



# RAFT FORMING GASTRORETENTIVE DRUG DELIVERY SYSTEM: A NOVEL APPROACH

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**Abstract:** In recent years various technologies have been made in research and development of sustained release oral drug delivery system to overcome various physiological difficulties such as variation in gastric retention and emptying time. To overcome this drawback and to maximize the oral absorption of various drugs, novel drug delivery systems have been developed. Gastroretentive drug delivery system having a novel approach i.e. raft forming system. In this review focus on raft forming system, drug design, and their in vivo and in vitro evaluation has been studied

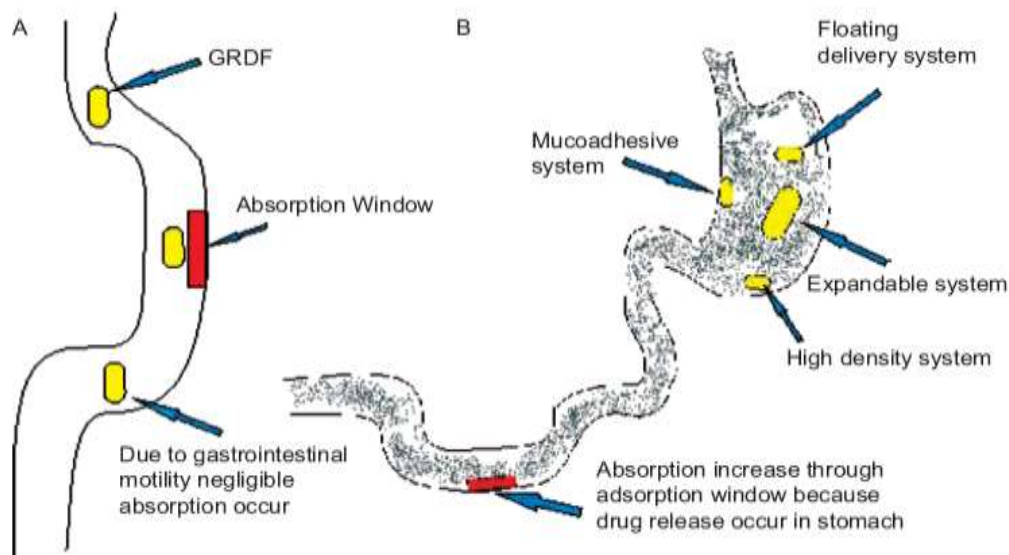
**Index Terms - Gastroretentive form, Raft forming system, Gastric residence time, Gastric emptying time.**

## I. INTRODUCTION

Some drugs are inherently long lasting and require only once a day oral dosing to sustain adequate drug blood levels and the desired therapeutic effect. These drugs are formulated in the conventional manner in immediate release dosage forms. However, many other drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results. Multiple daily dosing is inconvenient for the patient and can result in missed doses, made-up doses, and noncompliance with the regimen. When conventional immediate release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys associated with the taking of each dose. However, when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy. In contrast to conventional forms, modified release products provide either delayed release or sustained release of drug. Sustained release products are designed to release their medication in a controlled manner, at a predetermined rate, duration and location to achieve and maintain optimum therapeutic blood levels of drug. The US FDA defines sustained or extended release dosage form as one that allows reduction in dosing frequency from that necessitated by a conventional dosage form.

### 1.1 GASTRORETENTIVE DRUG DELIVERY SYSTEMS

Gastroretentive drug delivery systems (GRDDS) are the systems which are retained in the stomach for a longer period of time and thereby, improve the bioavailability of drugs. GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site, thus ensuring its optimal bioavailability<sup>1</sup>. Gastro-retentive dosage forms are also useful for local as well as sustained drug delivery for certain conditions, like H. pylori infection which is the cause of peptic ulcers. This dosage form improves bioavailability, therapeutic efficacy and may even also allow a possible reduction in the dose because of steady therapeutic levels of drug, for example Furosemide and Ofloxacin. The reduction in fluctuations in therapeutic levels minimizes the risk of resistance especially in case of  $\beta$ -lactam antibiotics (penicillins and cephalosporins)<sup>2</sup>



**Fig.1.1.1:** Drug absorption in the case of conventional dosage forms (A) and principles of GRDF (B).

### 1.1.1 Advantages of Gastroretentive Drug Delivery System

- 1) Gastroretentive dosage forms (GRDFs) beneficially alter the absorption profile of the active agent, thus enhancing its bioavailability. For example, a significant increase in bioavailability of furosemide from a floating dosage form (42.9%) has been reported compared with commercially available tablets (Lasix®)<sup>3</sup>
- 2) GRDFs greatly improve stomach pharmacotherapy through local drug release, which leads to high drug concentrations at the gastric mucosa (eradicating *Helicobacter pylori* from submucosal tissue of the stomach), making it possible to treat duodenal ulcers, gastritis and oesophagitis, and reduce the risk of gastric carcinoma<sup>4</sup>.
- 3) The formulations are not restricted to medicaments, which are principally absorbed from the stomach. Since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine e.g. Chlorpheniramine maleate.
- 4) It is advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.
- 5) GRDFs can be used as carriers for drugs with so-called absorption windows. These substances- namely antiviral, antifungal and antibacterial agents (e.g. sulfonamides, quinolones, penicillins, cephalosporins and tetracycline) - are taken up only from very specific sites of gastrointestinal mucosa<sup>5</sup>.
- 6) GRDFs have been recommended to achieve sustained drug delivery. Improved patient compliance and convenience have been reported due to less frequent drug administration and the nature of the drug's release kinetics<sup>6</sup>.
- 7) Reduction of fluctuation in drug blood concentration and maximum utilisation of the drug with a decrease in total adverse effects have been reported, with improved absolute bioavailability of the drug in GRDFs (e.g. famotidine)<sup>7</sup>.
- 8) For drugs with relatively short half life, sustained release may result in a flip-flop pharmacokinetics and also enable reduced frequency of dosing with improved patient compliance<sup>8</sup>.
- 9) An increased safety margin of highly potent drugs can be achieved due to better control of plasma concentration and expulsion of the floating system from the stomach after complete release of the drug<sup>9</sup>.
- 10) Gastroretentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency<sup>10</sup>.
- 11) Certain types of drugs can benefit from using gastro retentive devices. These include:
  - Drugs acting locally in the stomach;
  - Drugs those are primarily absorbed in the stomach;
  - Drugs those are poorly soluble at an alkaline pH;
  - Drugs with a narrow window of absorption;
  - Drugs absorbed rapidly from the GIT;
  - Drugs those degrade in the colon<sup>11</sup>.

### 1.1.2 Disadvantages of Gastroretentive Drug Delivery Systems

- 1) There are certain situations where gastric retention is not desirable. Aspirin and nonsteroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted.
- 2) Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems.

Furthermore, other drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract will not be benefited from incorporation into a gastric retention system<sup>11</sup>.

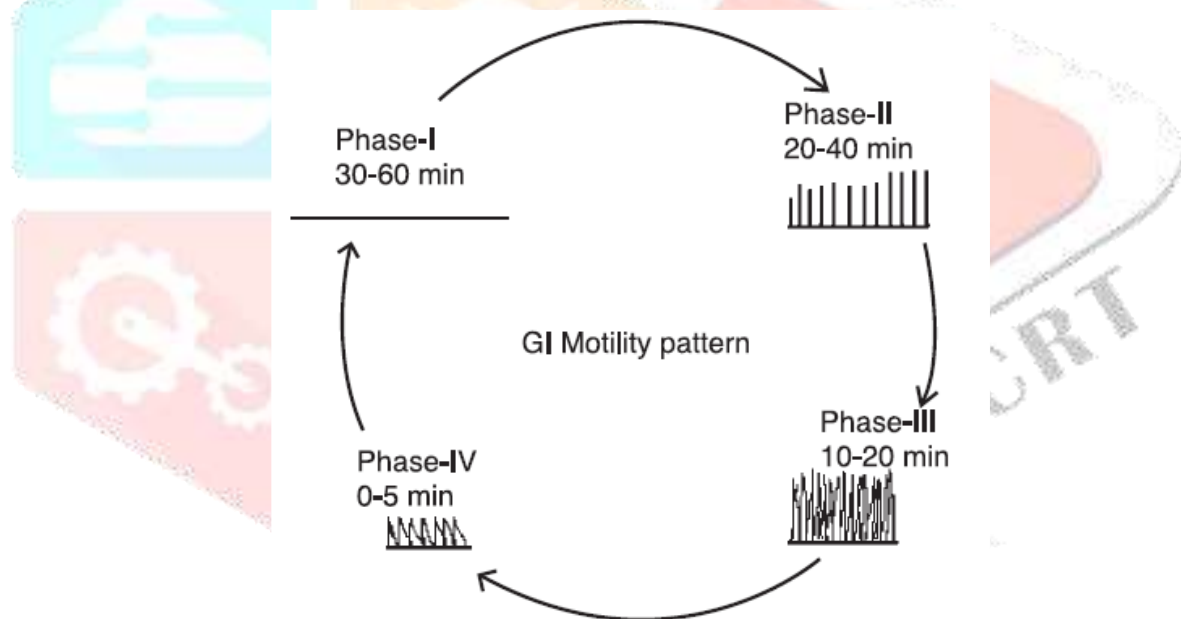
## 1.2 GASTROINTESTINAL TRACT PHYSIOLOGY

### 1.2.1 Stomach

The stomach is situated in the left upper part of the abdominal cavity immediately under the diaphragm. Its size varies according to the amount of distension: up to 1500 ml following a meal; after food has emptied, a collapsed state is obtained with resting volume of 25–50 ml. The stomach is anatomically divided into three parts: fundus, body, and antrum (or pylorus). The proximal stomach, made up of fundus and body regions, serves as a reservoir for the ingested materials, while the distal region (antrum) is the major site of mixing motions, acting as a pump to accomplish gastric emptying.

### 1.2.2 Gastrointestinal Motility

Two distinct patterns of gastrointestinal motility and secretion exist corresponding to the fasted and fed states. As a result the bioavailability of orally administered drugs will vary depending on the state of feeding. In the fasted state, it is characterized by an inter-digestive series of electrical event and cycle, both through the stomach and small intestine every 2–3 h. This activity is called the interdigestive myoelectric cycle or Migrating motor complex (MMC). MMC is often divided into four consecutive phases: basal (Phase I), pre-burst (Phase II), burst (Phase III), and Phase IV intervals<sup>16</sup>.



**Fig.1.2.1:** Schematic representation of inter digestive motility pattern<sup>12</sup>.

## II. APPROCHES OF GASTRO RETENTIVE DRUG DELIVERY SYSTEM

1. High density systems
2. Floating systems
  - a. Depending upon the effervescence generation
    - i. Effervescent system
    - ii. Non effervescent system
  - b. Depending upon the system
    - i. Monolithic system
    - ii. Multiple unit system
  - c. Other
    - i. Low density system
    - ii. Raft forming system
3. Expandable systems
4. Superporous hydrogels
5. Mucoadhesive or bioadhesive systems
6. Magnetic systems

## 7. Dual working systems.

### 1. High density system

These systems, which have a density of approximately  $3 \text{ g/cm}^3$ , are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. Above a threshold density of  $2.4\text{--}2.8 \text{ g/cm}^3$ , such systems can be retained in the lower part of the stomach. The formulation of heavy pellets is based on the assumption that the pellets might be positioned in the lower part of the antrum because of their higher density. They are frequently made of steel or some other heavy material. The main disadvantages of this approach are the dependence of the system operation on the state of the stomach and the need to use relatively large and heavy structures for obtaining the desired effect<sup>13</sup>.

### 2. Floating system

Floating systems, first described by Davis in 1968, are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased GRT and reduces fluctuation in plasma drug concentration<sup>14</sup>.

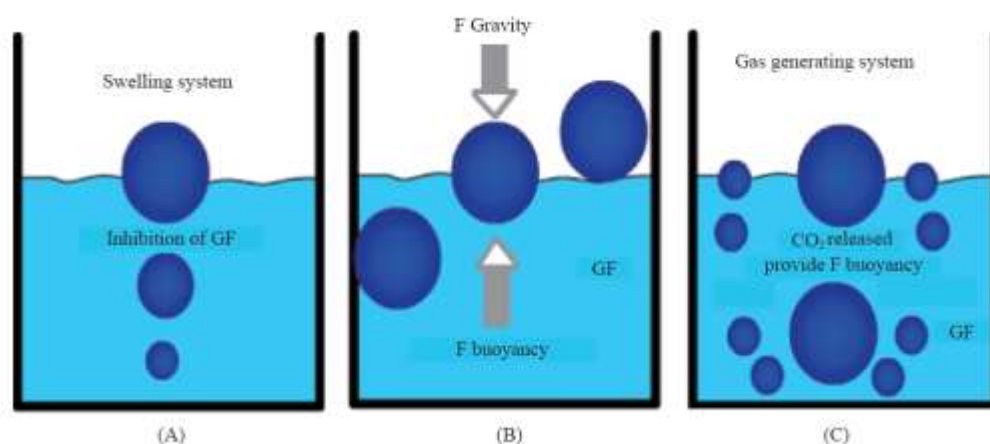


Fig. 2.1: Mechanism of floating systems

## III. CLASSIFICATION OF FDDS

Floating systems can be classified by different ways. Depending upon gas generation they are classified as effervescent and noneffervescent systems and depending upon the units in system they are classified as single unit or monolithic system and multiple unit system. While other classification of FDDS includes low density and raft forming/in situ gelling system.

### A. DEPENDING UPON THE EFFERVESCENCE GENERATION

#### i. Effervescent system:

Flotation of a drug delivery system in the stomach can be achieved by incorporating a floating chamber filled with vacuum, air, or an inert gas can be introduced into the floating chamber by the volatilization of an organic solvent or by the  $\text{CO}_2$  produced as a result of an effervescent reaction between organic acids and carbonate–bicarbonate salts. These devices contain a hollow deformable unit that converts from a collapsed to an expanded position and returns to the collapsed position after a pre-determined amount of time to permit the spontaneous ejection of the inflatable system from the stomach. Figure 4 describes a multiple-unit oral floating drug delivery system and explains the working principle of an effervescent floating drug delivery system<sup>15</sup>.

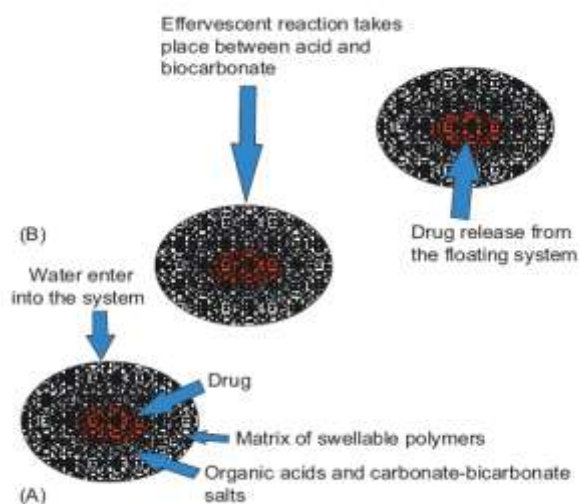


Fig. 3.1: (A) Multiple-unit oral floating drug delivery system. (B) Working principle of effervescent floating drug delivery system.

These buoyant systems utilize matrices prepared with swellable polymers like methocel, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid, or chambers containing a liquid that gasifies at body temperature. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach.

#### ii. Non Effervescent system:

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of  $< 1$ . The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass<sup>16</sup>.

### B. DEPENDING UPON THE NUMBER OF UNITS

#### i. Monolithic system

In single unit systems, such as capsules or tablets where effervescent substances are incorporated in the hydrophilic polymer and CO<sub>2</sub> bubbles are trapped in the swollen matrix. Monolithic dosage forms are also called as Single Unit Dosage Forms. Size is especially important in designing indigestible solid dosage forms (single unit systems). The human pyloric diameter is  $12 \pm 7$  mm. Solids are evacuated by the pylorus slowly and regularly. Indigestible materials, including solid pharmaceutical dosage forms, are evacuated by an Interdigestive Migration Myoelectric Complex (IMMC) peristaltic wave. Particles with diameter  $< 7$  mm are efficiently evacuated, and it is generally accepted that a diameter  $> 15$  mm is necessary for useful prolongation of retention especially during the fasting state. Chance determines whether a single unit system is lost during a particular gastric emptying, so that high variability in gastrointestinal transit time is a major drawback of these systems<sup>17</sup>.

#### ii. Multiple unit floating system

Multiple Floating System includes Microspheres, Microbeads, Microballoons etc. With multiple-unit dosage forms, gastric emptying generally involves both a steady rate of passage [assuming the units are smaller than the pyloric sphincter (i.e., less than about 1 mm in diameter)] and a pulsatile behaviour. In case of Floating multiple-unit dosage forms, it is postulated that the majority of particles will remain above stomach contents for an extended time period because particles act somewhat independently<sup>18</sup>. Multiple unit systems, such as those based on microparticles, avoid "all or nothing" emptying process by their statistical repartition throughout the gastrointestinal tract. However, it is essential that the units remain dispersed and suspended individually in the gastric fluid and not agglomerate into a mass floating at the top of the stomach<sup>17</sup>.

### C. OTHER CLASSIFICATION

#### i. Low density system:

Low density systems inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. Low density systems ( $< 1$  g/cm<sup>3</sup>) with immediate buoyancy have therefore been developed. They are made of low-density materials, entrapping oil or air<sup>19</sup>.

#### 3. Expandable system

Expandable dosage forms provide means to produce a drug delivery system that is too large to pass through the pylorus, yet sufficiently small to be swallowed. The diameter of the pylorus varies considerably among people, reportedly 12.8 - 7.0 mm; however, because the pylorus is a sphincter muscle, it can stretch depending on the force against it. The result is that even large dosage forms can pass from the stomach during strong migrating myoelectric complex contractions. To avoid this, the dosage form must be large (greater than about 20 mm) and strong in at least two dimensions. Among the challenges with this approach are the risks associated with either too rapid or slow a release. If the dosage form is caught in the oesophagus during swallowing, premature expansion could result in serious complications. A drug can be either contained in a polymeric composition of the gastroretentive system or included as a separate component. Several methods were suggested to provide for the self-unfolding effect:

- (1) The use of hydrogels swelling in contact with the gastric juice;
- (2) Osmotic systems, comprising an osmotic medium in a semipermeable membrane;
- (3) Systems based on low-boiling liquids converting into a gas at the body temperature, which imparts to the system a desired volume and provides for the drug release<sup>13</sup>.

#### 4. Super porous hydrogels

Although these are swellable systems, they differ sufficiently from the conventional types to warrant separate classification. With pore size ranging between 10 nm to 10  $\mu$ m, absorption of water by conventional hydrogels is a very slow process and several hours may be needed to reach an equilibrium state during which premature evacuation of the dosage form may occur. Superporous hydrogels, average pore size  $> 100$   $\mu$ m, swell to equilibrium within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores. Moreover, they swell to a large size and are intended to have sufficient mechanical strength to withstand pressure by the gastric contraction<sup>17</sup>.

## 5. Mucoadhesive system

The Mucoadhesive systems are intended to extend the GRT by adhering them to the gastric mucous membrane. Bioadhesion on soft tissues of certain natural or synthetic polymers has been exploited to control as well as to prolong the gastric retention of the delivery systems. The adhesion of the polymers with the mucous membrane may be mediated by hydration, bonding, or receptor mediated. In hydration mediated adhesion, the hydrophilic polymers become sticky and mucoadhesive upon hydration. Bonding mediated adhesion may involve mechanical or chemical bonding. Chemical bonds may involve covalent or ionic bonds or Van der Waals forces between the polymer molecules and the mucous membrane. Receptor mediated adhesion takes place between certain polymers and specific receptors expressed on gastric cells. The polymers could be anionic or cationic or neutral<sup>20</sup>.

## 6. Magnetic system

These systems appear as small gastroretentive capsules containing a magnetic material, whose elimination from the stomach is prevented by the interaction with a sufficiently strong magnet applied to the body surface in the region of the stomach. Despite numerous reports about successful tests, the real applicability of such systems is doubtful because the desired results can be achieved only provided that the magnet position is selected with very high precision<sup>13</sup>. The magnetic dosage forms contain a small internal magnet and an extra-corporal magnet that controls the gastrointestinal transit of the dosage form. Although these systems seem to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance<sup>19</sup>.

## 7. Dual working system

These systems are based on the two working principles of either floating and bioadhesion or swelling and bioadhesion. FDDS are formulated to persist floating on the gastric fluid when the stomach is full after a meal. However, as the stomach empties and the tablet reaches the pylorus, the buoyancy of the dosage form may be reduced. It may be that the dosage form will then pass through the pylorus into the small intestine. Thus, the buoyancy of an FDDS in the stomach may be limited to only 3-4 hrs. Furthermore, floating systems do not always release the drug at the intended site. In a bioadhesive drug delivery system, it is quite likely that the system becomes dislodged from the stomach mucosa wall when the system is full and the semiliquid contents are churning around due to the effect of peristalsis. A dual working system would overcome drawbacks associated with bioadhesive, swelling, and floating systems, and would have a significant effect on improving the therapeutic effect of the drug involved<sup>21</sup>.

## IV. RAFT-FORMING SYSTEMS

Here, a Gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO<sub>2</sub> bubbles on contact with gastric fluid. Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity and antibiotics. Because raft-forming systems produce a layer on the top of gastric fluid, they are often used for gastroesophageal reflux treatment.

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and other disorders. The mechanism involved in the raft formation includes the formation of a viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluid because of the low bulk density created by the formation of CO<sub>2</sub>. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO<sub>2</sub> to make the system less dense and able to float on the gastric fluids<sup>22</sup>.

### 4.1. THE DESIGN OF THE RAFT FORMING SYSTEM

The formulation of the raft forming system depends on the physicochemical properties of the drug molecule, the diseased condition for which treatment is required, the patient population and the marketing preference. Physico-chemical factors include molecular weight, lipophilicity and molecular charge; an anatomical and physiological factor includes membrane transport and pH of tissue fluid; formulation factors include pH, gelation temperature, viscosity, osmolarity, and spreadability.

To achieve the gastric retention of the dosage form, the dosage form must be able to satisfy the following criteria.

1. The drug should be released slowly from the system.
2. The dosage form must be able to withstand the force exerted by peristaltic waves in the stomach and the constant contractions, grinding and churning moments.
3. Should maintain specific gravity lower than gastric contents (1.004–1.01 g/cm<sup>3</sup>).
4. The dosage form must remain in the stomach for a prolonged period of time.
5. Better patient compliance.
6. Easy for administration for the patient.

After the release of the drug the device should be easily evacuated from the stomach<sup>23</sup>.

### 4.2. DRUGS USED FOR THE RAFT FORMING SYSTEM<sup>23</sup>

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The raft forming system is the potential approach for heart burn and esophagitis. This system is suitable for acid soluble drugs that are poorly soluble or unstable in intestinal fluids. Various drugs that can be used for the raft forming system are summarized in Table 1 with their category.

Thus the criteria of the drug to be considered for the selection of the drug for gastro retention are as follows:

1. Drugs that are locally active in the stomach.
2. Drugs that have narrow absorption window in the gastrointestinal tract.
3. Drug that are absorbed from the stomach and upper part of the gastrointestinal tract.
4. Drugs that are unstable in the intestinal or colonic environment.

5. Drugs that disturb normal colonic microbes.
6. Drugs that degrade in the colon.
7. Drugs that exhibit low solubility at high pH values (or are poorly soluble at alkaline pH)

Category	Drugs
Proton pump inhibitor	Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole, Esomeprazole
H <sub>2</sub> receptor antagonist	Cimetidine, Ranitidine, Famotidine, Nizatidine
Antacids	Aluminum hydroxide, aluminum phosphate, magnesium silicate, magnesium hydroxide, calcium carbonate.
Anti-cholinergic	Oxyphenonium, Propantheline, telezepine
Anti-helicobacter pylori drugs	Amoxicillin, Clarithromycin, Tetracycline Metronidazole, Tinidazole, colloidal bismuth

**Table 4.2.1:** Drugs that can be used for the raft forming system.

#### 4.3. ADVANTAGES OF RAFT FORMING SYSTEM<sup>24</sup>

1. They are used for the symptomatic treatment of heartburn and oesophagitis. It can be used in LPR. GERD, Laryngopharyngeal Reflux (LPR) refers to the backflow of stomach contents into the laryngeal and pharyngeal region
2. It does not interfere with the activity of promotility agent, antisecretory agents such as cimetidine.
3. Rapid and Long-duration of action can easily achieved by raft formation. It may show its action within seconds
4. It will not interfere with function of pyloric sphincter.
5. Better patient compliance can be achieved and it is well tolerated

#### 4.4. LIMITATION OF FLOATING RAFT FORMING SYSTEM<sup>25</sup>

1. These systems are formulated in the form of solution which is more susceptible to stability problems. These are due to chemical degradation (oxidation, hydrolysis, etc.) or microbial degradation.
2. The formulation must be stored properly because of the formulation is not stored properly it may cause stability problem. This is due to change in the pH of the system on prolonged storage or on storing inappropriate temperature conditions.
3. Exposure of certain polymer to radiations (e.g. UV, Visible, electromagnetic, etc.) induces the formation of gel within the package.

### V. APPROACHES OF RAFT FORMING SYSTEM

1. Based on producing a physical mechanism
2. Based on producing a chemical mechanism
3. Based on physiological stimuli mechanism

#### 5.1. RAFT FORMATION BASED ON THE PHYSICAL MECHANISM

##### • Swelling

Formation of the gel occurs when the liquid effervescent system comes in contact with gastric fluid. In situ formation of gel occurs when materials absorb water from the surrounding environment and expand to occur at the desired space. Swelling of the polymer occurs by the absorption of water which further lead to the formation of the gel. Certain biodegradable lipid substance such as myverol 18-99 (glycerol mono-oleate), is a polar lipid that swells in water to form lyotropic liquid crystalline phase structures<sup>26,27</sup>

##### • Diffusion

Diffusion is the method which involves diffusion of a solvent from a polymer solution into surrounding tissue, which further results in precipitation or solidification of the polymer matrix. The solution of polymer that can be used for such a mechanism is N-methyl pyrrolidone (NMP)<sup>26,27</sup>

Raft formation based on chemical mechanism

##### • Ionic crosslinking

In presence of the various ions present in the body fluids, like Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup>, Fe<sup>3+</sup>, etc., the ion-sensitive polysaccharides, e.g. carrageenan, gellan gum, pectin, etc., undergo transition in phase due to development of the polymer cross-linking, e.g. Sodium alginate undergoes gel formation in the presence of calcium chloride<sup>26,27</sup>

##### • Enzymatic cross-linking

Enzymes present in the body fluids may also cause cross-linking to form a polymer network and is considered, as the most convenient mode of gel formation<sup>26</sup>

## 5.2. RAFT FORMATION BASED ON PHYSIOLOGICAL STIMULI MECHANISM.

### • pH-dependent gelling

Polymers, such as polyacrylic acid and its derivative (Carbopol), polymethacrylate, etc., undergo gel formation because of change in the pH, due to the presence of various ionizable groups in the chemical structure of the polymer. Polymer with anionic groups leads to increase in swelling with an increase in the pH, while polymer with cationic groups shows a decrease in the swelling<sup>26</sup>.

### • Temperature-dependent gelling

The temperature-dependent phase transition from a less viscous solution to comparatively high viscosity gel is seen. Change in temperature causes an abrupt change in the solubility of polymer within the system and polymer-polymer interaction occurs to form a solvated macromolecule of hydrophobic nature. Temperature-sensitive polymers are most studied class for producing the in situ gel characteristics, e.g. Polyacrylic acid, polyacrylamide, etc.<sup>25,26</sup>.

## VI. POLYMERS USED FOR THE FORMULATION.

### Gellan gum

The structure of gellan gum, a polysaccharide of potential commercial usefulness is isolated from *Pseudomonas elodeu*. It is concluded that the polysaccharide is composed of tetrasaccharide repeating unit of one  $\alpha$ -L-rhamnose, one  $\beta$ -D-glucuronic acid and two  $\beta$ -D-glucose residues having the following structure.

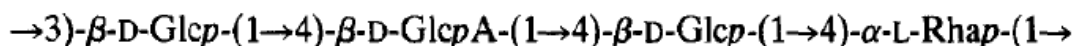


Fig. 6.1: Repeating unit of Gellan gum

Gellan (commercially available as Gelrite or Ketogel) is an anionic deacetylated exocellular polysaccharide. It has characteristic property of temperature dependent and cation induced gelation. This gelation involves the formation of double helical junction zones followed by aggregation of the double-helical segments to form a three-dimensional network by complexation with cations and hydrogen bonding with water<sup>28</sup>.

### Pectin

Pectins are anionic polysaccharides extracted from cell wall of most plants. Pectin contains a backbone of  $\alpha$ -(1-4)-D-galacturonic acid residues. It readily form gels in aqueous solution in the presence of divalent ions such as free calcium ions, which crosslink the galacturonic acid chains in a manner described by egg-box model. Pectin undergoes phase transition to gel state in presence of  $H^+$  ion when it is administered<sup>29</sup>. Calcium ions in the complexed form may be included in the formulation for the induction of pectin gelation. Pectins are commercially available as low methoxy (LM) pectin (degree of esterification (DE) < 50%) and high methoxy (HM) pectin (DE > 50%)<sup>30</sup>. LM pectins form a gel in the presence of divalent ions such as  $Ca^{2+}$ , and can also gel in the absence of  $Ca^{2+}$  when the pH is below about 3.3<sup>31</sup>.

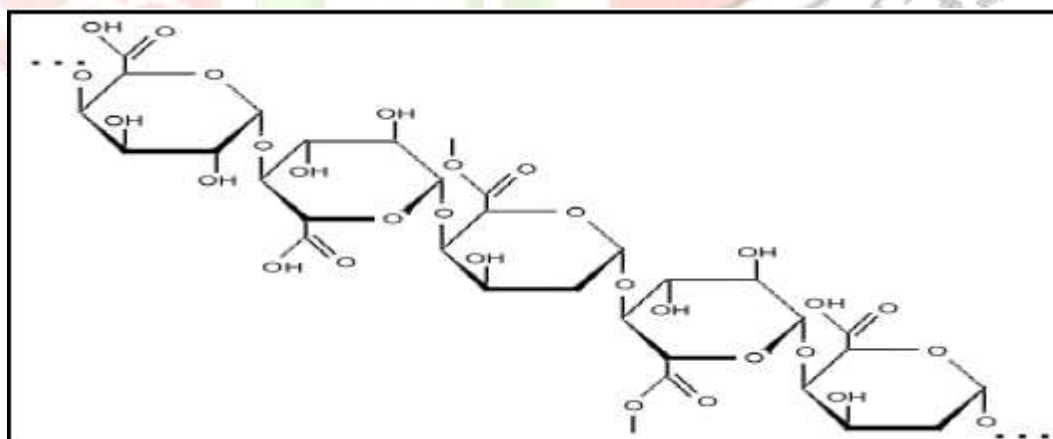
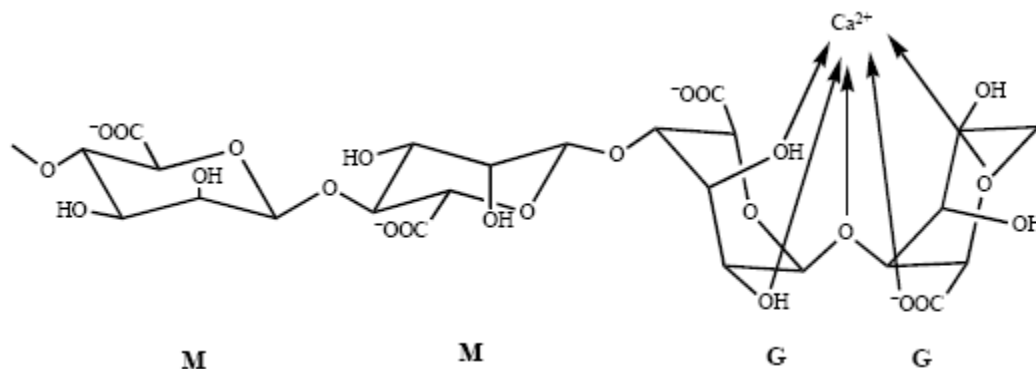


Fig. 6.2: Repeating units of Pectin

### Sodium alginate

Sodium alginate is widely used in pharmaceutical formulation as in situ gelling compound. Alginates are natural polysaccharide polymers isolated from brown seaweed (Phaeophyceae). Gelation property of sodium alginate depends on ionic interaction, such as monovalent metal ions form soluble salts with alginate whereas divalent and multivalent cations (except  $Mg^{2+}$ ) form gels or precipitates. Alginates with a high content of guluronic acid blocks (G residues) give gels of considerably higher strength compared to alginates rich in mannuronate (M residues), as the G residues exhibit transmittancy, swelling, and viscoelasticity of alginate gel membranes are highly affected by the M/G ratio. Alginic acid and its sodium and calcium salts are regarded as generally nontoxic and biocompatible<sup>32</sup>.

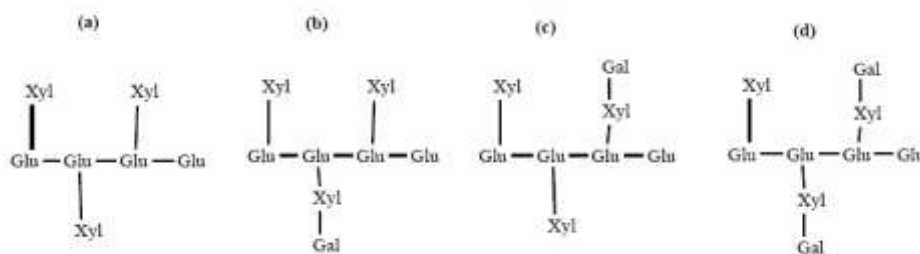




**Fig.6.3:** Probable binding mode between the calcium ion and two G residues.

### Xyloglucan

Xyloglucan polysaccharide derived from tamarind seeds, is composed of a (1-4)- $\beta$ -D-glucan backbone chain which has (1-6)  $\alpha$ -D-xylose branches that are partially substituted by (1-2)- $\beta$ -D-galactoxylose. The tamarind seed xyloglucan is composed of three units of xyloglucan oligomers with heptasaccharide, octasaccharide and nonasaccharide which differ in number of galactose side chains. When xyloglucan obtained from tamarind seed is partially degraded by  $\beta$ -galactosidase the resultant product exhibits thermoreversible gelation in dilute aqueous solution. Such gelation does not occur with native xyloglucan. Xyloglucan with a percentage of galactose removal of 44% exhibits a transition temperature between 22 to 27°C in dilute aqueous solution over the concentration range 1-2% w/w. The gelation is thermally reversible i.e. the gels revert back to their sol phase on cooling below the gelation temperature<sup>28</sup>.



**Fig. 6.4:** The unit structures of oligosaccharides from tamarind Xyloglucan (a) heptasaccharide (b), (c) octasaccharide and (d) nonasaccharide

### Carbopol

It is Mucoadhesive polymer that increases the formulation's mechanical strength, but also increases surface interaction with the ocular tissue and consequently contact time. Carbopol shows a solid-to-gel transition in aqueous solution as the pH is raised above its pKa of about 5.5; therefore, to have an easy administration, an acidic pH would be needed before carbopol phase transition.

## VII. EVALUATION OF RAFT FORMING SYSTEM

### 7.1. IN VITRO CHARACTERIZATION OF THE RAFT FORMING SYSTEM

#### 1. Viscosity of the Solution

The rheological property of the solution needs considerable attention, as it is decisive in determining palatability of the preparation and patient acceptance. The viscosity of sols has usually been measured at 20 °C using a cone and plate viscometer (Brookfield) with cone angle 1° 34' using a 1 ml aliquot of sample<sup>28</sup>.

#### 2. Measurement of Gel Strength

Gel strength is a very significant parameter as it governs the rate of release of drug from the gel. The gel strength may be measured at 37 °C using a rheometer by the method described, cylindrical gels of 1-2% w/v polymer prepared by placing a 30 ml sample of the solution in to a cellular tube, immersing the tube in 50 ml of pH 1.2 simulated gastric fluid and allowing to equilibrate for 24 hr. The cylindrical gels (15 mm diameter and 15 mm height) were placed in the rheometer and raised at a rate of 60 mm min<sup>-1</sup> so pushing a probe slowly through the gel. The changes in the load on the probe were measured as a function of the depth of immersion of the probe below the gel surface<sup>32</sup>.

#### 3. In Vitro Gelation Study

The gelation of solution can be observed in gelation cell. The cells are cylindrical reservoir capable of holding 3ml of the gelation solution (simulated gastric fluid of pH 1.2, without enzymes). Within the cells located at the bottom is a 250  $\mu$ l transparent plastic cup to hold the gel sample in place after its formation. 100  $\mu$ l of the formulation is placed in the cavity of the cup using a micropipette, and 2ml of the gelation solution (SGF) is added in the reservoir. Formation of gel in reservoir can be observed by visual examination<sup>25</sup>.

#### 4. Measurement of *In Vitro* Drug Release

Release studies from gels also have been performed using standard USP paddle dissolution test apparatus, stirring the sink solution at 50 rpm. The speed was slow enough to avoid breaking up the gel<sup>32</sup>.

#### 5. Determination of Drug Loading

One millilitre of the solution is added to 50 ml of buffer or appropriate solvent and sonicated for 10-15 min. The solution is filtered through a nylon syringe filter (0.45  $\mu$ m) and the concentration of the drug in the solution can be measured either spectrophotometrically or by HPLC<sup>33</sup>.

#### 6. Floating properties

The floating ability of the prepared formulations was evaluated in SGF (Simulated Gastric Fluid). The time the formulation took to emerge on the medium surface (floating lag time) and the time the formulation constantly floated on the dissolution medium surface (duration of floating) were evaluated<sup>22</sup>.

### 7.2. IN VIVO CHARACTERIZATION OF THE RAFT FORMING SYSTEM

#### 1.-Scintigraphy

$\gamma$ - Scintigraphy can be used to evaluate *in-vivo* buoyancy and *in-vivo* release performance of different type of GRDF. In this technology a stable radioisotope like In<sup>111</sup> is formulated within the developed system and administered in healthy human volunteers. Major drawbacks with such a technique are associated ionization radiations, limited topographic information, low resolution, and complicated and expensive preparation of radiopharmaceuticals<sup>34</sup>.

#### 2.Radiology

This method includes pre-clinical estimation of gastroretention. In comparison to  $\gamma$ -scintigraphy, radiology is a more simple and cost effective technique. However, limitations regarding exposure to X-rays decline its popularity because for optimum evaluation of buoyancy a high amount of contrasting agent (BaSO<sub>4</sub>) is generally required.

Radiographs were taken after ingestion of the dosage form, to locate the floating and non-floating (fabricated) dosage forms at various periodic time intervals<sup>35,36</sup>.

#### 3. Gastroscopy

This is considered a minimally invasive procedure since it does not require an incision. This technique involves visual inspection of GRDF in the stomach. Basically it is a type of peroral endoscopy which comprises optic fibres and a video camera. For more detailed information the evaluated system can be drawn out from the stomach. However, on the other hand the quality of study and its interpretation are highly dependent on the expertise of the endoscopist. Active uncontrolled bleeding, retained blood in the stomach, and retained food or antacids may also lead to an inadequate study<sup>35</sup>.

#### 4. Ultrasonography

Ultrasonic waves are used to produce images of body structures. The waves travel through tissues and are reflected back where density differs. The reflected echoes are received by an electronic apparatus that measures their intensity level and the position of the tissue reflecting them. The results can be displayed as still images or as a moving picture of the inside of the body. Most dosage forms do not have sharp acoustic mismatches across their interface with the physiological environment. Therefore, ultrasonography is not routinely used for the evaluation of FDDS<sup>37</sup>.

#### 5. Magnetic resonance imaging (MRI)

MRI is a non-invasive diagnostic technology. MRI uses a powerful magnetic field, radio frequency pulses, and a computer to produce detailed pictures of organs, soft tissues, bone, and virtually all other internal body structures. The images can then be examined on a computer monitor, transmitted electronically, and printed or copied to a CD. MRI does not use ionizing radiation (x-rays). In the last couple of years, MRI was shown to be a valuable tool in gastrointestinal research for the analysis of gastric emptying, motility, and intra-gastric distribution of macronutrients and drug models. The advantages of MRI include high soft tissue contrast, high temporal and spatial resolution, as well as a lack of ionizing irradiation. Also, harmless paramagnetic and supra-magnetic MR imaging contrast agents can be applied to specifically enhance or suppress signal of fluids and tissues of interest and thus permit better delineation and study of organs<sup>38</sup>.

Sr. no.	Brand name	Active ingredient	Company	Delivery system
1	Liquid Gaviscon®	Aluminum hydroxide and magnesium carbonate	GlaxoSmithKline, India	Effervescent floating liquid alginate preparations <sup>39</sup>
2	Topalkan®	Aluminum and magnesium mixture	Pierre fabre drug, France	Effervescent floating liquid alginate preparation <sup>40</sup>
3	Almagate Flot-Coat®	Aluminum and magnesium mixture	-	Floating dosage form <sup>41</sup>

**Table 7.1:** Marketed formulation of the raft forming system.

## VIII. CONCLUSION

Gastroretentive drug delivery offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper gastrointestinal tract (GIT) and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability. Among the various approaches for Gastric retention based on floating system, the 'Raft' forming system offers an important advantage of administration of drug as a liquid dosage form. Raft forming system promises to be a potential approach for heartburn and oesophagitis. Raft forming system is the most promising technique which undergoes sol to gel transition when coming in contact with gastric fluid or stomach pH. The raft system containing a gel-forming agent and alkaline bicarbonates or carbonates is the substance responsible for the formation of CO<sub>2</sub> to make the system less dense and float on the gastric fluids.

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