short
Stomach	20	15	Passive diffusion	1.2-3.5	Hydrochloric acid, pepsin, rennin, lipase, intrinsic factor	0.25-3.0
Duodenum	25	5	Passive diffusion, active transport, facilitated transport, ion pair, pinocytosis	4.6-6.0	Bile, trypsin, chymotrypsin, amylase, maltase, lipase, nuclease, CYP3A5	1-2
Jejunum	300	5	Passive diffusion, active transport, facilitated transport	6.3-7.3	Amylase, maltase, lactase, sucrase, CYP3A5	-
Ileum	300	2.5-5.0	Passive diffusion, active transport, facilitated transport, ion pair, pinocytosis	7.6	Lipase, nuclease, nucleotidase,	1-10
Cecum	10-30	7	Passive diffusion, active transport, pinocytosis	7.5-8.0	-	Short
Colon	150	5	Passive diffusion	7.9-8.0	-	4-20
Rectum	15-19	2.5	Passive diffusion, pinocytosis	7.5-8.0	-	Variable

Gastric pH

Gastric pH is an important consideration in selecting a drug substance, excipients, and drug carriers for designing intragastric delivery

systems. Radiotelemetry, a noninvasive device, has successfully been used to measure the gastrointestinal pH in human. The gastric pH is

not constant rather it is influenced by various factors like diet, disease presence of gases, fatty acids, and other fermentation products. This variation in pH may significantly influence the performance of orally administered drugs. It has been reported that mean value of gastric pH in fasted healthy subjects is 1.1 ± 0.15 . However, in fed state in healthy subjects are 3.6 ± 0.4 , and the pH returns to basal level in about 2 to 4 hours. Gastric pH may be influenced by age, pathological conditions and drugs. About 20% of the elderly people exhibit either diminished (hypochlorhydria) or no gastric acid secretions (achlorhydria) leading to pH value 5.0. pathological conditions such as AIDS may significantly reduce gastric acid secretion leads to

elevated gastric pH. In addition, drugs like H_2 receptor antagonists and proton pump inhibitors significantly reduce gastric acid secretion^{31, 32}.

Gastrointestinal motility patterns^{31, 32}

Based on fasted and fed state of the stomach, two distinct patterns of GI motility and secretions have been identified. As a result, the bioavailability of orally administered drugs will vary depending on the state of feeding. The fasted state is associated with various cyclic contractile events, commonly known as migrating myoelectric complex (MMC), which regulates GI motility patterns. The MMC is organized into alternating cycles of activity and quiescence and can be subdivided into four consecutive phases (see figure1)

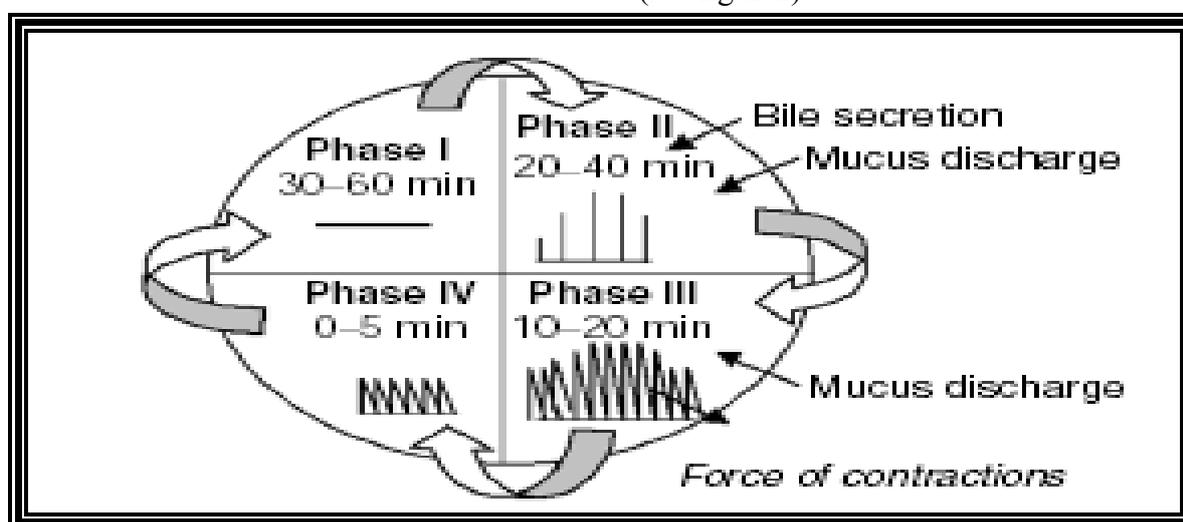


Figure 1: Motility patterns of the GIT

Phase I (basal phase): It is a quiescent period, lasts from 30 to 60 minutes with lack of secretory, electrical, and contractile activity. Phase II (preburst phase): It exhibits intermittent contractions, lasts from 20 to 40 minutes that gradually increase in intensity as the phase progresses. Bile enters the duodenum during this phase, whereas gastric mucus discharge occurs during the latter part of phase II and throughout phase III. Phase III (burst phase): It is characterized by intense distal and proximal gastric contractions, lasts from 10 to 20 minutes, also known as “housekeeper waves”, as it sweep all the undigested material out of the stomach down to the small intestine. Phase IV: It is a short transitory period, last from 0 to 5 minutes between phase III and I.

The different phases originating in the foregut continue to the ileum in a cycle in about 2 hours. Therefore, when one phase III reaches the ileum, another begins in the stomach and duodenum.

Factors Affecting Gastric Retention

Various methods have been applied- γ scintigraphy, radiology (x-ray), endoscopy, ultrasonography, radiotelemetry and magnetic marker monitoring in order to study the parameters affecting the process of gastric emptying and, hence, the gastric retention time of oral dosage forms include^{32, 37}:

- Density: The density of a dosage form also affects the gastric emptying rate. A buoyant dosage form, having a density of less than that of the gastric fluids, floats. A density of less than 1.0g/ml has been reported in the literature.

Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period.^{38, 39, 40} However, the floating force kinetics of such dosage forms has shown that the bulk density of a dosage form is not the most appropriate parameter for describing its buoyant capabilities. The buoyant capabilities are better represented and monitored by resultant weight measurements and swelling experiments.⁴¹

- Size and shape of dosage forms: Size and shape of dosage unit also affect the gastric emptying. Dosage form with a diameter of more than 7.5 mm have increased gastric retention time (GRT) compared with one having diameter of 9.9 mm. The shape of dosage form is also equally important as a formulation parameter. Tetrahedron and ring shaped devices have better GRT as compared with other shapes.^{39,40,42}
- Concomitant ingestion of food and its nature, caloric content and frequency of intake: Under fasting condition, the GI motility is characterized by periods of strong motor activity or MMC. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer. Feeding of indigestible polymers or fatty acid salts leads to increase the GRT. Increase in acidity and caloric value elevates GRT. Furthermore, GRT can be increased when successive meals are given compared with a single meal due to the low frequency of MMC.^{43, 44, 45}
- Simultaneous administration of drugs with impact on gastrointestinal transit time; for example, drugs acting as anticholinergic agents (e.g. atropine, propantheline), opiates (e.g. codeine) and prokinetic agents (e.g. metoclopramide, cisapride).
- Single or multiple unit formulation: multiple unit formulation show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release

profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

- Biological factors^{46, 47, 48}: Gender- Females have more GRT (4.6±1.2 h) compared with their age and race matched male counterparts (3.4±0.6 h), regardless of the weight, height and body surface.
- Posture- GRT can vary between supine and upright states of the patient. Studies were conducted in nonfasting human volunteers either in upright or in supine posture, who currently were given one optimized floating and one non-floating hydrophilic matrix capsules of the different sizes. In upright subjects, all the floating forms stayed continuously above the gastric contents irrespective of their size, whereas the non-floating units sank rapidly after ingestion and never rose back to the surface thereafter. Consequently, the floating forms showed prolonged and more reproducible GRTs compared to the non-floating forms. The significance and extent of prolongation were gradually lessened as the dosage form size increased, in case of non-floating forms. Moreover, in supine subjects, a size effect influenced the GRT of the floating and non-floating forms.^{49, 50, 51} Age- Elderly people have a significantly longer GRT.¹ Disease states- Diabetes and crohn's disease.¹

PHARMACOKINETIC AND PHARMACODYNAMIC ASPECTS OF GRDDS

These aspects are delineated in order to suggest rational selection of drugs for which controlled release gastroretentive dosage forms (CR-GRDF) would be a beneficial strategy (Hoffman A. *et al* 2004).

Pharmacokinetic Aspects

Absorption window validation

Most suitable category of the drugs for CR-GRDF is molecules that have poor colonic absorption but are better absorbed through the upper part of the GIT. Such drugs are said to have an absorption window.

Enhanced bioavailability

Once the drug has been validated as narrow absorption window, the possibility of improvement in bioavailability by continuous release of the drug to the specific site should be tested. For example, the bioavailability of riboflavin and levodopa CR-GRDF is significantly enhanced in comparison to non-GRDF CR polymeric formulations.⁵³

Reduced frequency of dosing

The drug which one having short biological half-life, sustained and slow delivery from CR-GRDF may result in a flip-flop pharmacokinetics and can reduce the frequency of dosing.

Targeted therapy for local ailments in upper GIT

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

Pharmacodynamic Aspects

Reduced fluctuation of drug concentration

Slow and continuous release from CR-GRDF maintains blood drug concentration within a narrow range. Thus, peak and valley plasma concentration-time profile can be minimized as occurs in case of conventional dosage form.

Extended time over effective concentration

For some drugs such as beta- lactam antibiotics, a minimum effective concentration should be maintained at all times as the clinical response is not associated with peak concentration, but with the duration of time of effective concentration.

Minimized adverse activity in other body sites

Retention of the drugs in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, adverse effects of the drugs in colon may be prevented. For example, beta-lactam antibiotics are absorbed only from small intestine, and whose release in colon leads to microorganism's resistance.

Improved selectivity in receptor activation

Minimization of fluctuation in the drug concentration enables certain selectivity in the elicited pharmacodynamic effects of drugs that activate different types of receptors at various concentrations.

Reduced counter-activity of the body

Many of the pharmacodynamic response provoke a rebound activity of the body that minimizes drug action, causes tolerance. Slow input of the drug e.g. furosemide, from a GRDF has been shown to minimize the counter activity.

APPROACHES TO GASTRIC RETENTION

Over the last decades, various approaches have been pursued to increase the gastroretention of dosage forms (see figure 2).

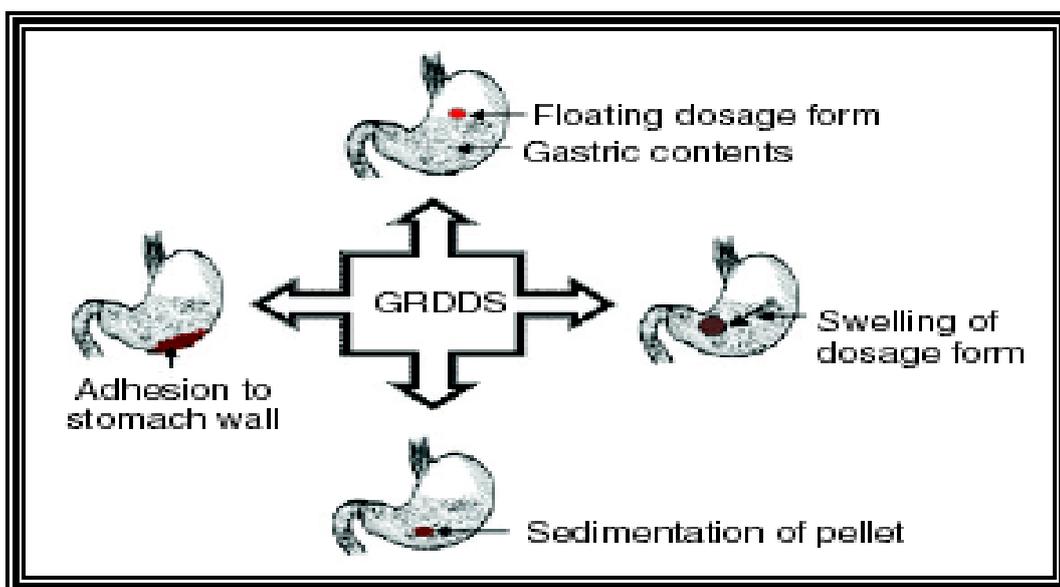


Figure 2: Approaches to gastroretentive drug delivery system

Floating system

Floating drug delivery system have a bulk density less than gastric fluid and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased GRT and reduces fluctuation in plasma drug concentration.^{54, 55}

Some of the marketed formulations are:

- **Valrelease-** Floating capsule of diazepam
- **Madopar-** Benserazide and L-Dopa combination formulation
- **Liquid Gaviscon-** Floating liquid alginate preparation
- **Topalkan-** Aluminium-magnesium antacid preparation
- **Almagate Flot-Coat-** Antacid preparation
- **Cifran OD-** floating tablet of Ciprofloxacin

Effervescent floating system

The buoyant delivery system utilizes matrices prepared with swellable polymers such as methocel or polysaccharides like chitosan, effervescent components like sodium bicarbonate and citric acid or tartaric acid. The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated and is entrapped in the hydrocolloid gel. This lead to an upward drift of the dosage forms and maintains it in floating condition.^{56, 57} The carbon dioxide generating components may be intimately mixed within the tablet matrix as a single-layered tablet or a bilayered tablet may be compressed which contains the gas generating mechanism in one hydrocolloid containing layer and the drug in the outer layer formulated for a sustained effect. Ischikawa et al developed a new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers surrounded on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into two sublayers to avoid direct contact between two agents. These sublayers were surrounded by a swellable polymer membrane containing

polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37°C, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. Carbon dioxide was generated by the neutralization reaction between the two effervescent agents, producing swollen pills with density less than 1.0g/ml.

Noneffervescent floating system

This buoyant delivery system, after swallowing, swells unrestrained via imbibition of gastric fluid to an extent that it prevents their exit from the stomach. The most commonly used excipients are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene.^{59,60} One of the approaches to the formulation of such floating dosage forms involves intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. The so formed swollen gel- like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.⁶¹ Nur and zhang developed floating tablets of captopril using HPMC K4M and carbopol 934P. They concluded that tablets of 2kg/cm² hardness floated immediately after immersion into floating media and tablets with hardness 4kg/cm² sank for 3 to 4 minutes and then came to the surface; however both tablets remained floating for 24 hours. The tablets with 8 kg/cm² hardness showed no floating capability. It was concluded that the buoyancy of tablet is governed by both the swelling of the hydrocolloid particles on the tablet surface and the presence of internal voids in the center of tablet when it comes to the contact of gastric fluid. Bodmeier et al prepared single unit floating matrix tablets based on polypropylene foam powder and matrix forming polymer and demonstrated the in-vitro floating performance and the ability to control drug release over

prolonged periods of time. Sheth et al developed an HBS system containing a homogeneous mixture of drug and the hydrocolloid in a capsule, which upon contact with gastric fluid acquired and maintained a bulk density of less than 1.0 thereby remain buoyant on the gastric contents of stomach until all the drug was released. Floating alginate beads, floating microparticles, microspheres, microballoons were also developed to achieve the gastric retention.

Bio/ mucoadhesive system

It is a potential approach to extend the gastric residence time based on GI self-protective mechanism. The self-protective mechanism of surface epithelium of stomach and small intestine is due to secretion of large amount of mucus through "goblet cells". Bio/mucoadhesive systems bind to the gastric epithelial cell surface and extend the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membrane. A bio/mucoadhesive substance is a natural or synthetic polymer capable of adhering to a biological membrane (bioadhesive polymer) or the mucus lining of the GIT (mucoadhesive polymer). These polymers should have molecular properties such as hydrophilic functional group, molecular flexibility, a specific molecular weight, chain length and confirmation. Polymers such as different viscosity grades of carboxymethylcellulose, carbopol, chitosan, alginic acid, polyethylene glycol, dextran shows a high level of adhesion.⁶² Akiyama and Nagahara proposed the use of muco-adhesive microspheres consisting of a drug and carbopol 934P, dispersed within a waxy matrix of polyglycerol esters of fatty acids.

Swelling system

The dosage forms swell to a size that prevents their passage through the pyloric sphincter resulting in the retention of dosage forms in the stomach for prolonged period. These systems are also referred to as plug type systems as these tend to remain lodged at pyloric sphincter. However, a balance between the rate and extent of swelling and the rate of erosion of the polymer is crucial to

achieve optimum benefits and to avoid unwanted side effects. Selection of the polymer with the proper molecular weight and swelling properties is an important criterion. Upon coming in contact with gastric fluid, the polymer imbibes water and swells as a result of cross-linking in the hydrophilic polymer network. An optimum amount of cross-linking is required to maintain a balance between swelling and dissolution.⁶⁶ Mamajek and Moyer patented a drug reservoir, surrounded by a swellable expanding agent. The whole system was coated by an elastic outer polymeric membrane, which was permeable to both the drug and body fluids and could control the drug release. The device gradually decreased in volume and rigidity as a result of depletion of drug and expanding agent and/ or bioerosion of the polymer envelope, enabling its elimination. Urquhart and Theeuwes developed a system containing tiny pills, with a very high swelling ratio enabling upto 50 fold volume increases. These pills were coated by wax to control drug release and dispersed in a matrix of polymeric hydrogel. In body fluids, the system swelled and the tiny pills released the drug in the stomach. The reservoir could leave the stomach following hydrolysis and bioerosion.

High density systems

High density systems, with a density of $\sim 3\text{g/cm}^3$ are intended to lodge in the rugae of the stomach body near the pyloric region, which is the part of the organ with the lowest position, and are capable of withstanding the peristaltic movements of stomach wall. Clarke et al. reported that the critical density to prolong the gastric residence of pellets ranges between 2.4 to 2.8 g/cm^3 . With pellets, the GI transit time can be extended from an average of 5.8 to 25 hours, depending more on density than on diameter of the pellets. However, in-vivo data do not confirm the effectiveness of this system, as the primary determining factor of gastric emptying is the state of stomach when it is administered.⁶⁹ Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder.

EVALUATION OF GRDDS

To evaluate any drug product for ensuring its performance and controlling the batch to batch quality, the routine test such as for general appearance, weight variation, hardness, friability, drug content and drug release must be performed. Along with these test, the gastro retentive performance of GRDDS must be evaluated.⁷⁰

Floating system

Floating properties

The time taken by the tablet to emerge on the water surface (floating lag time) and the duration the tablet constantly floats on the water surface (duration of floating) were determined in a dissolution vessel filled with 900 ml of simulated gastric fluid without pepsin (pH 1.2) maintained at 37°C using the USP dissolution apparatus.¹

Specific gravity

The specific gravity of floating system can be determined by the displacement method, using benzene as a displacing medium.⁷¹

Resultant weight

Besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight (RW) has been reported in the literature.⁵⁴ This apparatus measures the force equivalent to F (as a function of time) that is required to maintain the submerged object. The objects floats better if RW is on the higher positive side.

$$\begin{aligned} \text{RW or } F &= F_{\text{buoyancy}} - F_{\text{gravity}} \\ &= (d_f - d_s) g V \\ &= (d_f - M/V) g V \end{aligned}$$

Where RW= total vertical force, d_f = fluid density, d_s = object density, V= volume, g = acceleration due to gravity.

Bio/ mucoadhesive system

Bioadhesion measurements

A modified balance method is used to measure the force required to separate the sample disk, which is fixed between the base of cyanoacrylate adhesive and mucosal membrane of sheep or rabbit.⁷²

Swelling system

Weight gain and water uptake (WU)

Weight gain WU can be measured by immersing the dosage form in simulated gastric fluid at 37°C and determining these factors in terms of increase in tablet diameter and/ or thickness over time at regular intervals.

$$WU = (W_t - W_0) \times 100 / W_0$$

In which W_t and W_0 are the weights of the dosage form at time t and initially, respectively.⁷³ Furthermore, the GRDDS should be evaluated for in- vitro drug release and in- vivo visualization.

In- vitro drug release

In- vitro drug release studies are conducted using the USP paddle method by placing the dosage form in 900 ml preheated medium (0.1 N HCl buffer solution, pH 1.2, 37°C) and stirred at 100 rpm. The dissolution samples are withdrawn periodically, with replacement and diluted and the concentrations are determined on a spectrophotometer at selected wavelength.

Imaging and direct observation techniques for evaluation of GRDDS properties

In order to optimize the performance of GRDDS, a thorough in- vivo characterization should be conducted. γ – scintigraphy using γ – emitting radioisotopes compounded into dosage forms has become the state-of-art for evaluation of gastrointestinal transit times in healthy volunteers.⁷⁴ A small amount of a stable isotope e.g. ¹⁵²Sm is compounded into the DF during its preparation. Radiology is the state-of-art in preclinical evaluation of gastroretentivity. However, use of X-ray in biopharmaceutical studies involving healthy volunteers⁷⁵ has declined. A commonly used contrast agent is barium sulfate, often used in high concentration e.g. 40% or more.⁷⁶ In order to reduce the formulative change while attaining in- vivo imaging, contrast aluminium threads obtained from surgical gauze pads have been compounded into GRDDS during their preparation. Gastroscopy is peroral endoscopy, used with fiberoptic or video systems. It is applied for diagnosis e.g. of gastric ulcer.⁷⁷ It is suggested

that gastroscopy may be used to inspect visually the effects of prolonged stay in the stomach milieu on the GRDDS. Another technique, magnetic marker monitoring, follows magnetically marked dosage forms by magnetic source imaging and therefore requires very sensitive biomagnetic measurement equipment. The method has no radiation exposure and is completely safe.^{78,79} It enables assessment of the intragastric location of the dosage forms.⁸⁰

LIMITATION

GRDDS have great potential in improving the bioavailability of drugs that have an absorption window, but also have certain limitations. The major disadvantage of floating systems is requirement of a sufficiently high level of fluids in the stomach for the drug delivery.⁸¹ The dosage forms should be administered with a minimum of glass full of water (200 to 250 ml). In case of bioadhesive systems, high turnover rate of mucus aggravate the problem and also continuous attachment to mucosa leads to irritation. For swellable system, it must maintain a size less than the aperture of pyloric sphincter and may also cause bowel obstruction, intestinal adhesion and gastroplasty. For high-density system, the major drawback is the difficulty to manufacture them with a large amount of drug (>50%) and we are not able to maintain such a high density for long duration and no successful high-density system yet in market. Moreover, GRDDS are not appropriate for the drugs that have solubility or stability problem in gastric fluid or that are irritants to the gastric mucosa (e.g. NSAIDs) or those are absorbed throughout the GIT and those undergo significant first pass metabolism (e.g. nifedipine).^{82, 83}

Application of floating drug delivery system

- Recent study indicated that the administration of Diltiazem floating tablets twice a day might be more effective compared to normal tablets in controlling the Blood pressure of hypertensive patients.
- Modapar® HBS containing L-Dopa and Benserazide, here the drug was absorbed

over a period of 6-8 hours and maintained substantial plasma concentration for Parkinsonian patients. Cytotech® - containing Misoprostol, a synthetic prostaglandin -EL analogue, for prevention of gastric ulcer caused by non-steroidal anti-inflammatory drugs (NSAIDs).

- As it provides high concentration of drug within gastric mucosa, it is used to eradicate *H. pylori* (a causative organism for chronic gastritis and peptic ulcers).
- 5-fluorouracil has been successfully evaluated in the patients with stomach neoplasm.
- Developing HBS dosage form for tacrin provide better delivery systems and reduced its GI side effects.
- Treatment of gastric and duodenal ulcer.

Future potential

- Floating dosage form offers various future potential as evident from several recent publications. The reduced fluctuations in the plasma level of drug results from delayed gastric emptying.
- Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailability.
- Buoyant delivery system considered as a beneficial strategy for the treatment of gastric and duodenal cancers.
- The floating concept can also be utilized in the development of various anti-reflux formulations.
- Developing a controlled release system for the drugs, which are potential to treat the Parkinson's disease.
- To explore the eradication of *Halico-bector pylori* by using the narrow spectrum antibodies.

CONCLUSION

In this review an attempt is made to summarize controlled / sustained release drug delivery

system with prolonged gastric residence time. Gastric retention is useful for drugs having absorption window and/or local action in stomach. A careful consideration of physiological

events of GIT, physiological properties of the drug and formulation strategies make it possible for local targeting of the drugs in specific site of GIT.

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