INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Innovations In Oral Drug Administration: Exploring Gastro Retentive Raft Forming System

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ARTICLE INFO

Received: 01 March 2024
Accepted: 04 March 2024
Published: 11 March 2024

Keywords:
Oral drug delivery, Gastroretentive drug delivery systems (GRDDS), Raft forming systems, Drug bioavailability, Patient compliance.

DOI:
10.5281/zenodo.10805754

ABSTRACT

Oral drug delivery systems have become dominant due to their convenience, cost-effectiveness, and high patient compliance. However, challenges such as gastrointestinal heterogeneity and fast gastric emptying limit their efficacy. Gastroretentive drug delivery systems (GRDDS) address these issues by prolonging gastric residence time, enhancing drug absorption, and targeting specific regions of the gastrointestinal tract. Various techniques including raft forming systems have been developed to achieve controlled drug release and retention in the stomach. Raft forming systems create a buoyant gel layer in the stomach, improving drug bioavailability and providing targeted delivery for conditions like GERD and gastric ulcers. Formulation of GRDDS involves selecting suitable drug candidates and excipients like alginate, gellan gum, and pectin. While GRDDS offer advantages such as improved patient compliance and continuous drug release, they also have limitations related to stability and storage. Overall, raft forming systems represent a promising approach in oral drug delivery, offering enhanced therapeutic efficacy and patient convenience.

INTRODUCTION

Due to its many benefits—such as convenience of administration, formulation flexibility, cost effectiveness, ease of storage and transportation, and high patient compliance—oral drug delivery systems have replaced other drug delivery methods for human administration. On the other hand, the heterogeneity of the gastrointestinal tract, the pH of the commensal flora, the dosage form's stomach retention time, surface area, and enzymatic activity all pose difficulties for oral drug delivery systems, including inadequate bioavailability (1,2). The gastrointestinal tract (GIT) can present challenges for conventional

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

drug delivery systems, including partial drug release, decreased dose effectiveness, and frequent dose requirements. Consequently, the development of GRDDS may result from the inability of traditional drug delivery methods to keep medications in the stomach. These systems provide a number of advantages, including extended gastric residence time (GRT) of dosage forms in the stomach, which can reach several hours, improved drug absorption leading to higher therapeutic efficacy, and suitability for targeted distribution in the stomach (1,3). Many drug molecules (such as Pranlukast hydrate, Metformin HCl, Baclofen, etc.), whose primary sites of absorption are the stomach or the proximal portion of the small intestine, or whose absorption problem is in the distal part of the intestine, have bioavailability issues due to the fast gastric emptying associated with conventional oral medications (4,5). Drugs that are less soluble in an environment of higher pH in the intestine can also have their solubility increased by keeping them longer in the stomach (6). Numerous medications, such as Captopril, Metronidazole, Ranitidine hydrochloride, and others, are susceptible to deterioration in the colon (6,7). In addition to its systemic effects, GRDDS has shown promise in treating gastric and duodenal ulcers, including esophagitis, locally by eliminating Helicobacter pylori, which is firmly buried in the stomach's submucosal tissue (8,9). Successful controlled release GRDDS have been designed using a variety of formulation techniques, such as superporous hydrogel, bio/mucoadhesive, raft-forming, magnetic, ion-exchange, expandable, low- and high-density systems (10,11). One of the most useful and popular techniques for creating a stable and long-lasting drug delivery profile in the GI tract is the raft forming system. or the management of illnesses and infections of the gastrointestinal tract. This technique works by creating a cohesive gel that is viscous when it comes into contact with stomach contents. As a result, every liquid particle expands as it comes into contact with gastric fluids, creating a continuous layer that is referred to as "RAFT." This raft remains buoyant in stomach acid due to the production of carbon dioxide, which reduces its overall density. Antacids and prescription drugs are administered with this technique to treat gastrointestinal disorders and infections (12).

ANATOMY OF GI:

The mouth, throat, oesophagus, stomach, small intestine, and large intestine are the organs that make up the gastrointestinal tract. The tongue, pancreas, liver, gallbladder, salivary glands, and teeth are examples of accessory digestive organs.

From the lower oesophagus to the anal canal, the gastrointestinal tract wall retains a constant four-layered tissue structure. The order of these layers is from innermost to outermost: mucosa, submucosa, muscularis, and serosa/adventitia (13). Several organs assist in secreting the enzymes and absorbing nutrients from the diet. Understanding gastric physiology and motility is essential to comprehending gastro retention strategies, which are based on Davis' 1968 pioneering work on the floating medication delivery method (14). Starting from the mouth cavity entrance and ending at the rectum opening, the gastrointestinal tract is a continuous muscular tube. The GIT resembles a 9-meter tube that extends from the mouth to the anus. Through physiological processes like secretion, motility, digestion, absorption, and excretion, the role is to absorb nutrients and remove waste.

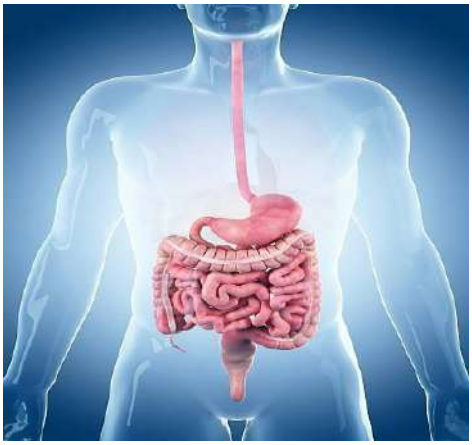

Figure 1: Anatomy of GI

ANATOMY OF STOMACH:

The cardia, fundus, body, and pyloric portion are the four main sections of the stomach. The cardia envelops the orifice where the oesophagus meets the stomach. The fundus is the circular area above and to the left of the cardia. The vast core section of the stomach, the body, is inferior to the fundus. There are three regions that comprise the pyloric portion. The stomach's body is connected to the first area, known as the pyloric antrum. The pylorus, the third region, is connected to the duodenum by the pyloric canal, the second region (14). With the exception of the stomach's extra, oblique layer of smooth muscle inside the circular layer, which helps with the execution of intricate grinding actions, the stomach wall is physically comparable to the other portions of the digestive tube (15). The stomach's surface is covered in secretary epithelial cells, which also extend into gastric pits and glands. There are four main types of these cells: (16)

1. Mucous cells: Release an alkaline mucus to shield the epithelium from acid and shear stress.
2. Parietal cells : This cells secrete Hydrochloric acid.
3. Chief cells: Release the proteolytic enzyme pepsin.
4. G cells: Release gastrin, a hormone.

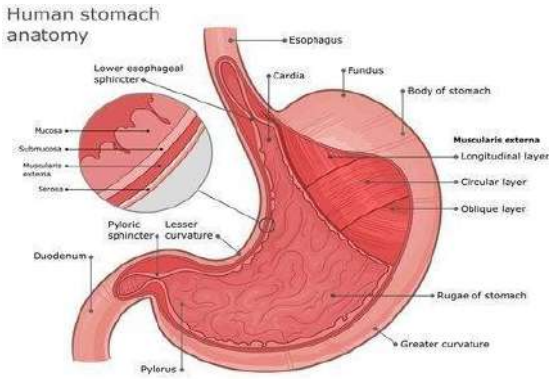

Figure 2: Anatomy of stomach

GASTRO RETENTIVE DRUG DELIVERY SYSTEM:

Gastroretentive systems have the ability to stay in the stomach area for several hours, thus extending the duration that medications spend in the stomach. Drugs that are less soluble in high pH environments become more soluble when stomach retention is prolonged. It also decreases medication waste and increases bioavailability. Applications for local drug administration to the stomach and proximal small intestines are also possible with it. Gastric retention contributes to improved product availability that provide patients significant advantages and novel therapeutic opportunities. The regulated gastric retention of solid dosage forms can be accomplished through the simultaneous administration of pharmacological agents that delay stomach emptying, mucoadhesion, floatation, sedimentation (high density), expansion, and changed shape systems. A number of recent cases have been documented that demonstrate the effectiveness of these systems for medications with bioavailability issues (17, 18, 19). Additionally, the primary goal in developing a an oral sustained-release dose type that is meant to be taken once a day was to increase the length of time the dosage form spend in stomach or upper small intestine in addition to extending the drug's 24-

hour distribution. Considering that patient-related variables including age, gender, ethnicity, food habits, and medical conditions might have a significant impact on a drug's release from a controlled release drug delivery system, it is preferable to design a CRDDS with Prolonged gastrointestinal tract residence time and drug release unaffected by these variables. [20–22]. Site specific drug release in the upper gastrointestinal tract for local or systemic effects is the goal of the GRDDS strategy, which aims to extend the stomach residence period.

SUITABLE DRUG CANDIDATE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEM (23,24).

1. Drugs with a limited window of absorption in the gastrointestinal tract, such as Levodopa, Riboflavin, and Para amino benzoic acid.
2. Mostly absorbed from the stomach and upper gastrointestinal system, such as Cinnarizin and Chlordiadepoxide.
3. Medications that operate locally in the stomach, such as Misoprostol and antacids.
4. Drugs that break down in the environment of the colon, such as Metronidazole, Ranitidine HCl, and Captopril.
5. Medicines that alter the usual bacteria in the colon, such as Amoxicillin trihydrate.
6. Medication that is poorly soluble at high pH levels, such as Verapamil, Chlordiazepoxide, and Diazepam.

ADVANTAGES OF GASTRO RETENTIVE DRUG DELIVERY SYSTEM

1. Drugs that are mostly absorbed through the stomach, such as antacids and ferrous salts, benefit from the gastroretentive systems.
2. The gastro retentive systems are beneficial for medications intended for localised action in the stomach for instance, antacids.
3. Poor absorption is to be expected in situations of some forms of diarrhoea where there is rapid digestion and a brief transit phase. In these circumstances, it might be beneficial to keep the medication in the stomach in order to obtain a comparatively better response (25).
4. By lowering dosage frequency, GRDDS enhances patient compliance.
5. Continuous drug release prevents variations in bioavailability caused by changes in plasma drug concentration and maintains a desired plasma drug concentration.
6. Drugs with a short half-life may have a greater therapeutic effect.
7. GRDDS can be used to develop medications whose intestinal pH is unstable (26).
8. Poor absorption is expected in cases of diarrhoea that cause rapid intestinal movement and shortened transit times. To obtain a comparatively better response in such cases, it can be beneficial to keep the medication floating in the stomach.
9. Floating type of GRDDS dose forms have a number of potential benefits as sustained release systems. Effective delivery of drugs with restricted upper gastrointestinal tract absorption can maximise absorption and improve their absolute bioavailability, even for those with poor bioavailability.
10. It is also anticipated that the variability in transit performance will be decreased by floating dose forms with SR properties. It may also be a helpful therapy approach for duodenal and stomach cancer (27).

DISADVANTAGES/LIMITATIONS OF GRFDDS:

1. Drugs with G.I. tract solubility or stability issues cannot be used in a floating system.

2. For medication delivery to float and function properly, these systems need a lot of fluid in the stomach.
3. The only medications deemed to be better choices are those that show a phase of elevated absorption in the stomach area (27).

APPROACHES FOR GRDDS (25)

Numerous strategies have been devised to enhance the retention of an oral dose form in the stomach. Among them are,

1. Floating drug delivery system

These low-density systems float in the stomach for an extended amount of time without slowing down the rate of gastric emptying because their bulk density is lower than that of gastric fluids (28). Methods of floating drug delivery system are as follows:

A. Effervescent system

- Gas generating system
- Volatile liquid containing system

B. Non effervescent system

- Expandable or swellable system
- Inherently low-density system
- Raft forming system

2. High density system:

Makes use of the dosage form's density as a tactic to create the retention mechanism. Because the dose form's density is higher than that of the gastric fluid, the sinking system stays at the bottom of the stomach (29).

3. Modified shape or unfolding system:

In this mechanism, the medication unfolds to a substantial extent to restrict entry to the pyloric sphincter (30).

4. Bioadhesive system:

The medicine sticks to the stomach mucosa in the bioadhesive system.

5. Superporous hydrogel system:

The average pore size of superporous hydrogel is greater than 100 μm, and it swells to equilibrium size in less than a minute as a result of rapid water uptake through capillary wetting through many linked open pores.

6. Magnetic system:

These devices resemble tiny, gastroretentive capsules that contain a magnetic substance that, when in contact with a powerful enough magnet applied to the stomach's area of the body, prevents the substance from being eliminated from the stomach (31).

RAFT FORMING SYSTEM

Several strategies to prolong the retention time have been tried, including retention of the dosage form in the stomach. The raft forming mechanism represents a sophisticated breakthrough in oral controlled medication delivery among the many attempts. Raft forming systems have drawn a lot of interest in terms of medicine delivery for gastrointestinal infections and diseases. One method that has been tested for maintaining drug delivery and targeting is the raft forming system. This method entails creating an effervescent floating liquid with in situ gelling capabilities. Additionally, the in situ gels maintains their integrity for over 48 hours, allowing for the continuous release of medication (32, 33). A continuous layer known as a raft is formed as part of the raft forming system's operation. The system forms a cohesive gel with a high viscosity when it comes into touch with stomach juices, and each part of the liquid expands to create a continuous layer known as a raft (33, 34). Because the generation of CO_2 results in low density, Because of its reduced bulk density, the gel layer floats on top of the stomach fluid. Consequently, the system stays afloat in the stomach for an extended amount of time without influencing the rate of gastric

emptying (35). Owing to the polymer's bioadhesive properties, Since in situ gelling produces a lighter gel than gastric fluid, it either floats over the contents of the stomach or adheres to the gastric mucosa, preventing the reflux of gastric content into the oesophagus by serving as a barrier between the two organs. Consequently, it results in dosage form retention and lengthens the duration of stomach residence, which prolongs the time that drugs are delivered to the gastrointestinal system [36]. The medicine is removed from the system gradually and at the desired pace when it is floating on the contents of the stomach. The stomach is cleared of the drug's leftover system once it has been released. As a result, the changes in plasma drug concentration are better controlled and the gastric retention duration is increased [32]. In order to treat problems connected to stomach acid like, GERD, heartburn, and oesophagitis, reflux-forming anti reflux treatments floating systems are typically employed [37]. The stomach acid's contents are covered in a thick, gel-like neutral layer or barrier by reflux-forming antireflux medications. The floating barrier keeps the lower oesophageal sphincter (LES) in place, keeping acidic stomach contents from refluxing into the oesophagus and relieving GERD patients' symptoms. The reason the formulations are called "raft forming anti-reflux preparations" is that the barrier floats like a raft on the surface of the contents of the stomach. GERD symptoms are treated with both conventional antacids and other treatment groups are not the same as raft-forming anti reflux medicines because of their distinct mechanism of action in relieving symptoms of GERD [38, 39, 40]. A formulation intended to generate a raft needs sodium or potassium bicarbonate. When gastric acid is present, the bicarbonate is transformed into carbon dioxide, which becomes trapped in the gel precipitate and turns it into foam that floats on the surface of the stomach contents. Formulations' antacid ingredients offer a comparatively pH-neutral barrier [38, 41]. Both raft strengthening and antacid applications are possible for calcium carbonate. It causes the release of calcium ions, which combine with alginate to create an insoluble gel [42, 43].

Figure 3: Raft forming system

FORMULATION OF THE RAFT FORMING SYSTEM

The patient demographic, the gel forming system's formulation, the clinical condition that requires treatment, the drug's physicochemical qualities, and marketing preferences all play a role. Anatomical and physiological parameters include membrane transport and tissue fluid pH; Molecular weight, lipophilicity, and molecular charge are examples of physico-chemical parameters; pH, gelation temperature, viscosity, osmolarity, and spreadability are examples of formulation factors. (44). The dosage form needs to be able to meet the following requirements in order to be retained in the stomach. These are listed in the following order:

- The medication should enter the body gradually.

- The formulation needs to be strong enough to endure the grinding, churning, and continual contractions caused by the stomach's peristaltic waves.
- The specific gravity (1.004–1.01 g/cm3) should be kept below the contents of the stomach
- A significant amount of time must pass while the dosage form is in the stomach.
- Improved adherence from patients.
- The patient can administer the medication easily.
- The device should be simple to remove from the stomach following the drug's release (45).

COMPONENT THAT GOES INTO MAKING THE RAFT FORMING SYSTEM

When creating a controlled release gastroretentive formulation, a suitable candidate needs to be chosen. Alkaline bicarbonates, also known as carbonates, and gel-forming agents are among the substances utilised in the formulation of this type of system. These components lead to a reduction in viscosity, causing the system to become lighter and float atop the stomach juices (46).

MEDICATIONS UTILISED IN THE RAFT FORMING SYSTEM

Raft forming systems have drawn a lot of interest in the administration of medications for gastrointestinal infections and illnesses as well as antacids. One possible treatment for esophagitis and heartburn is the raft-forming system. Drugs that are acid soluble but are unstable in intestinal secretions or poorly soluble can be used with this approach (36). The following are the drug selection factors for gastro retention, which should be taken into account while choosing a medication:

- Medication that acts locally in the stomach (47).
- Medication with a limited window for gastrointestinal absorption (47, 48).
- Drugs that are unstable in the intestinal or colonic environment; those that are absorbed from the stomach and upper gastrointestinal tract (49).
- Medications that alter the natural microorganisms in the colon (50).
- Pharmaceuticals that are poorly soluble at alkaline pH levels or those demonstrate decreased solubility in high pH environments (51).

EXCIPIENTS USED FOR FORMULATION

Different excipients are used in floating medication distribution systems to precisely aims the medicine's administration to the stomach or other specified area of the gastrointestinal tract. The drug administration system that forms a raft is formulated by using a combination of synthetic and natural polymers. A blend of natural and synthetic polymers is used in the formulation of the raft-forming medication delivery system. These consist of xyloglucan, guar gum, HPMC, poly (DL-lactic acid), poly (DL-lactide-co-glycolide), and poly-caprolactone (52).

The following qualities of a polymer used in in-situ gels should be present (53)

- Biocompatibility is a must.
- It ought to behave in a pseudoplastic manner.
- The polymer need to have the ability to increase viscosity as the shear rate increases.

ALGINIC ACID:

As a linear block copolymer, alginic acid is composed of β-D-mannuronic acid and α-L-glucuronic acid residues joined by 1,4-glycosidic linkages. Brown seaweed and marine algae like

Laminaria hyperborea, Ascophyllum nodosum, and Macrocystis pyrifera contain unbranched polysaccharides(54). Commercially, a wide variety of, salts of alginates and their byproducts are offered, such as potassium, magnesium, calcium, sodium, ammonium, and so forth. Sodium alginate is the one that is most frequently and extensively utilised in floating medication delivery systems among these. Sodium alginate is slowly soluble in water, generating a thick colloidal solution, and nearly insoluble in ethanol (95%), ether, and chloroform (55). To develop gels that can be used to deliver biomolecules such as proteins, peptides, and medicines, sodium alginate has been used [56].

GELLAN GUM:

One α-L rhamnose, one β-D-glucuronic acid, and two β-D-glucuronic acid residues make up the tetrasaccharide repeating unit of gellan gum, an anionic deacetylated exocellular polysaccharide. Pseudomonas elodea, also known as Sphingomonas elodea, secretes it (57). The composition is a gellan solution with a calcium chloride and sodium citrate combination. The stomach's acidic environment releases calcium ions when food is consumed orally, which causes the gellan to gel and create a gel in place. Consequently, alterations in temperature or the existence of cations (like Na+, K+, or Ca2+) trigger the formation of gellan gum (58).

XYLOGLUCAN:

Tamarind seeds are the source of xyloglucan, a polysaccharide derived from plants. Despite the fact that xyloglucan does not gel by itself, diluted solutions of the partially broken down material show a thermally reversible sol–gel transition upon heating due to the action of galactosidase (59). Drug administration via oral, intraperitoneal, ocular, and rectal routes may be possible with xyloglucan gels. Xyloglucan has demonstrated a very short gelation time, as little as 60 minutes.

PECTIN:

An anionic polysaccharide of plant origin, pectin is isolated from the cell walls of most plants. Between 50,000 and 180,000 is their typical molecular weight (61). The structure outlined by the egg-box model is how divalent ions, such calcium ions, link the galacturonic acid chains together when they are present, it easily gels in an aqueous solution (62). Pectin's solubility in water eliminates the need for organic solvents in formulations, which is the primary benefit of employing it for these purposes. When pectin is taken orally, divalent cations in the stomach cause it to change from a gel to a solid form. Pectins can gel in the presence of divalent ions like Ca2+ as well as in the absence of divalent ions.

CHITOSAN :

Chitosan is a polycationic polymer that is thermosensitive and biodegradable. It is produced by deacetylating chitin alkaline. The natural component of crab and prawn shell is chitin. Up to a pH of 6.2 (64), chitosan, a biocompatible cationic polymer, remains dissolved in aqueous solutions. When chitosan aqueous solution is neutralised to a pH higher than 6.2, a precipitate that resembles hydrated gel is formed. Chitosan granules are added to neutral (deionized distilled water) and acidic (pH 1.2) environments, and they instantly become buoyant, allowing for a regulated release of the medication.

CARBOPOL:

A well-known polymer that is pH dependant, carbopol remains in solution at acidic pH values and gels into a low viscosity at alkaline pH values. HPMC is used with Carbopol to improve the viscosity.

ISAPGOLA:

The Indian Pharmacopoeia officially recognises isapgol (Plantago ovata), a naturally occurring dietary fibre that is readily available. It is frequently used as a laxative in bulk and is composed of polysaccharides. The research looked into the possibility of using isapgol as a raft-forming agent (Mandlekar et al., 1997). It was discovered that isapgol is a viable option for raft formation and can be used to create antacid suspensions with raft- forming capabilities. The aim of the research was to evaluate the feasibility of producing an antacid suspension that forms rafts by utilising isapgol husk's gelling properties. (65).

XANTHAN GUM:

The component that formed the raft was alginate, and the antireflux suspension that contained alginate for raft formation had xanthan gum as a stabiliser (Rhone, 1992). Later, efforts were made to combine xanthan gum's bioadhesive characteristic with those of other polysaccharides to create a composition that would protect and heal the esophageal mucosa in the medical care of sgastroesophageal reflux disease, with xanthan gum playing a role in the formation of rafts. (Dettmar, Dickson, Hampson, & Jolliffe, 2003). A polysaccharide known as xanthan gum is created when Xanthomonas campestris bacteria digest a carbohydrate in a pure culture aerobic environment. Xanthan gum is resistant to common enzymes and has great solubility and stability in both acidic and alkaline environments, as well as in the presence of salts (65).

ADVANTAGES OF RAFT FORMING SYSTEM

Compared to tablets, the raft-forming technology offers a greater effective surface area since it creates a low density viscous coating on the stomach contents. Both of them increase the release of drug and bioavailability.

- Compared to other floating dosage forms, floating was acquired more quickly.
- By starting therapy once a day, patient compliance can be improved.
- Boost the effectiveness of therapy.
- Easy to administer to a patient

LIMITATIONS OF RAFT FORMING SYSTEM

- Because of the way these systems are designed, they are more prone to stability issues. These result from either microbial or chemical deterioration (oxidation, hydrolysis, etc.).
- Proper storage of the formulation is essential, as improper storage might lead to stability issues. This is caused by a shift in the system's pH after extended storage or improper temperature storage.
- Certain polymers undergo gel formation inside the package when exposed to radiations such as UV, visible, electromagnetic, etc.

CONCLUSION

In conclusion, gastroretentive drug delivery systems, particularly raft forming systems, represent a significant advancement in oral drug delivery technology. These systems offer prolonged gastric residence time, enhanced drug absorption, and targeted delivery to specific regions of the gastrointestinal tract. Through the selection of appropriate drug candidates and excipients, GRDDS hold promise for improving therapeutic efficacy and patient compliance. Despite some limitations related to stability and storage, the benefits of these systems in terms of drug bioavailability and patient convenience make them a valuable option in pharmaceutical research and development. Continued efforts in refining formulation techniques and addressing stability

challenges will further enhance the potential of gastroretentive drug delivery systems to meet the evolving needs of patient care.

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HOW TO CITE: Vignesh R., Kamaleshwari B., Kaviya G., Kovarthanan M., Mohan Raj U., Innovations In Oral Drug Administration: Exploring Gastro Retentive Raft Forming System, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 3, 289-302. https://doi.org/10.5281/zenodo.10805754