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Gastroretentive Drug Delivery System for Floating Tablet- A Review

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ABSTRACT

Over the years, oral dosage forms have become increasingly sophisticated with major role being played by control release drug delivery system. CRDDS release drug at a predetermined rate, as determined by drug's pharmacokinetics and desired therapeutic concentration. This help in achieving predictable drug plasma concentration required for therapeutic effect. Gastroretentive 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. Gastroretentive 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 gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach, low density (floating) systems that causes buoyancy in gastric fluid, mucooadhesive systems that causes bioadhesion to stomach mucosa , unfold able, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach, superporous hydrogel systems , magnetic systems etc.

Keywords: Gastroretentive, Floating systems, Control release, Site-specific drug release.

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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. This route has high patient acceptability, primarily due to ease of administration. Over the years, oral dosage forms have become increasingly sophisticated with major role being played by control release drug delivery system (CRDDS). CRDDS release drug at a predetermined rate, as determined by drug's pharmacokinetics and desired therapeutic concentration. This help in achieving predictable drug plasma concentration required for therapeutic effect. The successful functioning of an oral CRDDS is determined by-

1. Physicochemical properties of the drug molecule like, the aqueous solubility, intestinal permeability, pH- solubility profile, etc.
2. Pharmacokinetic profile of the drug.
3. The interaction of these properties with the anatomy and physiology of the GI tract.[1]

One such requisite for successful performance of oral CRDDS is that the drug should have the good absorption throughout the GI tract, preferably by passive diffusion. Drugs that are easily absorbed from gastrointestinal 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.[2] 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 gastrointestinal tract (GIT) [3]. 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.[4] To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a 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. Also prolonged

gastric retention time (Stomach could be advantageous for local action in the upper part of the small intestine e.g. treatment of peptic ulcer) etc. Gastroretentive 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. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs.[5] Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach, low density (floating) systems that causes buoyancy in gastric fluid [6] mucooadhesive systems that causes bioadhesion to stomach mucosa , unfold able, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach, superporous hydrogel systems , magnetic systems etc.

These efforts resulted in GRDFs that were designed, in large part, based on the following approaches.

(a) Low density form of the DF that causes buoyancy in gastric fluid.

(b) High density DF that is retained in the bottom of the stomach.

(c) Bioadhesion to stomach mucosa.

(d) Slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients.

(e) Expansion by swelling or unfolding to a large size which limits emptying of the DF through the pyloric sphincter. [7]

Basic Gastrointestinal Tract Physiology-

It is well recognized that the stomach may be used as a ‘depot’ for sustained-release (SR) dosage forms both in human and veterinary applications. The stomach is anatomically divided into three parts: that occurs fundus, body, and antrum (or pylorus). The proximal stomach, made up of the fundus and body regions, serves as a reservoir for ingested materials while the distal region (antrum) is the major site of mixing motions, acting as a pump to accomplish gastric emptying.[8]

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 inter digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the inter digestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 in the phases as described by Wilson and Washington. [9]

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.

2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

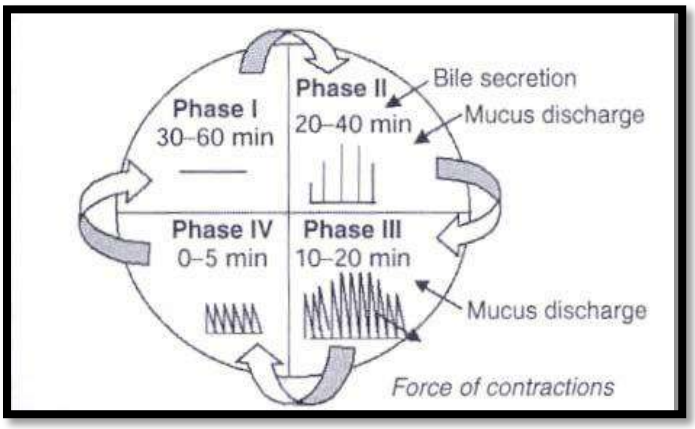

Figure. 1: Motility pattern in GIT

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state.[10] also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.

Suitable Drug Candidates for Gastroretention [11]

In general, appropriate candidates for GRDDS are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT:

1. Narrow absorption window in GI tract, e.g., riboflavin and levodopa.

2. Primarily absorbed from stomach and upper part of GI tract, e.g., calcium supplements, chlordiazepoxide and cinnaraz.

3. Drugs that act locally in the stomach, e.g., antacids and misoprostol

4. Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole

5. Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.

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 acid and corticosteroids etc.

Physiological factors controlling gastric retention of dosage forms:

The gastric retention time (GRT) of dosage forms is controlled by several factors such as density and size of the dosage form, food intake, nature of the food, posture, age, sex, sleep and disease state of the individual (e.g., gastrointestinal diseases and diabetes) and administration of drugs such as prokinetic agents (cisapride and metoclopramide).

Density of dosage form-

Dosage forms having a density lower than that of gastric fluid experience floating behavior and hence gastric retention.[12] A density of <1.0 gm/cm3 is required to exhibit floating property. However, the floating tendency of the dosage form usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium.[13]

Size of dosage form-

The size of the dosage form is another factor that influences gastric retention. The mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size, which may be small, medium, and large units. [14] In fed conditions, the smaller units get emptied from the stomach during the digestive phase and the larger units during the housekeeping waves. In most cases, the larger the size of the dosage form, the greater will be the gastric retention time because the larger size would not allow the dosage form to quickly pass through the pyloric antrum into the intestine. Thus the size of the dosage form appears to be an important factor affecting gastric retention.[15]

Food intake and nature of food

Food intake the nature of the food, caloric content and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the stomach influences the GRT of the dosage form. Usually, the presence of food increases the GRT of the dosage form and increases drug absorption by allowing it to stay at the absorption site for a longer time. The above results are supported by the experiments of Whitehead et al which show an increase in the relative heights of the floating units after meal consumption. Food habits affect the GRT in the following ways:-

Fed or unfed state –

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. 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 of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer. It was concluded that as meals were given at the time when the previous digestive phase had not completed, the floating form buoyant in the stomach could retain its position for another digestive phase as it was carried by the peristaltic waves in the upper part of the stomach.

Nature of meal –

Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

Caloric content –

GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.

Frequency of feed –

The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.[16]

Effect of gender, posture and age –

A study found that females showed comparatively shorter mean ambulatory GRT than males, and the gastric emptying in women was slower than in men. The authors also studied the effect of posture on GRT, and found no significant difference in the mean GRT for individuals in upright, ambulatory and supine state. On the other hand, the floating and nonfloating systems behaved differently. In the upright position, the floating systems floated to the top of the gastric contents and remained for a longer time, showing prolonged GRT. But the non-floating units settled to the lower part of the stomach and underwent faster emptying as a result of peristaltic contractions, and the floating units remained away from the pylorus. However, in supine position, the floating units are emptied faster than non-floating units of similar size.[17]

Effect of buoyancy—

On comparison of floating and nonfloating dosage units, it was concluded that regardless of their sizes the floating dosage units remained buoyant on the gastric contents throughout their residence in the gastrointestinal tract, while the non-floating dosage units sank and remained in the lower part of the stomach. Floating units away from the gastro duodenal junction were protected from the peristaltic waves during digestive phase while the nonfloating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase.

TYPES OF GASTRORETENTIVE DOSAGE FORM:

Floating system –

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. FDDS can be divided into non-effervescent and effervescent system.

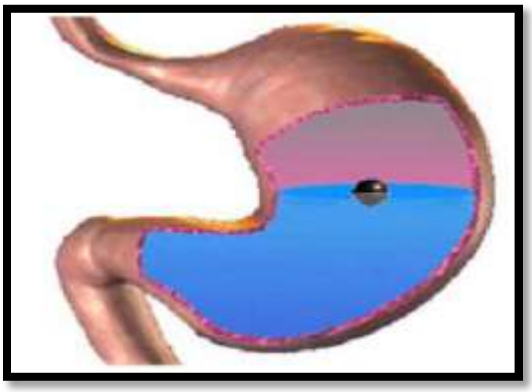

Figure 2: Floating System

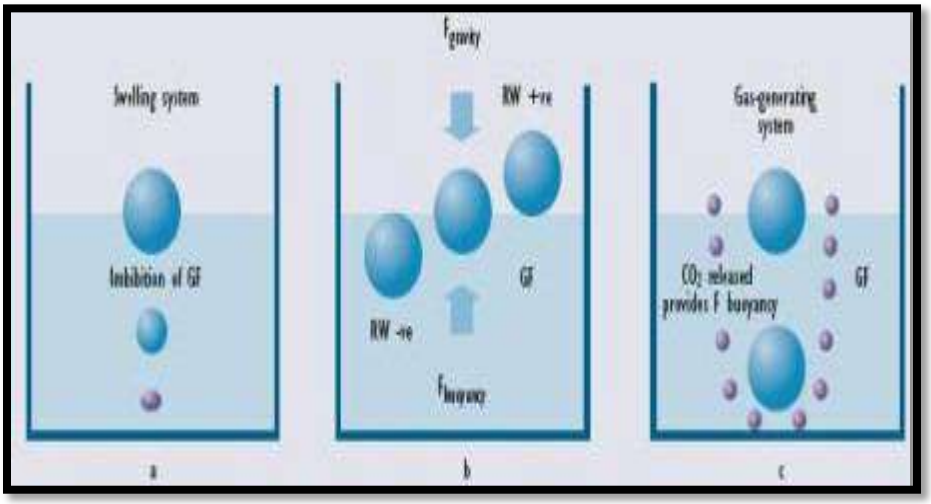

Figure. 3: The mechanism of floating systems

Non effervescent systems:

This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. One of the formulation methods of such dosage forms involves the mixing of the drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barriers.[18]

The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. This system can be further divided into four subtypes:

Colloidal gel barrier system-

Sheth and Tossounian first designated this 'hydrodynamically balanced system's. Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption. This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g., hydroxypropyl cellulose, hydoxyethyl cellulose, hydroxypropyl methyl cellulose (HPMC), polysacharides and matrix-forming polymer such as polycarbophil, polyacrylate and polystyrene. On coming in contact with gastric fluid, the hydrocolloids in the system hydrate and form a colloid gel barrier around its surface.[19]

Microporous compartment system-

This technology is based on the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.[20]

Alginate beads –

Multi-unit floating dosage forms have been developed from freeze dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40ºC for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hours.[21]

A)Hollow microspheres (microballoons) –

Hollow microspheres loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent diffusion method. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by

the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 h.

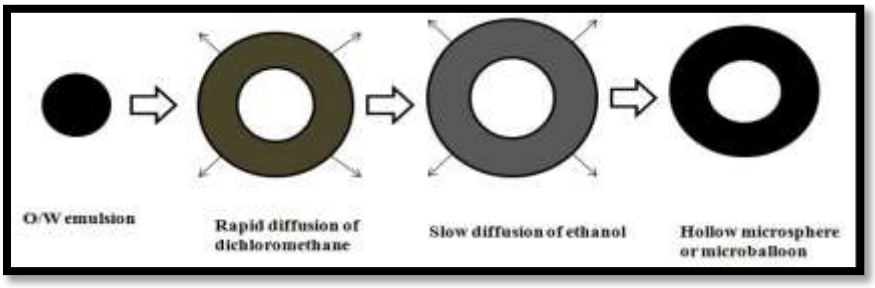

Figure. 4: Hollow microspheres

Effervescent systems-

These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). The system is so prepared that upon arrival in the stomach; carbon dioxide is released, causing the formulation to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate[22], multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinylpyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology, etc.

a. Volatile liquid containing systems-

These type of systems consist of two chambers separated by an impermeable, pressure-responsive, movable bladder. The first chamber contains the drug and the second chamber concotains the volatile liquid. The device inflates, and the drug is continuously released from the reservoir into the gastric fluid.

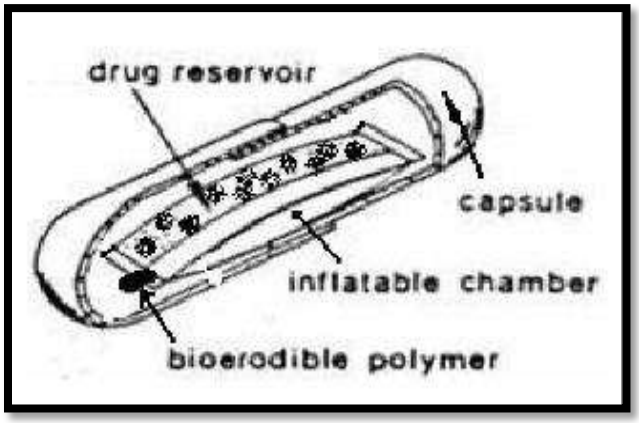

Figure. 5: Volatile liquid containing system

b. Gas – generating systems-

These buoyant delivery systems utilize effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the gellified hydrocolloid layer of the systems, thus decreasing its specific gravity and making it float over chime.

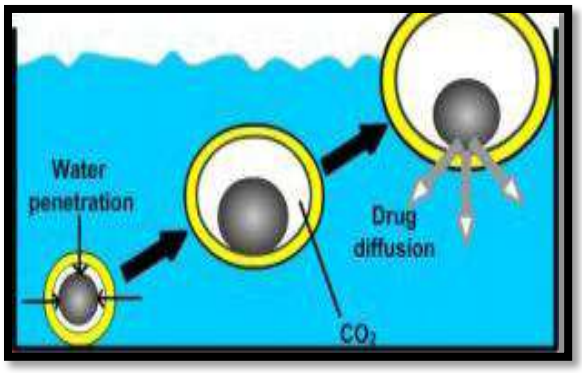

Figure. 6: Principle mechanism of floating by CO2 gas releasing method

Bio/muco–adhesive systems –

Bioadhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a site specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach.[23] Gastric mucoadhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastroretentive force. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan and gliadin, etc.

Mechanism of bio/muco-adhesion-

Binding of polymers to the mucin/epithelial surface can be divided into three categories:

a). Hydration – mediated adhesion-

Certain hydrophilic polymers have the tendency to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties. The prolong

ed gastroretention of the bio/muco-adhesive delivery system is further controlled by the dissolution rate of the polymer.

b). Bonding –mediated adhesion-

Adhesion of polymers to mucus/epithelial cell surface involves varying bonding mechanism. Physical or mechanical bonds can result from deposition and inclusion of the adhesive material in the crevices of the mucusa. Secondary chemical bonds, contributing to bioadhesive properties,

consist of dispersive intractions (i.e. van der Walls intractions) and stronger specific intraction, which include hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl (--OH) and the carboxylic groups (--COOH).[24]

c). Receptor – mediated adhesion-

Certain polymers have the ability to bind to specific receptor sites on the cell surface. The receptor mediated events serves as a potential approach in bio/muco- adhesion, hence enhancing the gastric retention of dosage forms. Certain plant lectins, like tomato lectins, interact specifically with the sugar groups present in mucus or on the glycocalyx.[25]

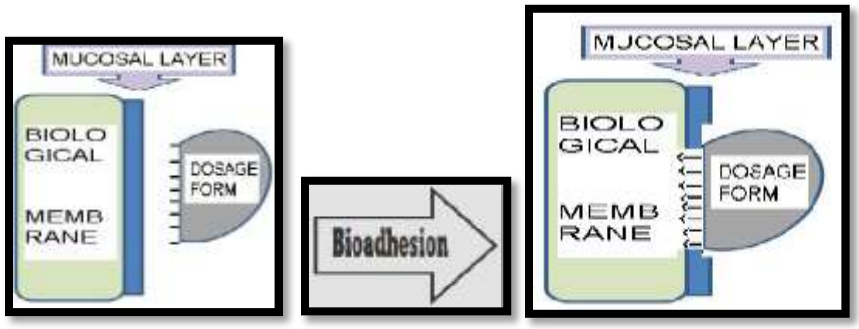

Figure. 7: Bio-adhesion system

Swelling systems –

These are the dosage forms, which after swallowing; swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as “plug type systems”, since they exhibit the tendency to remain lodged at the pyloric sphincter. The formulation is designed for gastric retention and controlled delivery of the drug into the gastric cavity.[26] Such polymeric matrices remain in the gastric cavity for several hours even in the fed state. Sustained and controlled drug release may be achieved by selection of proper molecular weight polymer, and swelling of the polymer retards the drug release. On coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive of these polymers is due to the presence of physical/chemical cross-links in the hydrophilic polymer network.

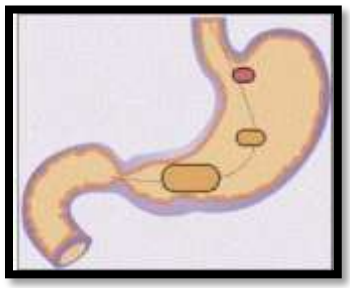

Figure. 8: Swellable tablet in stomach

High density systems –

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Dense pellets (approximately 3g/cm-3) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on the diameter of the pellets[27]. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to 1.5–2.4g/cm-3.

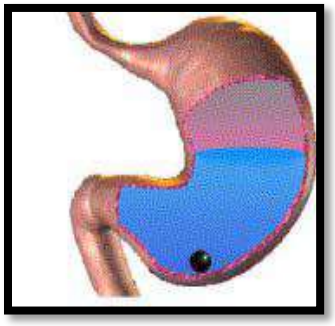

Figure. 9: High density systems

Magnetic system –

This approach to enhance the gastric retention time (GRT) is based on the simple principle that the dosage form contains a small internal magnet, and a magnet 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.

Table 1 - Polymers and other Ingredients Used in the Formulation of GRDDS[33,34]

Category	Materials
Polymers	HPMC K4 M, Calcium alginate, Eudragit S100 Eudragit RL, Propylene foam, Eudragit RS, ethyl cellulose, polymethyl methacrylate, Methocel K4M, Polyethylene oxide, β Cyclodextrin, HPMC 4000, HPMC 100, CMC, Polyethylene glycol, polycarbonate, PVA, Polycarbo-nate, Sodium alginate, HPC-L, CP 934P, HPC, Eudragit S, HPMC, Metolose S.M. 100, PVP, HPC-H, HPC-M, HPMC K15, Polyox, HPMC K4, Acrylic polymer, E4 M and Car-bopol
Inert fatty materials (5%-75%)	Edible, inert fatty materials having a specific gravity of less than one can be used to decrease the hydrophilic property of formu-lation and hence increase buoyancy. E.g. Beeswax, fat-ty acids, long chain fatty alcohols, Gelucires® 39/01 and 43/01.

Effervescent agents	Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di- Sodium Glycine Carbo-nate, CG (Citroglycine)
Release rate accelerants (5%-60%)	lactose, mannitol
Release rate retardants (5%-60%)	Dicalcium phosphate, talc, magnesium stearate
Buoyancy increasing agents (upto80%)	Ethyl cellulose
Low density material	Polypropylene foam powder (Accurel MP 1000®)

ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

Enhanced bioavailability[28] **-**

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.

Enhanced first-pass biotransformation[28] **–**

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.

Sustained drug delivery/reduced frequency of dosing [29] **-**

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.

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.

Reduced fluctuations of drug concentration[29] **–**

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.

Improved selectivity in receptor activation[30] **–**

Minimization of fluctuations in drug concentration also makes it possible to obtain certain

selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

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[30]**-**

For certain drugs that have non-concentration dependent Pharmacodynamics, such as beta-lactam 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.

Minimized adverse activity at the colon[31]**-**

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 pharmacodynamics 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 intestine30. 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.

CONCLUSION

GRDDS have potential in improving BA of drugs exhibiting 'absorption window'. However they have certain limitations i.e. The floating systems in patients with achlorhydria can be questionable in case of swellable systems, faster swelling properties are required and complete swelling of the system should be achieved well before the gastric emptying time. Not suitable for drugs that may cause gastric lesions e.g. Non- steroidal anti inflammatory drugs. One of the major disadvantages of the floating system is the requirement of high levels of fluids in the stomach for the delivery system to float and work efficiently. [32]

1. Require a higher level of fluids in the stomach.

2. Not suitable for Drugs that.

a. Have solubility problems in gastric fluid .E.g- phenytoin.

b. Cause G.I irritation. Eg: NSAIDS.

c. Are unstable in acidic environment.

3. Drugs intended for selective release in the colon E.g. 5- amino salicylic acid and corticosteroids etc.

4. The floating systems in patients with achlorhydria can be questionable in case of swellable system.

5. Retention of high density systems in the atrium part under the migrating waves of the stomach is questionable.

6. The mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.

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