1. INTRODUCTION

1.1. Floating drug delivery system

Oral administration is the most convenient mode of drug delivery and is associated with superior patient compliance as compared to other modes of drug intake. However, oral administration has only limited use for important drugs, from various pharmacological categories, that have poor oral bioavailability due to incomplete absorption and/or degradation in the gastrointestinal (GI) tract. Some of these drugs are characterized by a narrow absorption window (NAW) at the upper part of the gastrointestinal tract. This is because of proximal part of the small intestine exhibits extended absorption properties (including larger gaps between the tight junctions, and dense active transporters). Despite the extensive absorption properties of the duodenum and jejunum, the extent of absorption at these sites is limited because the passage through this region is rapid. Enhancing the gastric residence time (GRT) of a NAW the drug may significantly improve the net extent of its absorption.¹

![Diagram of drug release mechanism and floating drug delivery system]

Figure 1.1: (a) Drug release mechanism and (b) Floating drug delivery systems
Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus small intestinal transit time is an important parameter for drugs that are incompletely absorbed.

Floating drug delivery systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastric retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agent that delay gastric emptying.

Floating systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged
period of time. While the system is floating on the gastric contents, the drug is released slowly at 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. However, 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 reliably buoyant on the surface of the meal (Figure 1). Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres.

1.1.1 Concept of absorption windows

Absorption windows in the proximal gut can limit the bioavailability of orally administered compounds and can be a major obstacle to the development of controlled release formulations for important drugs. Methods to increase the residence of drug formulations at or above the absorption window are bioadhesive microspheres that have a slow intestinal transit and the floating drug delivery system, which is based on multiparticulates or large single unit systems. A good understanding of gastrointestinal transit in humans and the effect of factors such as food can be helpful in the design of rational systems that will have clinical benefit.

Pharmaceutical dosage forms with gastro retentive properties would enable an extended absorption phase of these drugs with narrow absorption window. After oral administration, dosage form would be retained in stomach and release drug there, in a controlled and prolonged manner so that drug could be supplied continuously to its absorption sites in upper GIT. Another interesting importance for the dosage form with prolonged residence time in the stomach is drugs are locally active in the stomach e.g. drugs used in the eradication of helicobacter pylori, which is now
believed to be the causative bacterium for chronic gastritis and peptic ulcer, drugs are unstable in the intestinal or colonic environment and drugs have a low solubility at high pH values.

1.1.2. Gastro intestinal transit

The transit of a drug in formulation through the GI tract will determine how long a compound will be in contact with its preferred absorptive site. In humans, the small intestine transit time is reasonably constant at around three hours for a drug formulation or for a meal to pass from the stomach to the ileocaecal junction. Transit through the colon is much longer and can be twenty hours or more. Hence, the time a drug will have in its absorption window can be relatively short, more so if the drug is preferentially absorbed in the proximal small intestine (e.g. jejunum) rather than throughout the small bowel consequently, the bioavailability of a drug, which is largely or excessively absorbed from the upper GI tract will be affected by factors that change GI transit.

Some important drugs have absorption windows in the small intestine and, as a result, they often display low bioavailability after oral dosing. In addition, they are difficult to formulate into extended release products because on arrival in the colon, absorption will be low or non-existent. Efforts have been made to improve absorption, and various different strategies have been described in the scientific literature and in published patents.

1.1.3. Basic anatomy and physiology of stomach
Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions\textsuperscript{15}.

![Stomach Diagram]

**Figure 1.2: Schematic illustration of the stomach anatomical structure**

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 both through stomach and intestine every 2 to 3 hours\textsuperscript{16}.

This is called the interdigestive myoelectric cycle (IMC) or migrating myoelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington\textsuperscript{17}.

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

2. **Phase II** (pre-burst 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 und digested 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.

![Diagram of gastric emptying phases](image)

**Figure 1.3: Phases involved in gastric emptying**

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 II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled towards the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate\(^\text{18}\).
1.1.4. Gastric motility and emptying of food from stomach

The stomach produces coordinated movements of the gastric contents due to three layers of smooth muscles. These layers are outer longitudinal muscle layer, inner circular muscle layer, and an oblique layer. It is difficult to control the environment of a dosage form in the gastrointestinal tract at all times following ingestion. The existing motility pattern at the time of administration affects the performance of oral dosage forms. The motility patterns are different in digestive or fasted and interdigestive or fed condition.

Particle size and feeding state strongly affect the residence time of the particles in stomach. Some other factors affecting gastric emptying are as follows: type of meal and its caloric content, volume, viscosity, and co-administered drugs. The rate of gastric emptying primarily depends on the caloric contents of the ingested meal.

It does not differ for proteins, fats, carbohydrates as long as their caloric content is the same. Generally an increase in acidity, osmolarity, and caloric value slows down gastric emptying. Stress increases gastric emptying rate where as depression slows it down. Generally females have a slower gastric emptying rate than males. Age and obesity also affect gastric emptying. Gastric emptying of dosage forms is different in fasted and fed conditions.

1.1.5. Requirements for gastric retention

From the discussion of the physiological factors in the stomach, it must be noted that, to achieve gastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions
and grinding and churning mechanisms. To function as a gastric retention device, it must resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease.

Figure 1.4: Mechanism of floating systems

1.1.6. Floating drug delivery technologies

FDDS can be divided into non-effervescent and gas-generating systems.

(a) 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 barrier. 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, polycarbonates and chitosan. This system can be further divided into four sub-types:

(i) Colloidal gel barrier system

Sheth and Tossounian first designated this ‘hydrodynamically balanced system’\(^{26}\). 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, hydroxyethyl cellulose, hydroxypropyl methyl cellulose (HPMC), polysaccharides and matrix-forming polymer such as polycarbophil, polyacrylate and polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface.

(ii) 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\(^{27}\). 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.

(iii) Alginate beads

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate\(^{28}\). 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 -40°C 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.

(iv) **Hollow microspheres / Microballons**

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 polyvinyl alcohol (PVA) that was thermally controlled at 40°C. 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.

(b) **Gas-generating (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, 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.

(i). Expandable systems

Expandable floating drug delivery dosage forms have been designed over the past 3 decades. They were originally created for possible veterinary use but later the design was modified for enhanced drug therapy in humans. These GRDFs are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that prolong their GRT. After drug release, their dimensions are minimized with subsequent evacuation from the stomach. Gastroretentivity is enhanced by the combination of substantial dimensions with high rigidity of the dosage form to withstand the peristalsis and mechanical contractility of the stomach. Positive results were obtained in preclinical and clinical studies evaluating the GRT of expandable GRDFs. Narrow absorption window drugs compounded in such systems have improved in vivo absorption properties.

(ii). Bio/Mucoadhesive 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. 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.

(iii). 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$^{34}$. 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$^3$.

1.1.7. Pharmaceutical aspects of floating drug delivery dosage forms

In designing of floating drug delivery system, following characteristics should be sought: i) retention in the stomach according to the clinical demand; ii) convenient intake; iii) ability to load substantial amount of drug with different physicochemical properties and release them in a controlled manners; and iv) complete matrix integrity of the SR formulation in the stomach, inexpensive industrial manufacture, optimization between the buoyancy time and release rate (buoyancy time increases by increasing drug : polymer level), lag time i.e. the time taken by the dosage form to float should be low$^{35}$. Most of the floating systems reported in literature are single unit system; these systems are unreliable and irreproducible in prolonging residence time in the stomach when orally administered, owing to their fortuitous (‘all-or-nothing’) emptying process. On the other hand, multiple unit dosage forms appear to
be better option since they reduce the inter subject variability in absorption and lower the probability of dose dumping\textsuperscript{36}.

Moes et al\textsuperscript{37}, have continuously monitored the floating kinetics to see the effect of different types of HPMC, varying HPMC/carbopol ratio and addition of magnesium stearate on floating behavior. HBS capsules of different density were used for study. Addition of magnesium stearate was observed to improve floating property significantly. HPMC of higher grade generally exhibits a greater floating capacity; but the effect was not statistically significant. For the polymers within the same viscosity (K4M and E4M), the degree of substitution of the functional group did not show any significant contribution. A better floating behavior was achieved at higher HPMC: Carbopol ratio. Carbopol appeared to have negative effect on the floating behavior of FDDS.

Floating formulations using swelling polymers such as HPMC and HPC do not show reproducibility in release and residence time because the swelling depends greatly on the contents of the stomach and the osmolarity of the medium and such formulations are observed to sink in the dissolution medium after a certain time. Floating lag time with such formulation is 9-30 min. Gel-forming capacity and the gel strength of polysaccharides varies from batch to batch because of the variation in the chain length and the degree of substitution, and the situation is exacerbated in the effervescent formulation by the disturbance of the gel structure through evolution of CO\textsubscript{2}. In addition, gel formers react very sensitively to differences in the osmolarity of the release media, with alterations in the release\textsuperscript{38}.

Another study reveals the influence of three basic fillers [microcrystalline cellulose (MCC), dibasic calcium phosphate (DCP) and lactose] on the floating behavior of coated tablets. Tablets containing lactose floated earlier than tablets
prepared with inorganic filler, DCP. Different densities could explain this; lactose-containing tablets had the lowest density (1g/cm$^3$ at hardness of 30 N), whereas DCP tablets had a higher density (1.9g/cm$^3$ at hardness of 30 N). In addition, lactose has higher water solubility and thus shows osmotic activity and faster uptake of the medium in the core of the tablet through coating. MCC, insoluble filler with a high water uptake and disintegration capability, resulted in the rupturing of the coating and disintegration of the tablet, CO$_2$ did not accumulate under the coating and escaped through the ruptured films, floating was therefore not achieved$^{39}$.

Doelkar et al$^{40}$ have showed the effect of film forming polymers on floating behavior of coated floating formulation. Films plasticized with water soluble plasticizers are more permeable for aqueous medium but should rapture earlier than films prepared with water insoluble plasticizers. Cellulose acetate, mechanically strong polymer, is too rigid and do not expand to large extent when comes in contact with dissolution medium. Ethyl polymer is mechanically weak polymer, it is not flexible and easily ruptures upon CO$_2$ formation; acrylic polymers are more suitable for the FDDS.

The floatation time decreases with increasing Eudragit RL content in Eudragit RS/RL coating and was longer with coatings containing acetyl tributyl citrate (ATBC) as plasticizer than with coating containing triethyl citrate (TEC).

1.1.8. 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).

a) **Density of dosage form**

Dosage forms having a density lower than that of gastric fluid experience floating behavior and hence gastric retention. A density of $<1.0 \text{ gm/cm}^3$ 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 \(^{41}\).

b) **Size of dosage form**

The size of the dosage form is another factor that influences gastric retention \(^{36}\). 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. 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.

c) **Food intake and nature of food**

Food intakes, 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. In a gamma scintigraphic
study of a bilayer floating capsule of misoprostol, the mean gastric residence time was 199 ± 69 minutes; after a light breakfast, a remarkable enhancement of average GRT to 618 ± 208 minutes was observed. 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.

d) Effect of gender, posture and age

A study by Mojaverian et al 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, in a comparative study in humans by Gansbeke et al, the floating and non-floating 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.

1.1.9. Advantages of Floating drug delivery system

1. The floating drug delivery systems are advantageous for drugs absorbed through the stomach. E.g. Ferrous salts, antacids.

2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.
3. Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.

4. The floating drug delivery systems are advantageous for drugs meant for local action in the stomach. E.g. antacids.

5. When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

1.1.10. Disadvantages of floating drug delivery system

1. Floating system is not feasible for those drugs that have solubility or stability problem in GI tract.

2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.

3. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.

4. Some drugs present in the floating system causes irritation to gastric mucosa.

1.1.11. Evaluation of floating drug delivery systems

Various parameters that need to be evaluated in gastro-retentive formulations include floating duration, dissolution profiles, specific gravity, content uniformity,
hardness, and friability in case of solid dosage forms. In the case of multiparticulate drug delivery systems, differential scanning calorimetry (DSC), particle size analysis, flow properties, surface morphology, mechanical properties and X-ray diffraction studies are also performed.

### 1.1.12. Applications of Floating Drug Delivery Systems

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

**a) Sustained Drug Delivery**

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.

Recently sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours) 49.

**b) Site-Specific Drug Delivery**

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, eg, riboflavin and furosemide.
Chapter 1

Introduction

Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets\(^5\).

A bilayer-floating capsule was developed for local delivery of misoprostol, which is a synthetic analog of prostaglandin used as a protectant of gastric ulcers caused by administration of NSAIDs. By targeting slow delivery of misoprostol to the stomach, desired therapeutic levels could be achieved and drug waste could be reduced\(^3\).

c) Absorption Enhancement

Drugs that have poor bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption. A significant increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric-coated LASIX-long product (29.5%)\(^5\).

d) Enhanced bioavailability

The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-CR-GRDF 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\(^5\).
e) Enhanced first-pass biotransformation

In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input\textsuperscript{52}.

f) Sustained drug delivery/reduced frequency of dosing

For drugs with relatively short biological half-life, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy\textsuperscript{52}.

g) 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\textsuperscript{52}.

h) Reduced fluctuations of drug concentration

Continuous input of the drug following CR-GRDF 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\textsuperscript{53}. 
i) **Improved selectivity in receptor activation**

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\(^5\).

j) **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\(^5\).

k) **Extended time over critical (effective) concentration**

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\(^5\).

l) **Minimized adverse activity at the colon**

Retention of the drug in the FDDS at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for FDDS 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\(^5\).
1.1.13. Suitable drug candidates for floating drug delivery

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

- Narrow absorption window in GI tract, e.g., riboflavin and levodopa.
- Primarily absorbed from stomach and upper part of GI tract, e.g., calcium supplements, chlordiazepoxide and cinnarazine.
- Drugs that act locally in the stomach, e.g., H$_2$ receptor antagonists, antacids and misoprostol.
- Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole.
- Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.

1.2. Drug profile

1.2.1. Famotidine

Famotidine is a H$_2$-receptor antagonist. Famotidine is used orally for the treatment of active duodenal or gastric ulcer, gastroesophageal reflux disease, endoscopically diagnosed erosive esophagitis, and as maintenance therapy for duodenal ulcer. Oral famotidine also is used for the management of pathological GI hypersecretory conditions. IV famotidine is used in hospitalized individuals with pathological GI hypersecretory conditions or intractable ulcers, or when oral therapy is not feasible.
Figure 1.5: Structure of Famotidine

Chemical Name: 3-[[2-[(Aminoiminomethyl) amino]-4-thiazolyl] methyl] thio] -N-(aminosulfonyl) propanimidamide.

Melting point: 161-163°C

Mol. weight: 337.449 g/mol

Molecular Formula: C_8H_{15}N_7O_2S_3

Physical state: Famotidine is a white to pale yellow crystalline compound.

Solubility: Famotidine is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol.

Mechanism of action

Famotidine binds to an H_2 -receptor located on the basolateral membrane of the parietal cell, blocking histamine effects. This competitive inhibition results in reduced basal and nocturnal gastric acid secretion and a reduction in gastric volume, acidity, and amount of gastric acid released in response to stimuli including food, caffeine, insulin, betazole, or pentagastrin.

Pharmacokinetics absorption

Famotidine is incompletely absorbed from the GI tract following oral administration and the drug reportedly undergoes minimal first- pass metabolism. The oral bioavailability of famotidine in adults is about 40–50%. Studies in a limited
number of children 11–15 years of age indicate a similar oral bioavailability of famotidine (mean bioavailability: 50%). The film-coated tablets, oral suspension, and orally disintegrating tablets of famotidine reportedly are bioequivalent.

**Distribution**

Distribution of Famotidine into human body tissues and fluids has not been fully characterized. The apparent volume of distribution of the drug is reported to be 1.1–1.4 L/kg in adults and does not appear to be altered substantially in patients with renal dysfunction. In children 1–15 years of age, a volume of distribution of 1.5–2.07 L/kg has been reported. Following oral or IV administration in rats, Famotidine is widely distributed, appearing in highest concentrations in the kidney, liver, pancreas, and submandibular gland. The drug is 15–20% protein bound.

**Elimination**

The elimination half-life of Famotidine averages 2.5–4 hours in adults with normal renal function. An elimination half-life of 2.3–3.38 hours has been reported in children 1–15 years of age. The elimination of Famotidine does not appear to be affected substantially by age in adults, but is prolonged in patients with renal impairment; adjustment of dosage or dosing interval may be necessary to avoid excess accumulation of the drug in patients with moderate or severe renal impairment.

**Dose**

- Benign gastric and duodenal ulceration, treatment, 40 mg at night for 4–8 weeks; maintenance (duodenal ulceration), 20 mg at night
- Reflux oesophagitis, 20–40 mg twice daily for 6–12 weeks; maintenance, 20 mg twice daily
Zollinger–Ellison syndrome, 20 mg every 6 hours (higher dose in those who have previously been receiving another H₂-receptor antagonist); up to 800 mg daily in divided doses has been used.

**Adverse effects**

Fever, hypertension, flushing, musculoskeletal pain (including muscle cramps), arthralgia, and tinnitus have been reported in 1% or less of patients receiving Famotidine, but a causal relationship to the drug has not been established in many cases. An acute episode of gout occurred in one patient during therapy with the drug.

### 1.2.2. Ranitidine HCl

Ranitidine HCl is a H₂-receptor antagonist. Ranitidine HCl is used orally for the treatment of active duodenal or gastric ulcer, gastroesophageal reflux disease, endoscopically diagnosed erosive esophagitis, and as maintenance therapy for duodenal ulcer. Oral Ranitidine HCl also is used for the management of pathological GI hypersecretory conditions. IV Ranitidine HCl is used in hospitalized individuals with pathological GI hypersecretory conditions or intractable ulcers, or when oral therapy is not feasible.

![Figure 1.6: Structure of Ranitidine HCl](image)

**Chemical name:** (E)-N-(2-((5-((dimethylaminomethyl) furan-2-yl) methylthio) ethyl)-N'-methyl-2-nitroethene-1,1-diamine

**Melting point:** 140°C
Molecular weight: 314.4g/mol

Molecular formula: \( \text{C}_{13}\text{H}_{22}\text{N}_{4}\text{O}_{3}\text{S} \)

Physical state: Ranitidine HCl is a white to pale yellow, granular substance.

Solubility: Ranitidine HCl is freely soluble in water, methanol and ethanol (95%) very slightly soluble in chloroform, dichloromethane.

Mechanism of action

Histamine is a natural chemical that stimulates the stomach cells to produce acid. Ranitidine HCl belongs to a class of medications, called H\(_2\)-blockers that block the action of histamine on stomach cells, thus reducing stomach acid production.

Pharmacokinetics

Absorption: Ranitidine HCl is incompletely absorbed from the GI tract following oral administration and the drug reportedly undergoes minimal first-pass metabolism. The oral bioavailability of Ranitidine HCl in adults is about 40–50%. Studies in a limited number of children 11–15 years of age indicate a similar oral bioavailability of Ranitidine HCl (mean bioavailability: 50%). The film-coated tablets, oral suspension, and orally disintegrating tablets of Ranitidine HCl reportedly are bioequivalent.

Distribution: Distribution of Ranitidine HCl into human body tissues and fluids has not been fully characterized. The apparent volume of distribution of the drug is reported to be 1.1–1.4 L/kg in adults and does not appear to be altered substantially in patients with renal dysfunction. In children 1–15 years of age, a volume of distribution of 1.5–2.07 L/kg has been reported. Following oral or IV administration in rats, Ranitidine HCl is widely distributed, appearing in highest concentrations in
the kidney, liver, pancreas, and submandibular gland. The drug is 15–20% protein bound.

**Elimination:** The elimination half-life of Ranitidine HCl averages 2.5–4 hours in adults with normal renal function. An elimination half-life of 2.3–3.38 hours has been reported in children 1–15 years of age. The elimination of Ranitidine HCl does not appear to be affected substantially by age in adults, but is prolonged in patients with renal impairment; adjustment of dosage or dosing interval may be necessary to avoid excess accumulation of the drug in patients with moderate or severe renal impairment⁵⁹.

**Dose**

- Benign gastric and duodenal ulceration, treatment, 40 mg at night for 4–8 weeks; maintenance (duodenal ulceration), 20 mg at night.

- Reflux oesophagitis, 20–40 mg twice daily for 6–12 weeks; maintenance, 20 mg twice daily.

- Zollinger–Ellison syndrome, 20 mg every 6 hours (higher dose in those who have previously been receiving another H₂-receptor antagonist); up to 800 mg daily in divided doses has been used⁶⁰.

**Adverse effects**

Fever, hypertension, flushing, musculoskeletal pain (including muscle cramps), arthralgia, and tinnitus have been reported in 1% or less of patients receiving Ranitidine HCl, but a causal relationship to the drug has not been established in many cases. An acute episode of gout occurred in one patient during therapy with the drug.
1.3. Polymer profile

1.3.1. Hydroxy propyl methyl cellulose\textsuperscript{61}

Nonproprietary Names


Synonyms

\textit{Benecel MHPC}; E464; hydroxypropyl methylcellulose; HPMC; \textit{Methocel}; methylcellulose propylene glycol ether; methyl hydroxy propyl cellulose; \textit{Metolose}; \textit{Tylopur}.

Chemical Name and CAS Registry Number: Cellulose hydroxypropyl methyl ether [9004-65-3]

Empirical Formula and Molecular Weight

Hypermellose as a partly $O$-methylated and $O$-(2- hydroxyl propylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Molecular weight is approximately 10,000–1,500,000.

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{structure.png}
\caption{Structure of HPMC}
\end{figure}

Where \( R \) is H, CH\(_3\), or CH\(_3\)CH(OH)CH\(_2\)
Functional Category

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations.

Description: Hypromellose is an odorless and tasteless, white or creamywhite fibrous or granular powder.

Density (bulk): 0.341 g/cm$^3$

Melting point: 170–230°C

Solubility: Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol.

Stability and Storage Conditions: Hypromellose powder is a stable material, although it is hygroscopic after drying. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

1.3.2. Chitosan-C$^{62}$

Nonproprietary Name

BP: Chitosan hydrochloride, PhEur: Chitosani hydrochloridum.

Synonyms

2-Amino-2-deoxy-(1,4)-b-D-glucopyranan; deacetylated chitin; deacetylchitin; b-1,4-poly-D-glucosamine; poly-D-glucosamine; poly-(1,4-b-D-glucopyranosamine).
Chemical Name and CAS Registry Number

Poly-b-(1, 4)-2-Amino-2-deoxy-D-glucose [9012-76-4]

Empirical Formula and Molecular Weight

Partial deacetylation of chitin results in the production of chitosan, which is a polysaccharide comprising copolymers of glucosamine and N-acetylglucosamine. Chitosan is the term applied to deacetylated chitins in various stages of deacetylation and depolymerization and it is therefore not easily defined in terms of its exact chemical composition. Chitosan is commercially available in several types and grades that vary in molecular weight by 10,000–1,000,000 and vary in degree of deacetylation and viscosity.

Structural Formula

![Figure 1.8: Structure of Chitosan-C](image)

Functional Category

Coating agent, disintegrant, film-forming agent, mucoadhesive, tablet binder, viscosity increasing agent and gel forming agent.

Applications in Pharmaceutical Formulation or Technology

- Chitosan is used in cosmetics and is under investigation for use in a number of pharmaceutical formulations.
• Chitosan has been processed into several pharmaceutical forms including gels, films, beads, microspheres.

• Furthermore, chitosan may be processed into drug delivery systems using several techniques including spray-drying, coacervation, direct compression, and conventional granulation Processes.

**Description**

Chitosan occurs as odorless, white or creamy-white powder or flakes. Fiber formation is quite common during precipitation and the chitosan may look ‘cotton like’.

**Typical Properties**

Chitosan is a cationic polyamine with a high charge density at pH <6.5; and so adheres to negatively charged surfaces and chelates metal ions. It is a linear polyelectrolyte with reactive hydroxyl and amino groups (available for chemical reaction and salt formation).

**Acidity/alkalinity:** pH = 4.0–6.0 (1% w/v aqueous solution)

**Density:** 1.35–1.40 g/cm³

**Moisture content:** chitosan adsorbs moisture from the atmosphere, the amount of water adsorbed depending upon the initial moisture content and the temperature and relative humidity of the surrounding air.

**Particle size distribution:** <30 mm

**Solubility:** sparingly soluble in water; practically insoluble in ethanol (95%), other organic solvents, and neutral or alkali solutions at pH above approximately 6.5.
Chitosan dissolves readily in dilute and concentrated solutions of most organic acids and to some extent in mineral inorganic acids (except phosphoric and sulfuric acids).

**Stability and Storage Conditions**

Chitosan powder is a stable material at room temperature, although it is hygroscopic after drying. Chitosan should be stored in a tightly closed container in a cool, dry place.

**Safety**

Chitosan is being investigated widely for use as an excipient in oral and other pharmaceutical formulations. It is also used in cosmetics. Chitosan is generally regarded as a nontoxic and nonirritant material. It is biocompatible with both healthy and infected skin. Chitosan has been shown to be biodegradable. LD50 (mouse, oral): >16 g/kg.