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Raft Forming System- A Novel Approach for Improving Gastric Retention

Satyajit Panda*, P. Madhusrota, G. Sethi
Department of pharmaceutics, Institute of Pharmacy & Technology, Salipur, Cuttack (Odisha) – 754202, India

Abstract:

Gastroretentive drug delivery systems (GRDDS) have received significant interest in the past few decades as they can overcome several drawbacks associated with most of the conventional and controlled release drug delivery systems particularly fast gastric-emptying time and non-site specificity for the drugs administered orally. In the current review, a special focus is given on raft forming approach which comes under gastroretentive floating drug delivery system. The Rafting drug delivery systems are useful approach to avoid this variability with increase in the retention time of the drug delivery systems for more than 12 hr. Raft forming tablets are the dosage forms which creates a gel like structure in presence of acidic environment of stomach known as Raft. In the current discussion we have summarized some of the important factors affecting the design of gastroretentive drug delivery systems along with their requirements. Raft systems incorporate alginate gels which have carbonate components that react with gastric acid of the stomach causing formation of CO_2 air bubbles and this enables floating. Several advantages, disadvantages of Raft have been discussed. A detailed survey on various methodologies used for designing of Raft along with marketed preparation and evaluation of raft forming drug delivery systems are covered. This review attempts to discuss various factors like physiological factors, physicochemical.

Keywords: GRDDS, Raft, Alginic acid, Gastric retention, Gaviscon

INTRODUCTION:

Gastro oesophageal reflux occurs commonly in normal persons. Patients who have either symptoms or tissue damage resulting from reflux are said to have gastro oesophageal reflux disease (GERD). The gastro oesophageal reflux is also called as heart burning.[1, 2] Acid reflux may happen all the time, particularly subsequent to eating or during the evening. GERD can likewise cause hack or have asthma side effects. It can likewise make your voice sound dry and rough. Different treatment choices accessible for GERD are taking drugs like antacids, H_2 antagonist, proton pump inhibitor, etc.; surgery to strengthen the barrier between the stomach and the oesophagus may be a treatment option for acid reflux and endoscopic treatments help strengthen the muscle that keeps food and acid from going up into the oesophagus.[3,4] Raft forming anti reflux preparation is one of the upcoming new approaches to overcome the problem of severity of acidity, Peptic ulcer and gastritis problems. They are generally used in the treatment of gastric acid-related disorders, especially GERD, acid reflux and oesophagitis**.** [5]

Raft-forming anti-reflux preparations forma thick, coagulated nonpartisan layer or obstruction on the highest point of the gastric corrosive substance. The floating barrier remains located at the lower oesophageal sphincter (LES) and prevents the acidic gastric content from getting refluxed into the oesophagus and provides symptomatic relief to GERD patients. Since this obstruction drifts on the of the stomach substance like a raft on water, the hindrance is known as a raft and the definitions are called as "raft-forming anti-reflux preparations. The one of a kind component of activity to give help in symptomatic GERD isolates raft-forming anti-reflux arrangements from conventional antacids and other therapeutic classes for treatment of GERD. [6]

GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS (GRDDS):

Anatomy of the Stomach:

The gastro intestinal tract can be divided into three main regions. [7]

- Stomach
- Small intestine- duodenum, jejunum, and ileum
- Large intestine

The GI tract is basically a cylinder around nine meters in length that goes through the centre of the body from the mouth to the anus and includes throat (pharynx), oesophagus, stomach, small intestine (consisting of duodenum, jejunum and ileum) and large intestine (consisting of caecum, appendix, colon, and rectum).[8]

The stomach is an organ with a limit with regards to capacity and blending. The antrum region is responsible for the mixing and grinding of gastric contents. [9]

The stomach is anatomically divided into three parts: - Fundus, body, antrum (pylorus) [10] - Likewise called distal stomach, which goes about as a site of blending movements to drive gastric substances for emptying**.** Pyloric sphincter has a measurement of 12.8±7mm in people and fills in as a sifter and stricture to entry huge particles. [11]

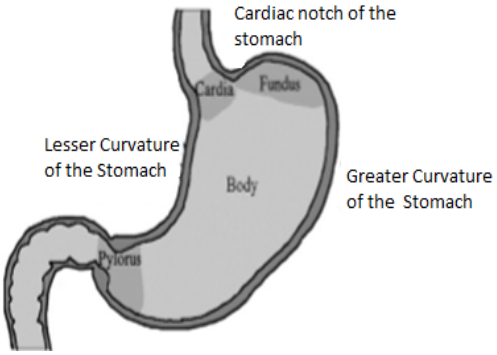


Figure 1: Anatomy of stomach

Gastric purging happens both in fasting just as sustained states. if there should arise an accurance of fasted express an inter digestive arrangement of electrical occasions happens in cyclic way both through the stomach and small digestive system each 2-3hr. The interdigestive myoelectric cycle or moving myoelectric complex (MMC) administers the movement and the travel of measurements forms. [[12]]

It consists of 4 phase [13]

Phase I: Additionally called quiet period with uncommon low plentifulness withdrawals, going on for 30-60 min.

Phase II: It contains middle adequacy compressions with bile discharge, going on for 20-40 min.

Phase III: Additionally called maid waves, it types exceptionally high adequacy constrictions offering most extreme pyloric opeing and productive departure of stomach substance. It goes on for 10-20 min.With a recurrence of 4-5 min. [14]

Phase IV: Transitional phase between phase III and I of two back to back cycles. It goes on for under 5 min**.** [15]

In sustained states, motility is prompted 5-10 min after ingestion and perseveres as long as nourishment stays in stomach, commonly 3-4 hr , Action is same as stage II of IMMC. Gastro retentivity of medication was required to expand the bioavailability of medication and to lessen the unwanted impacts brought about by presentation of medication to different areas of GIT.[16]

The stomach is an expanded section of the digestive tube between the oesophagus and small intestine. In the empty state the stomach is contracted and its mucosa and sub mucosa are thrown up into folds called rugae. There are 4 major types of secretory epithelial cells that cover the stomach and extend into gastric pits and glands. [17]

1. Mucous cells- emit soluble bodily fluid
2. Parietal cells – emit HCl
3. Boss cells- emit pepsin
4. G cells- emit hormone gastrin.

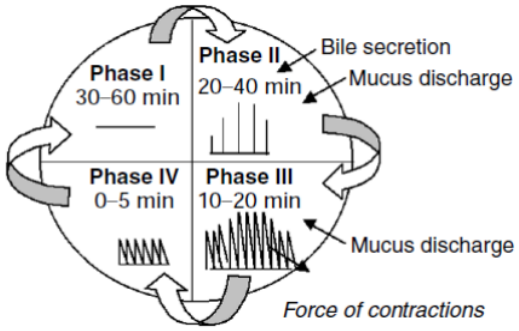
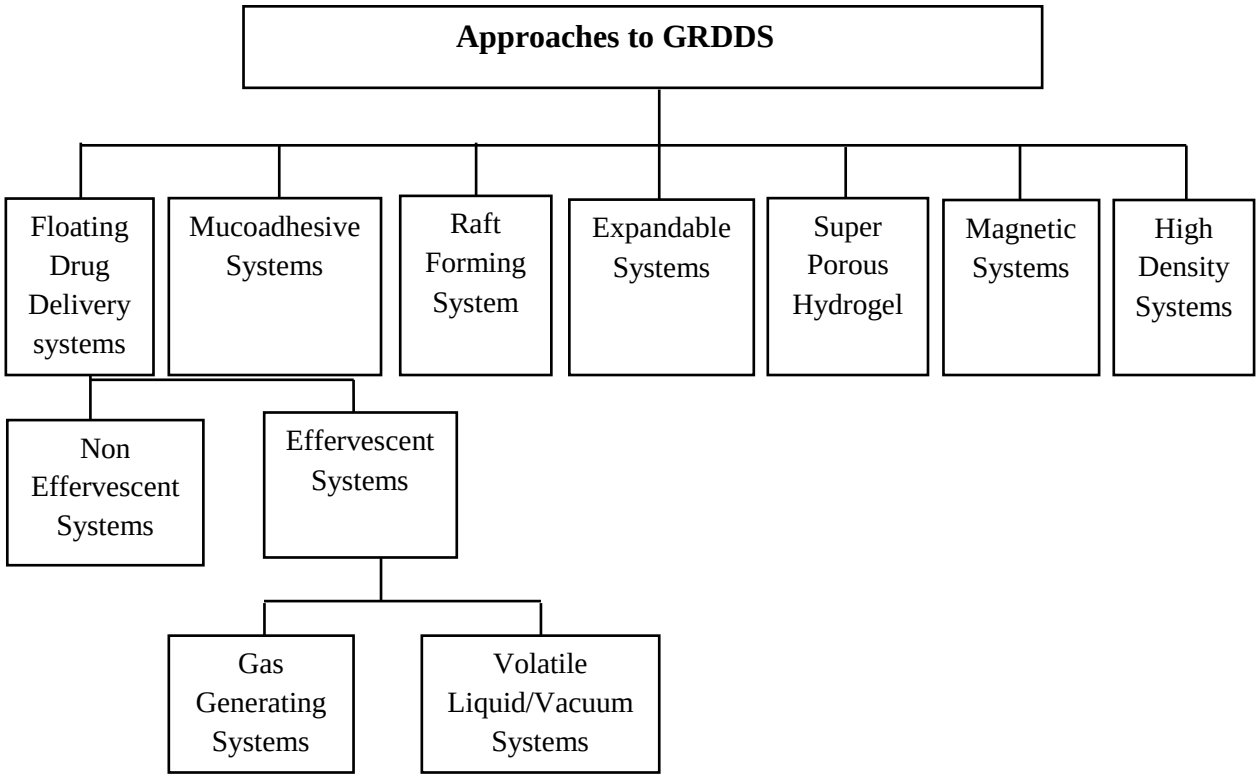


Figure 2: Gastric motility pattern

Approaches to Gastric Retention [18]:



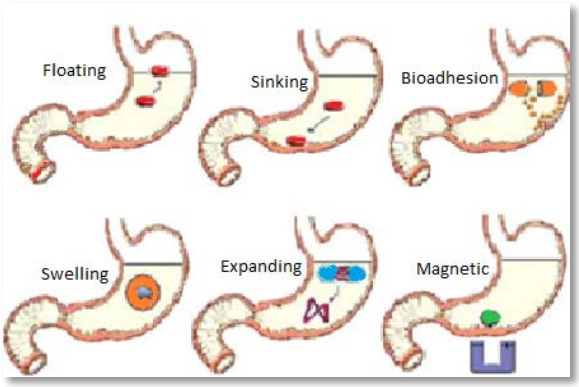


Figure 3: Types of GRDDS

Factors Affecting Gastro Retentive Drug Delivery Systems:

These are various factors to be considered for the development of gastro retentive dosage forms formulation to prolong the dosing intervals and thus improve patient compliance. They are demonstrated as follows.

(A) Factors Related to Dosage Forms:

1. **Density**: Gastro residence time (GRT) is a component of measurements structure lightness that is reliant on the thickness. The thickness of a measurements structure likewise influences the gastric exhausting rate and decides the area of the framework in the stomach. Measurement structures having a thickness lower than the gastric substance can buoy to the surface, while high thickness frameworks sink to base of the stomach. The two positions may segregate the dose framework from the pylorus. A thickness of < 1.0 g/ cm^3 is required to show floating property**.** [19]

2. **Size of dosage form**: The size of the dose structure is another factor that impacts gastric maintenance. The mean gastric living arrangement times of non-drifting measurement structures are exceptionally factor and significantly reliant on their size, which might be little, medium, and enormous units. In nourished conditions, the little units get discharged from the stomach during the stomach related stage and the bigger units during the house kepping waves. By and large, the bigger the size of the measurement structure, the more prominent will be the gastric maintenance time in light of the fact that the bigger size would not permit the dose structure to rapidly go through the pyloric antrum into the digestive tract. Consequently the size of the measurements structure seems, by all accounts to be a significant factor influencing gastric maintenance. [20]

3. Shape of dosage form: Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT, for example 90% to 100% retention at 24 hr contrasted and different shapes**.** [21]

4. Food intake and its nature: Under fasting conditions: GI motility is portrayed by times of solid motor activity or the relocating myoelectric complex (MMC) that occurs every 1.5 to 2 hr. The MMC clears undigested material from the stomach and, if the composition of MMC remains same, then GRT of the unit can be relied upon to be extremely short. Be that as it may, in the fed state, MMC is delayed and GRT is significantly longer. [22]

5. Nature of meal: sustaining of toxic polymers or unsaturated fat salts can change the motility example of the stomach to a nourished state, thus decreasing the gastric emptying rate and prolonging drug release. [23]

6. Caloric content: GRT can be expanded by four to 10 hr with a feast that is high in proteins and fat. [24]

7. Frequency of feed: The GRT can increment by more than 400 min when progressive suppers are given compared with a single meal due to the low frequency of MMC.

(B) Patient Related Factors:

1. Gender: Mean mobile GRT in guys (3.4 ± 0.6 hr) is less contrasted and their age and race coordinated female partners (4.6 ± 1.2 hr), regardless of the weight, height and body surface. [25]

2. Age: Old individuals, particularly those more than 70, have an altogether longer GRT.

3. Posture: GRT can vary between supine and upright ambulatory conditions of the patient. [26]

4. Concomitant drug administration: Anticholinergics like atropine and propantheline, opiate like codeine and prokinetic operators like metoclopramide and cisapride. [27]

5. Disease states: Gastric ulcer, diabetes, hypothyroidism increment GRT. Hyperthyroidism, duodenal ulcers decrease GRT.

6. Volume of GI fluid: The resting volume of the stomach is 25 to 50 ml. At the point when volume is enormous, the discharging is quicker. Liquids taken at body temperature leave the stomach faster than colder of hotter fluids. [28]

7. Buoyancy: On comparison of floating and non-floating doseage units, it was seen that by a little change in size to skimming measurements of the dose units they stayed light on the gastric substances throughout their residence time in the gastrointestinal tract, while the non-floating dosage units sank and remained in the lower part of the stomach. Floating units from the gastro duodenal intersection were shielded from the peristaltic waves during digestive phase while the non-floating forms stayed close to the pylorus and were exposed to impelling and retropelling floods of the stomach related stage. It was likewise seen that out of the coasting and non-skimming units, the drifting units possessed a more extended gastric living arrangement energy for little and medium units while no huge contrast was seen between the two kinds of enormous unit measurements forms. [29]

8. Single or multiple formulations:

Various unit plans demonstrate an increasing discharge profile. The irrelevant impending of execution because of the disappointment of units permits co-organization of units with various discharge profiles or containing in consistent substances, and thus, they permit a bigger edge of wellbeing against dose structure disappointment contrasted and single-unit dosage forms.[30] Sungthongjeen *et al*.[31] developed a multiple-unit floating system which was prepared by extrusions spheronization and comprised of medication stacked centre pellets and afterward, it was

covered with twofold layers of an inward gas forming layer(sodium bicarbonate) and an outer with gas-entrapped membrane of an aqueous colloidal polymer dispersion. Thus, this framework accomplished quick skimming and lightness over a time of 24 h with continued medication discharge. Sungthongjeen *et al*.[32] prepared the floating multilayer coated tablets in which theophylline was inside the core of the tablet, and it was further coated with a protective layer of hydroxyl propyl methyl cellulose (HPMC) and a gas forming layer of sodium bicarbonate and a polymeric membrane of high flexibility (EudragitRL30D), respectively. The polymeric film had high flexibility (Eudragit RL30D) and was capable to entrap generated CO_2 and had subsequent good floating properties. Ichigawa *et al* [33] developed a floating system by coating the sustained release granules with tartaric acid layer, sodium bicarbonate layer, and polymeric film which consisted of polyvinyl acetate and shellac.

Requirements for Gastric Retention: [34]

Successful gastric retention is possible when the dosage form must comply with following necessities.

- Measurement structure must most likely withstand the powers brought about by peristaltic waves in the stomach and the consistent withdrawals and granulating and strirring components.
- To function as a gastric retention device, it must resist premature gastric emptying.
- If its purpose has been served, the device should be removed from the stomach with ease**.**

RAFT FORMING SYSTEMS:

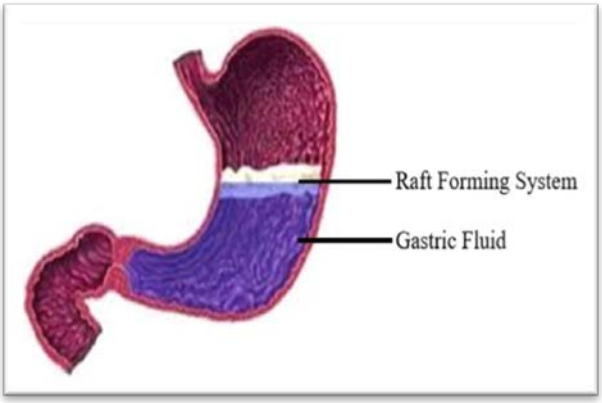


Figure 4: Schematic illustration of the barrier formed by raft forming system

Raft forming systems produce a layer on the highest point of gastric fluids. Here, a gel forming solution (for example Sodium alginate arrangement containing carbonates or bicarbonates) swells and structures a gooey firm gel containing entangled CO_2 rises on contact with gastric fluid.

The system accociated with the raft formation incorporates the development of thick firm gel in contact with gastric fluids, where in each part of the liquid swells framing a persistent layer called raft. This raft drifts on gastric liquids due to low mass thickness made by the development of CO_2.

Raft forming systems incorporate alginate gels [35].The raft in this way shaped buoys on the gastric liquids and anticipates the reflux of the gastric substance (for example gastric corrosive) into the oesophagus by acting as a barrier between the stomach and oesophagus.

This system is utilized for conveyance of acid neutralizers and medication conveyance for treatment of gastrointestinal diseases and disarrange.

The raft floats due to the lightness made by the arrangement of CO_2 and go about as a boundary to counteract the reflux of gastric substances like HCl and catalysts into the throat. .As a rule, these systems contain a gel shaping specialist and soluble bicarbonates or carbonates in charge of the development of to make the system less quick and buoy on the gastric liquids.

A patent assigned to Reckitt and Colman items Ltd, describes a raft forming definition for the treatment of *Helicobacter pylori* (H .pylori) diseases in the GI.

Advantages of Raft Forming Systems: [36, 39]

- They are utilized for the symptomatic treatment of acid reflux and oesophagitis. It can be used in Laryngo pharyngeal reflux (LPR), GERD. LPR refers to the back flow of stomach contents into the laryngeal and pharyngeal region.
- It does not interfere with the activity of promotility agent, antisecretory agents such as cimetidine.
- Rapid and Long-length of activity can without much of stretch accomplished by raft formation. It might demonstrate its activity inside seconds.
- It will not interfere with function of pyloric sphincter.
- Better patient consistence can be accomplished and it is much endured.
- **Restrictions :** [40]
- These systems are formulated in the form of solution which is more susceptible to stability problems. These are due to chemical degradation
- Chance of oxidation, hydrolysis or microbial degradation are there.
- The detailing must be put away appropriately in such a case that the definition isn't put away appropriately it might cause stability problem.
- Change in the pH of the system on prolonged storage or on storing inappropriate temperature conditions.
- Exposure of certain polymer to radiations (e.g. UV, Visible, electromagnetic, etc.) initiates the arrangement of gel inside the bundle.

Potential Candidates for Rafting Drug Delivery Systems: [41]

- Drugs that are essentially caught up in the stomach e.g. Amoxicillin.
- Drugs that are poorly soluble in alkaline pH e.g. Furosemide, Diazepam.
- Drugs that have narrow absorption window e.g. Levodopa, Methotrexate.
- Drugs that degrade in the colon e.g. Ranitidine, Metformin HCl.

- Drugs that disturb normal colonic microbes e.g. Antibiotics against Helicobacter pylori
- Drugs rapidly absorbed from the GI tract e.g. Tetracycline.
- Drugs acting locally in the stomach.
- Narrow ingestion window in GI tract e.g. Riboflavin and levodopa.
- Basically consumed from stomach and upper part of GIT e.g. Chlordiazepoxide and cinnarazine.
- Drugs that irritate ordinary colonic microscopic organisms normal e.g. Amoxicillin trihydrate.
- Locally dynamic in the stomach e.g., Acid neutralizers and Misoprostol.
- Drugs that debase in the colon e.g., Ranitidine HCl and metronidazole.

Drugs those are Unsuitable for Raft Forming Drug Delivery Systems:[42, 43]

- Drugs that have very restricted corrosive solvency e.g. Phenytoin and so on.
- Drugs that endure shakiness in the gastric condition e.g. Erythromycin etc.
- Drugs that causes gastric irritation and bleeding e.g. Aspirin
- Drugs proposed for specific discharge in the colon e.g. 5-amino salicylic acid and corticosteroids etc.

METHODOLOGIES USED FOR THE FORMULATION OF THE RAFT FORMING DRUG DELIVERY SYSTEMS: [44]

Raft forming drug conveyance systems are an upset in oral medication conveyance. These systems are liquids at room temperature but undergo gelation when comes in contact with body fluids or change in pH. These have a unique property of temperature dependent and cation-induced gelation. Gelation includes arrangement of the twofold helical junction zones pursued by collection of the twohold helical segments which form three dimensional networks by complexation with cations and hydrogen bonding**.**

Various methodologies dependent on their components utilized for setting off the raft arrangement in the GIT.

Raft formation based on physical mechanism:

Swelling: *In situ* formation may also occur when absorbs water from encompassing condition and grow to happen desired space. One such substance is myverol 18-99 (glycerol mono-oleate), which is polar lipid that swells in water to frame lyotropic fluid crystalline stage structures. It has some Bioadhesive properties and can be debased *in-vivo* by enzymatic activity. [45]

Diffusion: This strategy includes the dispersion of dissolvable from polymer arrangement into encompassing tissue and results in precipitation or solidification of polymer grid. N- Methyl pyrrolidone (NMP) has been shown to be useful solvent for such system. [46]

Ionic crosslinking: Polymers may experience stage change in nearness of different particles. A portion of the polysaccharides fall into the class of particle delicate ones. While k-carrageenan structures unbending,weak gels in answer of limited quantity of K^+, i-carrageenan structures flexible gels fundamentally within the sight of Ca^{2+}. Gellan gum monetarily accessible as Gelrite® is an anionic polysaccharide that experiences *in situ* gelling within the sight of mono- and divalent cation, including Ca^{2+}, Mg, K^+ and Na^+. Gelation of the low-methoxy pectin can be caused by divalent cations, especially Ca^{2+}. In like manner, alginic corrosive experiences gelation in nearness of divalent/polyvalent cations e.g. Ca^{2+} due to the interaction with guluronic acid block in alginate chain. [47]

Raft formation based on physiological stimuli mechanism:

pH dependent gelling : Another formation of *in-situ gel* is depends on Change in pH . Certain polymers such as polyvinyl acetaldiethyl aminoacetate (AEA), Mixtures of poly methacrylic acid (PMA) and poly ethylene glycol (PEG) shows change from sol to gel with change of pH. The polymers with an enormous number of ionizable gatherings are known as polyelectrolytes. Swelling of hydrogel increments as the outer pH increments on account of pitifully acidic (anionic) gatherings, yet diminishes if polymer contains feebly essential (cationic) groups. [48]

Temperature dependent gelling: These hydrogels are liquid at room temperature (20^0C-25 ^{0}C) and undergo gelation when in contact with body fluids (35^0C-37^0C), due to an increase in temperature. This approach move temperature-induced phase transition. A few polymers experience unexpected changes in solvency in light of increment in natural temperature (lower basic arrangement temperatures, LCST). At the LCST, hydrogen bonding between the polymer and water becomes unfavourable, contrasted with polymer-polymer and water-water communications, and an unexpected progress happens as the solvated macromolecule quickly dehydrates and changes to a more hydrophobic structure. [49]

A PORTION OF THE MARKETED PREPARATIONS: [50]

ALGICON (Rorer)

A swiss pharmaceutical organisation established in 1945, careful hardware and mechanisms, contact focal and other vision care pdt.

Figure 5: Drug Algicon

Mechanism of Action of Algicon:

Potassium Bicarbonate & Sodium Alginate works by forming a protective layer that floats on the top of the stomach contents, preventing reflux and keeping the stomach contents away from the lining of the food pipe. [51]

GASTROCOTE (Boeringer Mannheim)

It mainly used neutralising stomach corrosive, acid reflux, peptic ulcer. Dose – grown -ups and kids over 6years a couple of tablets to be bitten 4 times each day, after principal dinners and sleep time. kids under 6 years gastrocote tablets are not to be given.

Figure 6: Drug Gastrocote

Mechanism of Action of Gastrocote:

Gastrocote tablets contain a blend of drugs called stomach settling agents and alginates. Acid neutralizers work by killing the stomach acids and alginates help to protect the lining of the gullet from stomach acid. [52]

BISODOL (White Hall)

Bisodol indigestion relief tablet treat pain and discomfort of acid indigestion, heart burn and trapped wind.

Figure 7: Drug Bisodol

Mechanism of Action of Bisodol:

Bisodol Sodium bicarbonate, calcium carbonate and magnesium carbonate are antacids. They act by neutralising the hydrochloric acid produced by the stomach and thus reducing gastric and duodenal irritation**.** [53]

GASTRONE (Sanofi Winthrop)

It is used to promote release of acetylcholine and control degradation of acetylcholine to stimulate gastro intestinal motility. Used in gastrointestinal symptoms in chronic gastritis**.**

Figure 8: Drug Gastrone

Mechanism of Action of Gastrone:

Gastrin bind to cholecy to kinin B receptors to stimulate the release of histamines in entrochromaffin like cells and it induces the insertion of k^+ ATPase pumps into the apical membrane of parietal cell.

FLUID GAVISCON (Reckitt Benckiser Health Care)

It is used to treat the symptoms of too much stomach acid such as stomach upset, heart burn and acid indigestion. Aluminium and magnesium antacids work quickly to lower the acid in stomach.

Figure 8: Drug FluidGaviscon

Mechanism of Action of Liquid Gaviscon:

This causes an increase in intra oesophageal pH and a decrease in pepsin activity. Antiurolitic –aluminium carbonate and aluminium hydroxide present in this preparation bind phosphate ions in the intestine to form insoluble aluminium phosphate, which is excreted in the faces. [53]

GAVISCON ADVANCE TABLETS (Reckitt Colman) [54, 55]

Gaviscon advance is an extra strength treatment for heartburn and indigestion including hiatus hernia and gastro oesophageal reflux disease also known as GERD. It does not cure the condition but rather is used to control the unpleasant symptoms and for me it works a treat. Gaviscon advance is a thick creamy suspension that is available in two flavours: Peppermint flavour and aniseed flavour. It is quite pleasant to taste but a lot of people can't bear the taste of aniseed.

Figure 9: Drug Gaviscon

Mechanism of Action of Gaviscon:

The Gaviscon liquid is a thick suspension that on swallowing slides down the oesophagus into the stomach. It forms a barrier over the top of the stomach contents preventing the acid from rising into the oesophagus. Anyway it has very high sodium content, so it will lessen their sodium admission. It is sugar and gluten free. It is safe to use in pregnancy and during breast feeding. Some people may be allergic to some of the ingredients**.**

POLYMERS USED FOR FORMULATION:

Alginic Acid: [56]

Alginic Acid is a linear block copolymer polysaccharide consisting of β-D-mannuronic acid and α-Lglucuronic acid residues joined by 1, 4-glycosidic linkages. The extent of each square and the plan of squares along the atom shift contingent upon the algal source.Weaken fluid arrangements of alginates structure firm gels on expansion of di and trivalent metal particles by a helpful procedure including continuous glucuronic build ups in the α-Lglucuronic corrosive squares of the alginate chain. Alginic acid can be chosen as a vehicle for formulations, since it exhibits favourable biological properties such as biodegradability and nontoxicity**.**

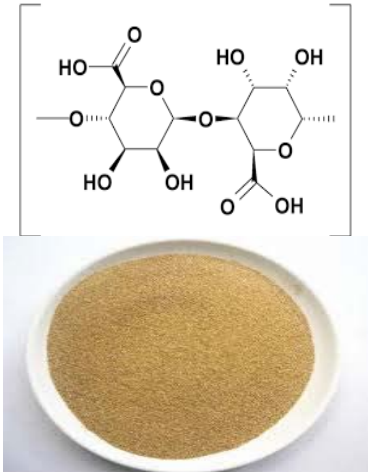


Figure 10: Alginic acid

Pectin: [57]

Pectin is non-toxic and economic polysaccharide extracted from apple pomaces and citrus peels. On the base of both extraction procedure and source gelatin is a mind boggling structure. Actually, it is a D-galacturonic acid with 1–4 linkages. It is used as a bulking agent, food additive, and a gelling agent due to the pectin ability to form gel based on degree of esterification and molecular size, it is an alluring candidate for pharmaceutical care, for example, as drug carrier for controlled released applications.

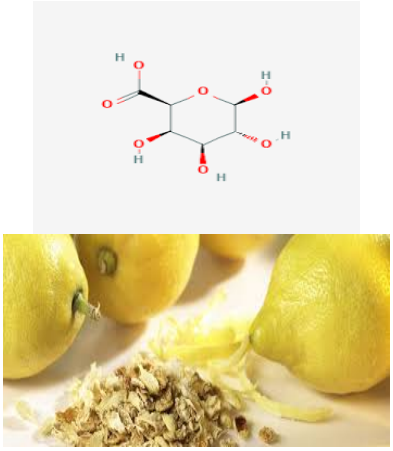


Figure 11: Pectin

Chitosan:[58]

It is composed of glucosamine and N-acetylglucosamine and is linear cationic polysaccharide. Chitosan is prepared by the deacetylation of chitin that is obtained from crustacean shells. It is biodegradable, biocompatible, and non-toxic. It is odourless creamy or white flakes or powder and partially insoluble in 95% ethanol and soluble in water. It is used as viscosity enhancer, mucoadhesive, film-forming agent, tablet binder, coating agent, and disintegrant**.**

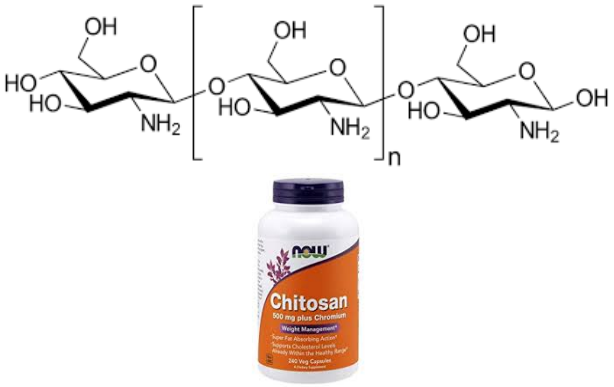


Figure 12: Chitosan

Xanthan gum: [59]

Bacterium Xanthomonas campestris produced xanthan gum naturally. This gum appears as odourless, free-flowing fine powder or cream. Polysaccharide B-1459, Keltrol, Rhodigel, Merezan, and Corn sugar gum are soluble in warm or cold water and are insoluble in ethanol and ether. This gum is steady material and is polysaccharide in nature with D-glucose spine like cellulose. Their aqueous solutions are durable in existence of enzymes, bases, salts, acids, and stable at pH range 3–12 and temperature between 10–60°C. It is non-toxic and non-irritant and used in cosmetics and food products, in topical and oral pharmaceutical formulations and preparations. It is also used as stabilizing agent, gelling agent, viscosity-increasing agent, suspending agent, emulsifying agent, and thickening agent**.**

Fig 13: Xanthan gum

Guar gum: [59]

Guar gum belongs to family Leguminosae and derived from *cyamopsis tetragonolobus* kernels. It is otherwise called Guaran, Cluster bean, Cyamopsis, Calcutta-lucerne, and Guarina. It is a whitish-yellow powder and has taste or scent. It is water soluble and is not soluble in organic solvents. Guar gum has ability to increase viscosity and

used in solid dosage forms as a disintegrant and binder in pharmaceutical industries**.**

Figure 15: Guar gum

Gellan Gum: [60]
Gellan gum (commercially available as Gelrite™ or Kelcogel™) is an anionic deacetylated exocellular polysaccharide secreted by *Pseudomonas elodea* with a tetra saccharide repeating unit of one α-Lrhamnose, one β-D-glucuronic acid and two β-D-glucuronic acid residues .Gellan gum produces temperature ward or cations instigated *in situ* gelling. Chemical structure of the polysaccharide has a tetra saccharide repeat unit consisting of two glucose (Glc) residues, one glucuronic acid (GlcA) residue, and one rhamnose (Rha) residue. These are linked together to give a tetra saccharide repeat unit**.**

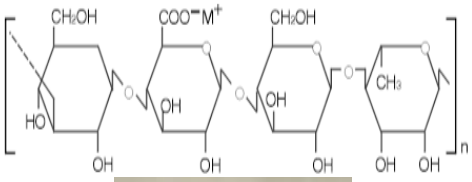


Figure 14: Gellan gum

Okra gum: [61]
Okra gum obtained from the pods of *Hibiscus esculentus*, yields high viscosity mucilage at low concentrations. It is polysaccharides having hydrophilic nature, currently used in pharmaceutical industry as a swelling polymer in dosage forms. Okra gum contains different coil polysaccharides consisting of rhamnose, galactose, and galacturonic acid are used as a tablet binding agent and to produce tablets with good friability, hardness and drug release profiles. Due to its chemically inert, safe, biodegradable, non-irritant, eco-friendly, and biocompatible properties, it has advantage over most commercial synthetic polymers because it is widely harvested and do not require toxicology studies. Okra gum is beneficial as a retarding polymer in the formulation of sustained release tablets as extraction in water give highly viscous solution with slimy appearance**.**


Figure 16: Okra gum

Gum karaya: [61]
Gum Karaya is known as Sterculia gum obtained from *Sterculia urens* Roxburgh and other species of Sterculia (Family – Sterculiaceae). After acid hydrolysis, Gum Karaya commonly produces D-galactose, D-galacturonic acid, L-rhamnose, and small proportions of D-glucuronic acid. It is sparingly soluble in water, poorly soluble in 0.1 N HCl and simulated gastric fluid and it is slightly insoluble in ethanol (95%), other similar organic solvents and alkali solutions at pH. As the gum Karaya swells in water, therefore in various plans, it is utilized as discharge rate controlling polymer. It had higher disintegration and low hydration limits. Under scrutiny, zero-request medication discharge is seen alongside disintegration of networks.


Figure 17: Gum Karaya

Psyllium husk: [62]
Psyllium obtained from the plant *Plantago psyllium*, the husk and seed of Plantago ovata is referred to as psyllium. Psyllium is classified as a mucilaginous fiber due to its powerful gel forming ability in water. Psyllium husk is biocompatible, inert, swellable, biodegradable, inexpensive, and easily available. The seed contains sterols, unsaturated fatty acids ranging 5–10% lipids, traces of cyclopentano pyridine-type alkaloids, proteins (15–18%), aucubi, and trisaccharide, carbohydrates planteose, and 10–12% mucilage of the heteroxylan type. Psyllium husk serves as reliable means for GRDDS as it shows release retardant properties. Specialists have additionally centered around delayed maintenance of dose structure use in the GIT,stomach**.**


Figure 18: psyllium husk

Xyloglucan:[63]

Xyloglucan is a polysaccharide derived from tamarind seeds and is composed of a (1-4)-β-D glucan backbone chain, which has (1-6)-α-D xylose branches that are partially substituted by (1-2)-β D galactoxylose. At the point when xyloglucan is part corrupted by β-galactosidase, the resultant item shows thermally reversible gelation by the lateral stacking of the rod like chains. The sol-gel change temperature fluctuates with the level of galactose end. It forms thermally reversible gels on warming to body temperature. Its potential application in oral conveyance abuses the proposed moderate gelation time (several minutes) that would permit *in situ* gelation in the stomach following the oral administration of chilled xyloglucan solution**.**

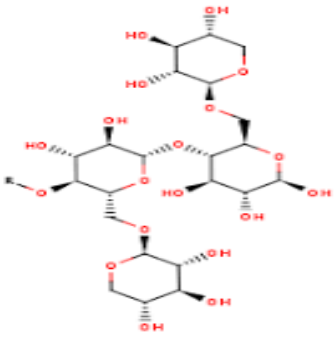


Figure 19: Xyloglucan

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 therefore; to have an easy administration an an, cidic pH would be needed before carbopol phase transition**.**

Figure 20: Carbopol

Tamarind gum: [64]

Tamarind is xyloglucan also called as *Tamarind Kernel* Powder is collected from seed of the tamarind tree under the family of Tamarindusindica. Tamarind gum; a polysaccharide composed of galactosyl: xylosyl: glucosyl in the ratio of 1:2:3. Higher plant primary cell walls has major structural polysaccharide called xyloglucan and used as binder, gel-forming agent, stabilizer, and thickener in pharmaceutical and food industries. Tamarind gums used in formulating matrix tablets are evaluated for its drug release characteristics by wet granulation technique. Different concentrations of polymers are used in tablets preparation. Reduction in medication discharge is seen with increment in polymer content**.**

Figure 21: Tamarind gum

Colocasiaesculenta gum: [65]

Colocasiaesculenta is a plant of Araceae family widely cultivated in tropical areas of Southeast Asia. Underground tubers (corns and cormels) containing rich in carbohydrates. Colocasia tubers mucilage hydrates and swells rapidly on coming in contact with water. The isolated tubers mucilage having sustained release properties and mucilage suitable for various GRDDS as a swelling polymer**.**

Figure 22: Colocasiaesculenta gum

Locust bean gum (LBG):

LBG otherwise called Carob bean gum and it is gotten from the seeds of the leguminous plant *Ceratonia siliquaLinn.*, consists basically of neutral galactomannan polymer made up of 1, 4-linked D-mannopyranosyl units with every fourth or fifth chain unit is substituted on C6 with a D-galactopyranosyl unit. There is variation in ratio of D-galactose to D-mannose based on varying origins of the gum source materials and growth effecting conditions of the plant during production. LBG is more effective to use as a gelling, stabilizer, and thickening agent and shows a wide variety of application in preparation and development of various novel drug delivery systems. [66,67]

Figure 23: Locust Bean Gum

EVALUATION PARAMETERS OF THE RAFT FORMING SYSTEM:

A*) In Vitro* Evaluation Parameters:

a) Floating/buoyancy test: [68]

It is determined in order to measure the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. Test is usually performed in simulated gastric fluid (SGF) which is maintained at 37 ^{0}C. The time between presentation of dose structure and its lightness on the mimicked gastric liquid and the time during which the dose structure stays light were estimated. The ideal opportunity for which the dose structure constantly glides on the disintegration media is named as skimming time. The time taken for measurements structure to develop on the outside of the medium is called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remains buoyant is called Total Floating Time (TFT).

b) Specific Gravity / Density:

Density can be determined by the displacement method using Benzene as displacement medium.

c) Texture analysis:

Texture analysis is done to determine the firmness, consistency and cohesiveness of the formulation. This analysis mainly indicates the syringeability of sol so the formulation can be easily administered *in-vivo*. Higher value of adhesiveness of gels is needed to maintain an intimate contact with surfaces like tissues. [69, 70]

d) Sol–gel change and gelling time:

Raft forming system is a bubbly fluid which includes the development of thick durable gel in contact with gastric liquids. The sol–gel progress temperature might be characterised as the temperature at which the stage change of sol meniscus is first noted when kept in a example tube at a particular temperature and afterward warmed at a predetermined rate. Gel arrangement is demonstrated by an absence of development of meniscus on tilting the cylinder. Gelling time is the time for first detection of gelation as defined above**.** [71]

e) Weight variation test: [72]

Twenty tablets were haphazardly chosen, weighed independently and the normal weight was determined. Not more than two of the individual weights deviate from the average weight by 5% as per IP 2010.

Table 1: IP standards for weight variation test

Average weight of tablets	% deviation
80mg or less	10
More than 80mg but less than 250mg	7.5
250mg or more	5

(f) Friability: [72]

Friability was determined by using roche friabilator. Six tablets were gauged and put in the friabilator. This friabilator was then worked at 25 rpm for four minutes. The tablets were then de-cleaned and weighed. It should not be more than 1%. %Friability was calculated as per the following equation:

$$\% \text{ Friability} = \frac{W1 - W2}{W1} \times 100$$

(g) Hardness: [72]

The Monsanto hardness tester was utilized to decide the tablet hardness. Scale was changed in accordance with zero and burden was steadily expanded until the tablet cracked. The estimation of the heap by then gave the proportion of the hardness of tablet. Hardness was communicated in kg/cm^2.

(h) Drug Content: [72]

Twenty tablets were weighted and powdered in a mortar. Accurately weighted quantity of the powder equivalent to about 168 mg of Ranitidine Hydrochloride was diluted to 100 ml with 0.1 N HCl in 100 ml volumetric flask. It was stirred for 15 min and filtered. 1 ml of the filtrate was diluted with 0.1 N HCl to produce 100 mcg / ml solution. The absorbance of the resulting.solution was measured at λmax 312.5 nm and the content of Ranitidine Hydrochloride was calculated from the absorbance obtained.

i) pH: [73]

The pH was measured of *in situ* solutions of cephalexin using a calibrated digital pH meter at 25^{0}C. All measurements of pH were made in triplicate.

j) Drug–excipient interaction study: [74]

Fourier transforms infra-red spectroscopy and thermal analysis. Fourier transform infra-red spectroscopy is performed to study compatibility of ingredients. During the gelation process, the nature of interacting forces can be evaluated using this technique. This technique employs potassium bromide pellet method. Thermo gravimetric analysis can also be conducted for *in situ* forming polymeric systems to quantitate the percentage of water in hydrogel. Differential scanning calorimetry can also be used to observe if there are any changes in thermo grams as compared with the pure ingredients used thus indicating the interactions**.**

B) *In Vivo* Evaluation parameters: [75]

a) Radiology:

X-beam is broadly utilized for assessment of inward body frameworks. Barium Sulfate is generally utilized Radio Opaque Marker. In this way, $BaSO_4$ is consolidated inside dose structure and X-beam pictures are taken at different interims to see GR.

b) X-Scintigraphy:

Like X-beam, transmitting materials are joined into measurements structure and after that picture is taken by scintigraphy. Generally utilized discharging material is 99Tc.

c) Gastroscopy:

Gastroscopy is peroral endoscopy utilized with fiber optics or video frameworks. Gastroscopy is utilized to review outwardly the impact of prolongation in stomach. It can likewise give the point assessment of GRDDS.

d) Magnetic Marker Monitoring:

In this system, dose structure is attractively set apart with joining iron powder inside, and pictures can be taken by extremely delicate bio-magnetic measurement equipment.

Preferred position of this strategy is that it is radiation less thus not perilous.

(e) Ultrasonography:

Utilized once in a while, not utilized by and large since it isn't discernible at digestive system.

f) ^{13}C Octanoic Acid Breath Test:

^{13}C Octanoic acid is incorporated into GRDDS. In stomach because of compound response, octanoic acid frees CO_2 gas which turns out in breath. The important atom which will come in CO_2 is replaced with ^{13}C isotope. So time up to which $^{13}CO_2$ gas is seen in breath can be considered as gastric maintenance time of measurement structure. As the dose structure moves to digestive tract, there is no response and no CO_2 discharge.

UTILIZATION OF RAFTING DRUG DELIVERY SYSTEMS: [76]

Boating drug conveyance offers few applications for medications having poor bioavailability due to the tight ingestion window in the upper part of the gastrointestinal tract. It holds the dose structure at the site of ingestion and along these lines upgrades the bioavilability. These are outlined as pursues.

(1) Sustained drug delivery:

FDDS can stay in the stomach for significant lots and henceforth can discharge the medication over a drawn out time frame. The issue of short gastric living arrangement time experienced with an oral CR plan henceforth can be overwhelmed with these frameworks. 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. e.g. Sustained release Rafting capsules of Nicardipine Hydrochloride.

(2)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 . e.g. Riboflavin and Furosemide.

(3) 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 Rafting drug delivery systems, thereby maximizing their absorption. e.g. A significantly increase in the bioavailability of Rafting dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric coated LASIX-long product (29.5%).

CONCLUSION

Controlled release gastroretentive dosage forms approve prolonged and unchanging input of the drug to the upper parts of the gastrointestinal (GI) tract and improve the bioavailability of medications that are characterized by a narrow absorption window. Based on the literature survey, it may be concluded that gastroretentive drug delivery offers various potential advantages for drug with poor bioavailability due to their restricted absorption in the upper gastrointestinal tract (GIT). They can be delivered effectively there by maximize their absorption and enhancing absolute bioavailability. And hence, it can be concluded that these dosage forms serve the best in the treatment of diseases related to the GIT, GERD and for extracting a prolonged action from a drug with a short half-life. Generally, the raft systems contain a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense and float on the gastric fluids. The system enclose a gel forming agent e.g alginic acid, sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) on exposure with gastric fluids. The raft thus formed drifts on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the oesophagus by acting as a barrier between the stomach and oesophagus. Drug absorption in the gastrointestinal tract is a highly flexible procedure and prolonging gastric retention of the dosage form reduces the time for drug absorption. Raft forming system promises to be a potential approach for heartburn and oesophagitis. Despite the number of difficulties to be worked out to achieve this, a large number of companies are focusing towards commercializing this technique. Finally it can be concluded that these dosage forms serve the best in the treatment of diseases concerned to the GIT.

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