# REVIEW ON GASTRO RETENTIVE DRUG DELIVERY SYSTEM: TREATMENT OF HELICOBACTER PYLORI INFECTIONS

**Aarati Maurya[1], N. G. Raghavendra Rao[1]*, Anuj Pathak[1], Balwan Singh[1], Irfan Ali[1,2]**

**Abstract:**
The recent technological investigations have been devoted towards different oral controlled release formulations. Floating formulations have now become the most fascinating and popular dosage forms in the present time. They introduced various novel technologies are used to enhance the retention time of the formulation in gastric region, there by achieving a zero order release. The conventional oral drugs are absorbed in the upper region of the Gastro intenstinal part or have a narrow absorption window have poor bioavailability because of shorter residence time. Pharma companies have acquire much attract in pharmaceutical investigations in the area of controlled release formulations most widely on floating formulations. The main goal of present review on GRDDS focusing on its present, future, and treatment of h. Pylori infections. To enhance the bioavailability and the increase the gastric residence time (GRT), controlled release drug delivery system can be used. One such system is the Gastroretentive drug delivery system, which was developed to convey the narrow absorption window drugs with enhanced bioavailability. In this review covers the advantages, disadvantages, ongoing floating techniques, advanced process to increase the floating gastric residence time of formulations, and research advancements made in GRDDS are deliberate.

**Keywords:** Gastroretentive formulations, Gastric floating Time, Physiology of Stomach, floating time, Helicobacter Pylori.

[1]Department of Pharmaceutics, KIET School of Pharmacy, KIET Group of Institutions, NCR-Delhi, Meerut Road, Muradanagar, Ghaziabad - 201206, U.P, India. Affiliated to Dr APJ Abdul Kalam Technical University, Lucknow, India.
[2]Department of Pharmaceutics, School of Pharmaceutical Education and Research, Jamia Hamdard, New Delhi 110062, India

***Corresponding Author:** Dr.N. G. Raghavendra Rao
*Professor, KSOP, KIET Group of Institutions, NCR-Delhi, Meerut Road, Muradnagar, Ghaziabad - 201206, U.P, India. Email Address: raghavendra.rao@kiet.edu, drngraghu@gmail.com, Contact No: +91 9966794479.

## INTRODUCTION:

In spite of gigantic headways in the study of delivery of drug, oral route is the favored route of administration as a result of minimal effort of treatment, simplicity of organization, understanding consistence, patient compliance and so on. During the recent many years, various systems for oral delivery have been generated as medicament repositories from which the drug can be delivered through a characterized length of time at an already determined and regulated rate. It's obvious from the ongoing logical, scientific and patent writing that a growing enthusiasm for novel oral controlled delivery system that are intended to be regained in the superior gastrointestinal tract for a slow and anticipated timeframe manage correct, both in academia and pharmaceutical commercial research gatherings.

A significant limitation in controlled drug delivery by oral route is that not every drug is absorbed consistently through the whole GIT. A few medications are invested in a specific portion of gut just or are ingested to a diverse degree in individual fragments of alimentary tract and digestive tract. This clearly shortens the time frame during which the medicine can be absorbed after it, which leads to lower bioavailability. Hence, the accomplishment of controlled drug delivery by oral route has confronted a few troubles related with physiological difficulties, similar to little GRT and uncertain gastric emptying time (GET)(1). Extended GRT enhances bioavailability, expands the length of release of drug, decreases wastage of drug and enhances the dissolvability of drug which are little soluble in a high pH system (2,3). This has set off the consideration on the road to the advancement of different floating formulations innovations to convey few drugs having 'short absorption window' there by enhance

bioavailability.

Floating measurement structures intended to hold in the stomach area for delayed time and delivery joined drugs and along these lines empower sustained and delayed contribution medication to the superior region of the gastrocolic part subsequently guaranteeing its ideal bioavailability. Consequently, they prolong the intervals of dosing and in addition increment the patient compliance past the degree of already present controlled delivery systems. This appeal is particularly powerful in drug release of sparingly soluble and insoluble substances. Floating measurements frames extraordinarily improved the pneuma-totherapy/drug therapy of the GIT through specific release of drug, prompting elevated drug levels at the acidic mucosa, enabling it conceivable to treating gastric and duodenal ulcers, esophagitis and so forth diminishing the danger of coeliac carcinoma and regulate non-systemic, zero order release delivery antacid formulations (4). Consequently, this innovation has produced colossal consideration over the most recent couple of many years likely from its possible utilization to enhance oral formulations of few significant drugs for which delayed gastro retention can extraordinarily enhance their bioavailability (5). Numerous innovative endeavors designed to evolve different slow-delivery floating drug delivery formulations in particular, high density formulations that is held in lower part of gastric area (6), low density system leading to floating in gastric fluid (7), bioadhesive formulations that leads to bio adhesion to gastric mucosa (8), unfoldable, extendible, or on the other hand swellable mechanisms that restrict the formulation from being emptied through the stomach's pyloric sphincter (9), superporous hydrogel systems (10), magnetic systems and so on.

This review focuses on the anatomical and physiological angles in planning GRDDS, approaches of gastroretentive drug delivery system, significant elements controlling gastro retention, recent approaches, therapy of H.Pylori infection and the future aspects of different gastroretentive technologies.

## FACTORS AFFECTING GRDDS (11-17):

**Bulk of dosage form**: GRT is reliant on the buoyancy of dosage form which is influenced by dosage form density. Dosage forms with low density than the stomach fluids, may float in them and those with high-density drop to the lower of the gastric area. Both sites discrete the formulation from the pylorus. A density of less than 1.0 gm/cm$^3$ is necessary to show buoyant.

**Texture and size of formulation:** These are significant in forming not easily digested unit dosage forms. In many cases, the bigger the formulation the more noteworthy will be the GRT because the bigger size of the formulation will not permit it to rapidly enter the intestine via pyloric sphincter. Dosage forms that have a width of more than 7.5 mm show a better GRT in comparison to the one having 9.9 mm.

**Ingestion of food, its nature and intake frequency:** All these have significant action on the gastro retention of the formulation. Normally, the existence of nutriment in the intestinal region enhances the duration of residence of the formulation and thereby, the consume of drug rises by allowing the medicine to prevail in the gastrointestinal region for a longer time frame. A rich protein feed and fats can expand the GRT by 4-10 hrs.

**Biological factors such as gender, age, posture, BMI, etc.:** In males, gastric emptying rate is faster than the females. Posture does not have any effect on GRT whether in upright, ambulatory or supine state. Gastric emptying is slowed down in elderly persons (above 70 years).

**Simultaneous administration of drugs:** Gastro retention may be altered by some drugs like anti-cholinergic, Opiates, prokinetic agents like Metoclopramide etc.

## ANATOMY AND PHYSIOLOGY OF STOMACH:

**A. Stomach Anatomy:** The human stomach looks like the English alphabet "J". The volume different from 1.12L – 1.5 L. Figure 1 shows the Anatomy of stomach. The fundus, body, and antrum are the three sections of the stomach. The upper part of the stomach i.e., the fundus and body serve as a reservoir for ingested food while the bottom part antrum, has the function of grinding or mixing and has propelling action (like a pump). The posterior end made one novel strategy in this arena is GRDDS. By continually dispensing the medication for a protracted length of time prior to it reaching its absorption site, GRDDS can augment the regulated delivery of medications with an absorption window (18). Floating formulations are advantageous for such API by enhancing their zero-order release (19). Managing the continuous pharmacological extent over an extended time period and thus decreased

in hampering in the pharmacological extent lowers the pharma-ceutical devastation, few drugs are sparingly soluble at huge pH conditions thereby increase such drugs solubility (some drugs are having weakly alkaline nature like domperidone, papaverine) of parts of stomach function as a depot for not digested substances (20, 21). Gastric emptying scintigraphy happens two of them in the fasting states and the nourished states. When the starved state is going on, an inter digestive series of electrical events occurs that cycles both through the stomach as well as abdomen several 2-3 hrs, which is known as inter assimilate myloelectric cycle or migratory myoelectric complex (MMC) that is further divided in to four phases. Following the consumption of a mixed meal, the rhythm of contractions shifts from a fasted to a fed condition, which is also known as a shift in the digestive motility pattern. (22).

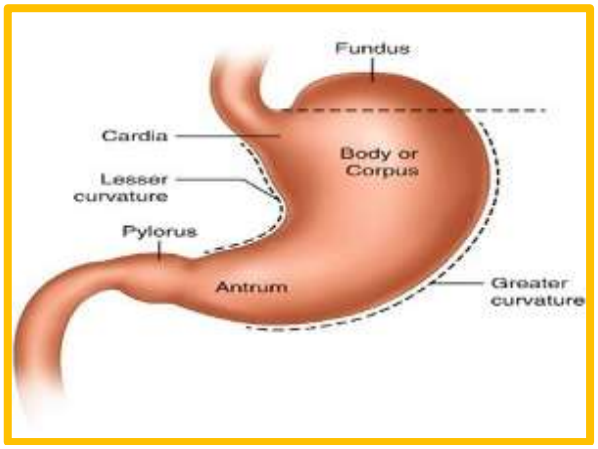



**Fig 1:** Anatomy of Stomach

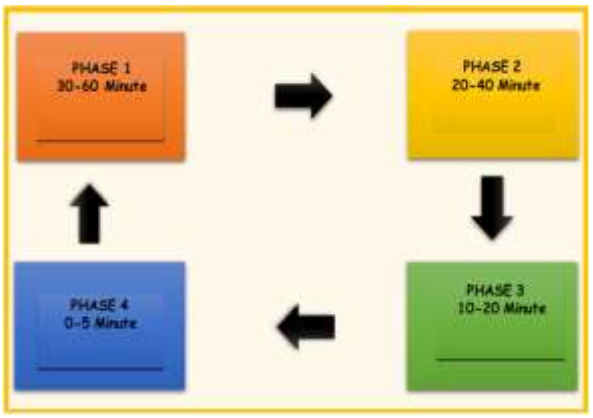
**B. Stomach Physiology:**

**Structure:** There are four primary parts of the stomach. Storage is the primary role of the fundus and body, whereas the cardia has a mixing or grinding role. Table 1 displays the pH range.

**Table 1:** pH range of different parts of GIT

| S no | GIT | pH |
|---|---|---|
| 1 | Stomach | 1-3 |
| 2 | Small intestine | 5-7.5 |
| 3 | Large intestine | 7.9-8 |
| 4 | Rectum | 7.5-8 |

The activity of gastric emptying is obtained in abstain as well as nourish states but the specimen of motivity is different in the two states. When the abstain state is going on, an interdigestive sequence of electrical events occur, that cycles both through the stomach as well as intestine. These events are called as migrating myoelectric complex (MMC) (23). There are four steps to the migrating motor complex:




- **Phase 1:** 40-60 mins, quiescent period with occasional contractions
- **Phase 2:** 20-40 mins, increasing contractions as the phase progresses along with increasing frequency and intensity
- **Phase 3:** 10-20 mins, burst phase, intense contractions, also called "housekeeper wave" as all the material in the stomach is cleared out from the stomach and send to the intestine
- **Phase 4:** 0-5 mins, happens between Phase 3 and Phase 1.

**ADVANTAGES OF GRDDS:**

1. The absorption of drug is improved due to prolonged floating time and more time is spent by the formulation at the absorption site.
2. The bioavailability of drug is enhanced.
3. Controlled delivery of drugs is obtained.
4. Since the API is released steadily at a controlled release, mucosal irritation is minimized.
5. Treatment of various GIT disorders like pyrosis, providing local exertion.
6. Provides facilitate of administration and better patient acceptance.
7. Dosing frequency is reduced.
8. Provide drug delivery to specific locations.

**DISADVANTAGES OFGRDDS:**

The main disadvantage of GRDDS is the need of enough liquid in the gastric region so that the dosage form can easily float. This can be easily avoided by coating the formulation developed by using bio adhesive polymers which will cohere to the the moist, inner lining of the stomach (24).

1. The floating retention of the formulation in the gastric region is afflicted by different factors like coeliac excitability, pH and existence of nutriment. These factors never remain continuous and thus, the suitable floating can never be achieved.

2. API causing exasperates and abrasion to the mucosal lining of the gastric region neither appropriate for this type of dosage form.
3. The gastric emptying time varies greatly.
4. Patients shouldn't receive floating dose forms prior to bedtime.
5. Few API having solubility or stability problem in gastric liquid are unsuitable for Floating delivery.
6. The formulation must be consumed with a glass of water.
7. The drugs getting absorbed all through the intestinal tract and undergoing first-pass metabolism, are not suitable candidates.

**TABLE 2:** Differentiate between Floating dds vs. Conventional dds:

| S.No | Parameter | Conventional DDs | GRDDs |
|---|---|---|---|
| 1. | Toxicity | High risk | Less risk |
| 2. | Patient compliance | Low | Enahance patient compliance. |
| 3. | Drugs with a short intestinal absorption window | Unsuitable. | Suitable. |
| 4. | Drugs with a rapid GIT absorption rate | Hardly any benefit. | Significant benefit. |
| 5. | Drug that breaks down in the colon | Hardly any benefit. | extremely advantageous. |
| 6. | Localised stomach-based drug action | Hardly any benefit. | Significant benefit. |
| 7. | Poorly soluble drugs at an alkaline pH | Hardly any benefit. | Significant benefit. |
| 8. | Dose dumping | High risk of dose dumping. | No risk of dose dumping. |
| 9. | Drugs that undergo degradation in colon | Significant benefit. | Hardly any benefit. |

**DRUG CANDIDATES SUITABLE FOR GRDDS** (2, 3, 25, 26)**:**

Following are the suitable drugs for floating formulations.

1. Medicaments are active locally in acidic pH the stomach (e.g., antacids, misoprostol).
2. Medicaments with narrow absorption window (e.g., L-DOPA, riboflavin).
3. Drugs those are unstable in the colonic area (e.g., ranitidine HCl, captopril).
4. Drugs having poor solubility at high pH values (e.g., verapamil).
5. Drugs disturbing colonic microbes that are normal (drugs for H. pylori,amoxicillin).

Widely used drugs for floating drug delivery system are shown in Table 3.

**Table 3:** Trading-wise drugs used in floating Formulations:

| Formulation | Widely used Drugs used for floating Formulations |
|---|---|
| Tablets | Cephalexin, Ziduvudine, Losartan, Furosemide, Ciprofloxacin, Captopril, Aspirin, Nimodipine, Amoxycillin trihydrate, Ampicillin etc. |
| Capsules | Nicardipine, L-Dopa and benserazide, Misoprostol, Diazepam, Propranolol. |
| Microspheres | Verapamil, Aspirin, Tranilast, Ibuprofen, Terfenadine, Orlistat. |
| Granules | Diclofenac sodium, Prednisolone, Fluorouracil, Isosorbide dinitrate, Ranitidine HCl. |
| Films | Albendazole, Quinidine gluconate, Cinnarizine. Several basic drugs-Riboflavin. |
| Bilayer tablet | Misoprostol, Atenolol, Loratadine, Curcumin β-cyclodextrin complex. |

Few drugs are not suitable for development of floating formulations (27, 28).

1. Pharmaceutical medicaments having very limited gastric solubility e.g. phenytoin etc.
2. Drugs that suffer not stable in the acidic environment e.g. erythromycin etc.
3. Medications designed for colonic selective release

Limitations of the designing of Floating delivery systems (29-32).

1. Some medications, such as those that produce stomach lesions and are unstable in very acidic environments, should not be utilised.
2. The efficiency of this method may be questioned due to excessive mucus turnover and bio adhesion in an acidic media.
3. In cases where swellable systems exist, the floating systems in patients with achlorhydria may be in doubt.

**Need For GRDDS** (33)**:**

- The oral conventional form of drug delivery has many advantages, one of which is non-specificity of the site of delivery.
- The absorption of some drugs is site-specific only. The focus is on such drugs having site specificity.
- One of the site-specific deliveries for drug is Gastro-retentive delivery. This delivery is done either in the stomach or in the gut. This is targeted by holding the formulation in the stomach releasing the drug from the formulation in a controlled way to a certain site in the gastrointestinal tract.

**Characteristic Controlling Gastric Floating Formulations** (34):

1. **Size of the Particle**: To enter across the pyloric valve into the small intestine the drug molecule size must be in the range of 1-2 mm (35).

2. **Density:** The density of formulation also affects gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high-density systems sink to bottom of the stomach (36). Both positions may isolate the dosage system from the pylorus. A density of less than 1.0 gm. /$cm^3$ is required to exhibit floating property of the drug (37, 38).

3. **Texture of Formulation**: Texture of the drug delivery system is important in designing indigestible single unit solid dosage forms. Size should be greater than 7.5 mm in diameter[38] and Ring and tetrahedron devices with flexural modulus of 22.5-48 KSI (keto pound/inch) shows 90-100% GRT (gastric retention times) (39).

4. **Food Intake and Its Nature**: Food consumed, volume of food, consistency of food, and frequency of feeding has a profound effect on the gastric retention of dosage forms. The presence or absence of food in the gastrointestinal tract influences the GRT of the dosage form. Usually the presence of food in GIT improves the GRT of the given dosage form and thus the absorption of drugs increases by allowing or allowed to stay at the gastric region for a maximum time (40).

5. **Effect of Gender, Age & Posture** (41)**:**

- SEX: Woman have low acidic resident time than males.
- AGE: Age > 70 shows longer GRT.
- POSITION/ATTITUDE: varies between spine and upright ambulatory states.

6. **Medicament Character:** Medicaments with contact on gastrointestinal transit time e.g. codeine and pharmacokinetic agents e.g. metoclopramide cisapride enhances gastro retention time (42).

7. **Other Factors (**42):

- The relative molecular mass and hydrophobicity of the drug depending on its photoionization are important parameter.
- Diseased state of a person.
- Administration of drugs that affects gastrointestinal transit time.

**Polymers used In GRDDS:**

For a targeted delivery of drug throughout the intestinal tract, polymers are utilized. The various types of polymeric substances used for the delivery of the dosage form in GRDDS. The types of polymers used are Natural polymers like albumin, Gelatin, Starch, etc., and Synthetic polymers like HPMC, Carbopol, ethyl cellulose, etc. This article gives information on the various polymers that are used in GRDDS (43).

**Natural polymers (**44-45**):**

The natural gums are obtained from plants and are hydrophilic in nature. They have high molecular weight. These natural polymers are insoluble in inorganic solvents such as hydrocarbon, ether, etc. The natural gums are soluble in water or they absorb the water and then they swell up giving a jelly-like solution.

**Natural Polymers from Plant Origin Suitable to GRDDS:** Plant sources, which are naturally available, can be used to create natural polymers. They have no negative effects on human beings. Most of the natural polymers are non-toxic, non-irritant, and biocompatible as these plant materials are having rich in carbohydrates. Natural polymers are isolated from natural sources using organic solvents and are inexpensively and easily gathered in big numbers during various seasons. Due to its widespread application in industries, their productions are now being promoted in emerging countries. The percentage yield and fragments in natural materials may vary with different species and also differences in their seasonal collection from different region and at different times. They might produce at a sluggish pace. Applications of natural polymers used in GRDDS are mentioned in table 4.

**Table 4:** Applications of natural polymers in GRDDS

| Sl No | Natural polymers | Applications |
|---|---|---|
| 1 | Colocasia esculenta gum | Swelling agent, Binders, Mucoadhesive, Sustained effect |
| 2 | Guar gum | Swelling agent, Binders, Mucoadhesive, Sustained effect |
| 3 | Gum karaya | Swelling agent, Binders, Mucoadhesive, Sustained effect |
| 4 | Limonia acidissima gum | Swelling agent, Binders, Mucoadhesive, Sustained effect |
| 5 | LBG(Locust bean gum) | Swelling agent, Binders, Mucoadhesive, Sustained effect |
| 6 | Mimosa pudica gum | Swelling agent, Binders, Mucoadhesive, Sustained effect |
| 7 | Okra gum | Swelling agent, Binders, Mucoadhesive, Sustained effect |
| 8 | Tamarind gum | Swelling agent, Binders, Mucoadhesive, Sustained effect |
| 9 | Tara gum | Swelling agent, Binders, Mucoadhesive, Sustained effect |
| 10 | Xanthan gum | Swelling agent, Binders, Mucoadhesive, Sustained effect |
| 11 | Carrageenan | Swelling agent, Binders, Sustained effect |
| 12 | Chitosan | Swelling agent, Binders, Sustained effect |
| 13 | Pectin | Swelling agent, Binders, Sustained effect |
| 14 | Psyllium husk | Swelling agent, Binders, Sustained effect |

**Synthetic polymers:**
With the advancement in the pharma industry, the use of these Synthetic polymers is also becoming very significant in the pharmaceutical industry. The synthetic polymer is used as binders, film coating agent, etc. Synthetic polymers are either completely synthetic or they are altered versions of natural polymer called as semi-synthetic.

Different types of synthetic polymers are –
1. Biodegradable polymers like Lactides, Poly alkyl cyanoacrylates, etc.
2. Non-biodegradable polymers like Polymethyl methacrylate, epoxy polymers, etc.

Various polymers have various applications like –
- Modified starch, HPMC and Carbopol 974p are employed to decrease the release of drug from formulation.
- Ethyl cellulose is employed in controlled release systems in order to increase the lag period of time.
- PLGA and Chitosan have their application in delivery of Vaccines.
- Chitosan coated PLGA polymers are used in Targeted drug delivery system.
- Polyvinyl alcohol and Polyacrylidine adsorb the harmful substances present in the blood.

**TECHNOLOGIES OF GRDDS:**
Different technologies for GRDDS are **s**hown in figure 2.
1. Floating Formulations (FDDS)
2. Bio-adhesive or Muco-adhesive systems
3. Expandable systems
4. Unfoldable and Swellable systems
5. High Density (Sinking)System
6. Super Porous Hydrogel systems
7. Magnetic systems

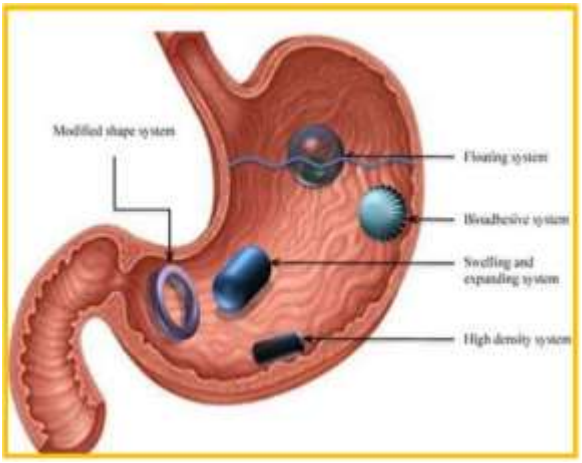



**Fig.2** Technologies of GRDDS

**1. FLOATING DOSAGE FORMULATION:**
This formulation has squat bulk density than the acidic fluids to remain float in the gastric fluid for an extended time as showed in fig 3. As the dosage formulation is floating on the gastric fluid, the drug is released from the system at a specific rate. After the release of drug, the remaining system is emptied. This leads to increase gastric residence time and a fine control over the variation in the plasma drug concentration (46, 47).

The main requirements for this system are(48-50):
- Content must be released slowly
- It must have a selected gravity less than that of chime (hydrochloric acid content) (1.004-1.01gm/$cm^3$).
- It should develop a tenacious gel barrier.

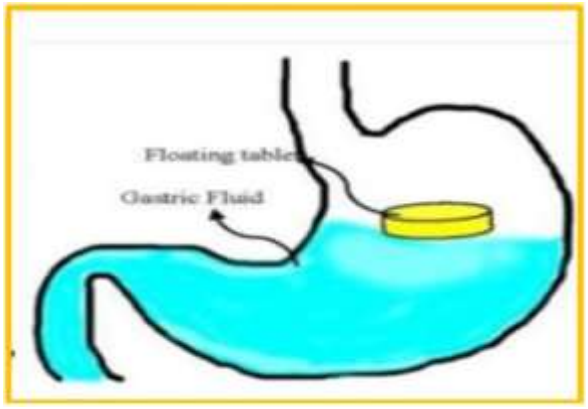



**Fig.3:** Floating formulations

**FDDS is further divided into:**

**1. Effervescent system:**

They contain gas-creating substances (sodium bicarbonate, tartaric acid or citric acid) to attain floating ability. The gas which is generated is $CO_2$. Once gas-generating agents come in meet with the acidic pH solution, immediately carbon dioxide is generated from the drug delivery system reducing the density of the system and thus causing it float on the gastric content. The buoyancy can also be attained by utilising swellable polymers like Hydroxypropyl methyl cellulose, chitosan (2, 48).

**Effervescent is further divided into following:**

**A. Gas generating systems:** It utilizes effervescent reaction between carbonate/ bicarbonate salts and citric/tartaric acid. $CO_2$ is released in water shown in fig 4. The dosage form is put into the beaker, it will sink to the bottom of the beaker and with the release of gas it will rise up and float (51-53).

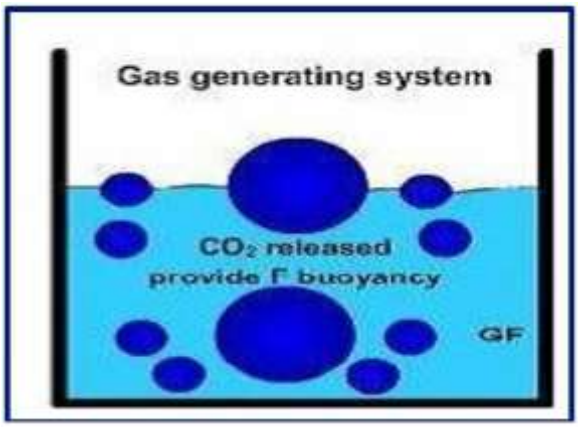



**Fig.4:** Gas generating system

**B. Evaporative liquid containing formulations:** It consists of an inflatable chamber with a liquid like ether that releases gas at body temperature leading to floatation of the chamber in the stomach. The inflatable chamber consists of a pool of medicines in a gelatin capsule. The capsule releases the stored drug after intake with the inflatable chamber leading to the formation of gas bubbles and permits unconstrained ejection of the inflatable systems from the stomach (54).

**C. Raft forming systems:** Gel forming polymer like sodium alginate is used mixed with gas generating agents like sodium carbonate. Once gel developed and this gel come in contact with the gastric fluid, the gas carbon dioxide produced is trapped within the gel, the gel swells forming a layer called as rafts. These rafts remain on the gastric fluid and shown in fig 5. Such systems are used for delivering antacids like aluminium hydroxide, calcium carbonate, etc. The mechanical strength of this system is weak and can be destroyed by MMC.

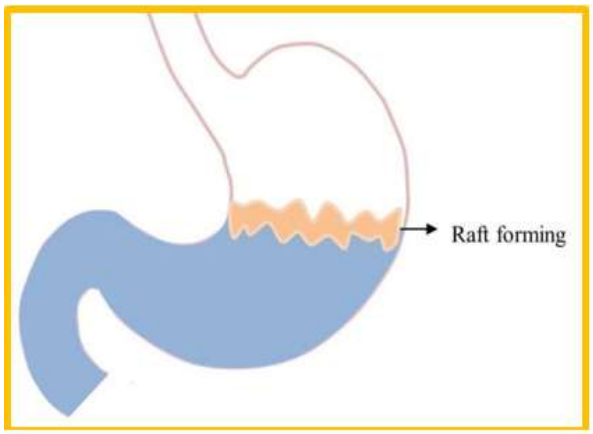



**Fig.5:** Raft forming system

**1. Non-Effervescent system:**

This system uses swellable cellulose type polymers or gel forming polymers or matrix forming polymers like HPMC, chitosan, Carbopol, agar, sodium alginate, etc.

**Non-Effervescent system can be classified as follows:**

**A. Colloidal gel barrier system:** This formulation comprises of drug with gel-forming hydrocolloids so that it can remain float in the gastric fluids. This method contains different highly soluble gel-forming cellulose type hydrocolloid of high level like HPMC, HEC, polysaccharides, matrix forming polymer like polystyrene, polyacrylate. Drug release from Colloidal gel barrier system has shown in figure 6 and 7.When the formulation comes in meet with the stomach juice, the hydrocolloids, hydrate then they may lead to the formation of colloid gel barrier on its surface (55).

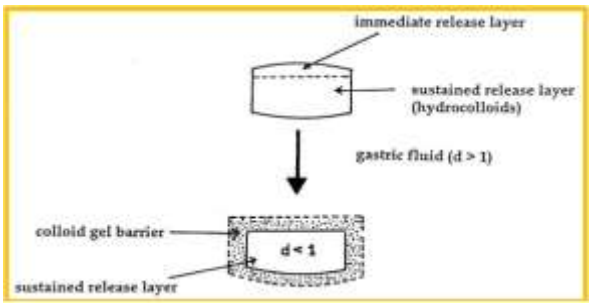



**Fig.6:** Colloidal gel barrier system

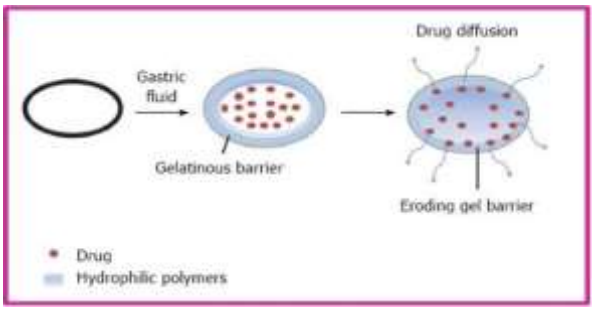



**Fig.7:** drug release from Colloidal gel barrier system

**B. Microporous membrane systems:** In this, the drug is encapsulated in a very small pores or channels with diameters in the micron or nanometer range compartment with pores on it's above and below (Fig 8). The side walls are secure to prevent association with acidic fluid with the API. The floating compartment containing the accidental air leads to the floatation of the transport device above the simulated digestive fluid. The simulated digestive fluid across through the opening, diffuse the drug and conveys the diffused drug across the intestine for assimilation.

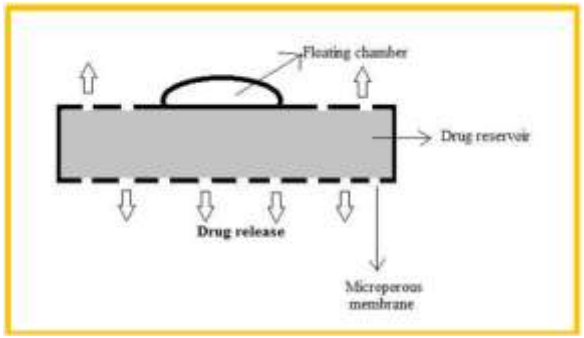



**Fig.8:** Microporous membrane systems

**C. Alginate beads:** This system makes use of spherical beads (Fig 9) of roughly having 2.5 mm diameter (56). These beads are formed by placing the sodium alginate solution into aqueous calcium chloride solution leading to the precipitousness of calcium alginic acid. They are divided, quickly frozen in liquid nitrogen, and then freeze-dried at 40 ° C for 24 hours, resulting in the production of a porous system that can float for more than 12 hours.

Sodium alginate + Calcium Chloride → Calcium alginate + NaCl

**Fig.9:** Floating Alginate beads

**D. Hollow Microspheres/Micro balloons:** Their preparation is done by Solvent Evaporation Method shown in fig 10. Mostly used polymers are polycarbonate, calcium alginic acid, Eudragit S etc. The above formulations can float over acidic dispersion media containing surface active agents for about 12hrs (57). Release pattern from microballons shown in fig 11.

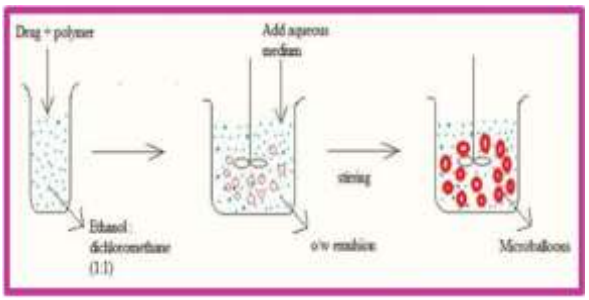



**Fig. 10:** Formation process of Hollow Microspheres system

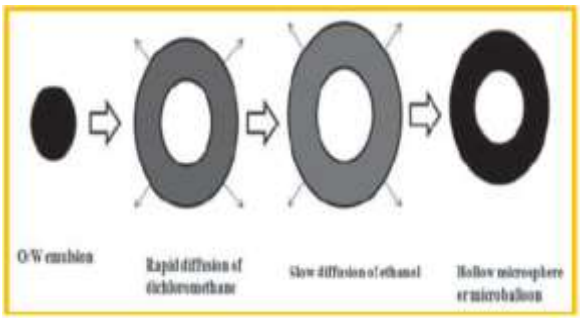



**Fig.11:** Release from Hollow Microspheres system

**2. Mucoadhesive systems:**

Bio-adhesive formulations are utilized as a delivery device inside the lumen to upgrade drug absorption in a site-explicit way shown in fig 12. This technology includes the utilization of muco-adhesive polymeric materials, which can hold fast to the epithelial membrane surface in the stomach (58). Bio-adhesive polymeric systems hold fast to

gastric epithelial membrane cells or mucous membrane. That expands the gastric retention by expanding the closeness and time of contact between floating formulation and the biological membrane. The commonly used excipients in these systems are chitosan, gliadin, alginate, Carbopol etc. Surface epithelium adhesive capabilities have been observed and used for the creation of GRDDS reliant on bio-adhesive polymers. A drug's capacity to adhere to a mucus layer boosts the duration that it remains in one particular organ site, which improves its local or systemic activity.

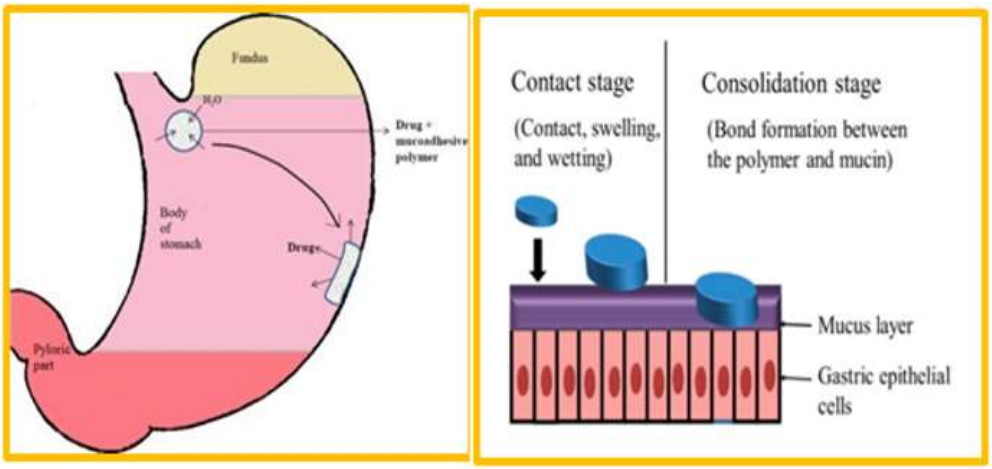



**Fig.12:** Muco-adhesive systems

The muco-adhesion of dosage form depends on their ability to attach to the mucosal surface by several ways. The mechanisms are as follows (59, 60):

**A.** The Wetting Theory: Relies on the bio adhesive polymer's ability to disseminate and create intimate contact with the mucous layers.

**B.** The Diffusion Theory: Suggests that mucin strands are physically ensnared by flexible polymer chains, or that mucin strands are interpenetrated into the permeable structure of the polymer substrate.

**C.** The Absorption Theory: Recommends that bioadhesion depends on some forces like Vander Waal forces, hydrogen bonding etc.

**D.** The Electron Theory: It says that there is the presence of some appealing geostatic forces between the bioadhesive substance and the glycoprotein mucin.

**2. Expandable systems:**

Gastric retention of drug delivery systems conceivably improved by enlarging its size before reaching the diameter of pylorus. If the formulation is able to achieve a size larger than pylorus shown in fig 13, then the gastric retention of that dosage form may be prolonged. So, this immense size should be attained fastly or else the formulation will be emptied from the stomach. Thus, the requirements for developing an expansible system for prolonging residence time are a small setup for oral admission; an extended floating form and a small form empowering removal following drug discharge from the system. They should also be capable to withstand contractility and peristalsis of the stomach (61).

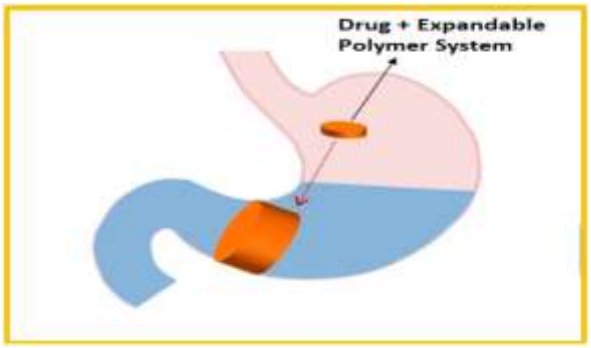



**Fig. 13:** Expandable System

**3. Unfoldable and swellable systems:**

Unfoldable and swellable systems have been used for developing an efficient gastroretentive drug delivery system. They utilize environment-friendly polymers. Their idea is based on a carrier like a capsule that can be extended in the gastric region. This system with expanded size but with absence of high rigidity are not able to hold in the gastric region leading to brief hinder and disease of the stomach. So, rigidity of these systems is also essential for designing such a gastroretentive delivery.

Swellable systems are likewise held in the intestinal tract due to their mechanical properties. The swelling oh the formulation occurs due to osmosis of aqueous and also, the formulation is sufficiently small to be swallowed by the simulated acidic liquid shown in fig 14. This size-

expanding drug delivery system conceivably poses a danger of permanent floating in the gastric area and could prompt life-threatening impacts upon taking in the formulation. Also, they are economically cheap. A main benefit of these formulations is in the autonomy of their efficiencies on the filling condition of the stomach (61).

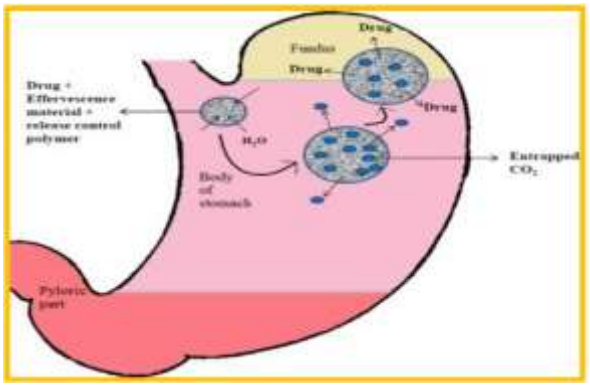



**Fig. 14:** Swellable System

**4. High Density (Sinking)System:**

The retention mechanism for this system is alluviation, as they are frequently low amount to be floated within the pleat of the body of stomach near the colonic region properly showed in fig 15. The density of the dose form should exceed the density of the gastric fluid (1.004 gm/cm$^3$). They are formed by coating the drug on a heavy core or by mixing with inert substances like zinc oxide, iron oxide etc. The density is increased by 1.5-2.4 gm/cm$^3$. For significant prolongation of the GRT, the density should be close to 2.5 gm/cm$^3$. But the efficacy of this system in humans is little (62).

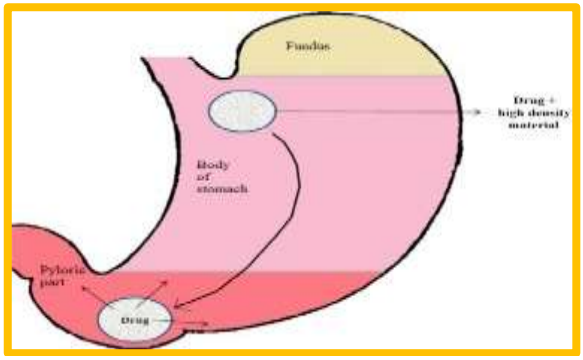



**Fig.15:** High density System

**5. Super Porous Hydrogel Systems:**

The conventional hydrogels are slower and take a few hours to achieve the equilibrium during which the pervious swollen having aperture size greater than 100 micrometer swells to adjust size may happen within a few minutes shown in fig 16. Due to the quick retention of water by capillary wetting via various open pores interconnected, they swell to an enormous size and are expected to have adequate mechanical solidarity to deal with the pressure because of the gastric contraction, which is acquired through the articulation of hydrophilic particulate materials.

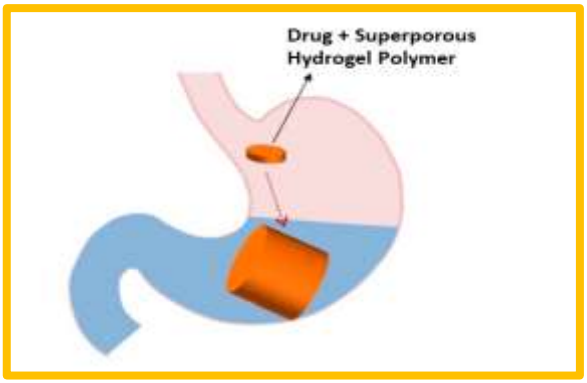



**Fig. 16:** Super Porous Hydrogel Systems

**6. Magneto Methods:**

Magneto method is grounded on a basic principle that the formulation consists a small inner magnet and a magnet is placed on the stomach from outside to bring the magnetic dosage form to the favorable position (Fig 17). Some authors have noticed that the gastric resident time and blood plasma drug engrossment were enhanced in the presence of the external magnet. These systems used for performing an *in-vivo* experiment in rabbits by using bio adhesive granules containing ultra-fine ferrite. The found out that by an external magnetic field, all the granules in the stomach were retained for more than 2 hrs. Since, this system requires specific positioning of the magnet, so it faces low patient compliance. Hence, these systems require more future research studies focusing more on their clinical importance.

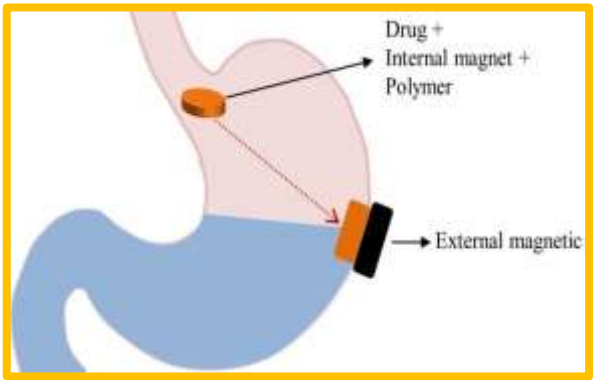



**Fig 17:** Magnetic system

**THERAPY FOR *Helicobacter pylori* INFECTION BY GRDDS:**

***Helicobacter pylori*** is one of the most well-known pathogenic bacterial contaminations, including some staid diseases like peptic ulcers,

gastric lymphoma, acute duodenal disease, etc., A very large proportion of the global population is being affected by the above-mentioned diseases. *H. pylori* is primarily found in the gastric mucosa or at the point where the mucous layer and the stomach's antral epithelial cells meet.

The disclosure of these bacterial parasites has reformed for the therapy of peptic ulcer. Most antibiotic drugs are less effective against *H. pylori* in culture and single antimicrobial therapy is not enough for complete removal of *H. pylori* infection. This is a direct result of low concentration arriving at the microorganism under the mucosa, precariousness of the drug in the pH of the gastric liquid and presence of the antibiotic in the stomach for a short period of time. For the complete removal of *H. pylori*, a coalescence of more than one antibiotic and anti- secretory agents is needed, yet these regimens are not completely compelling. Also, other problems are also there like patient compliance, bacterial resistance, side effects, etc. Other techniques have been used for the achieved removal of H. *pylori* from the abdomen.

Since the conventional formulations don't stay in the stomach for longer period of time, they are not able to convey the antibacterial substances to the site of disease in compelling concentrations and in complete active forms. One approach to improve the adequacy in complete removal of *H. pylori* is the delivery of the antibiotic natively in the stomach, so that more medicine will be able to permeate the mucosal barrier and operate on *H. pylori* thanks to increased stability and a longer residence period. The cause for partial eradication of *H. pylori* from the stomach is short residence time of antibiotics in the stomach and destruction of antimicrobials by the acid in stomach. Thus, it is important to configure such formulations that not just ease the weaknesses of conventional formulation but in addition deliver the antibiotics to the diseased cells. The absorption of antimicrobial drugs into the mucous layer from the gastric lumen is accepted to be more successful for complete removal of *H. pylori* in comparison to the absorption from the basolateral membrane.

The main attention of researcher's main aim to development of new drug delivery systems was extension of residence time in the stomach for complete removal of *H. pylori* effectively. Various drug delivery systems developed are polyelectrolyte coated multi-layered liposomes (Nanoparticles), floating in situ gelling systems, etc (63-66).

**Formulations strategies for treatment of H. pylori:**

Specific approach to enhance the efficiency in controlling the diseases is to administration of some of the antibacterial substances act natively in the stomach. Improved stability and prolonged retention time of drug will enable extra antibacterial substances to pass through the gastric mucus membrane then they operate on H. pylori. The negative aspect for the partial eradication of H. pylori is likely the short residence duration of antimicrobial agents in the stomach, preventing appropriate action of antimicrobial substance concentrations in the gastric mucous membrane or epithelial cell surfaces where H. pylori occurs. (67). Another reason may be few antimicrobial agents are decomposed in gastric acid. Both the stomach lumen and the gastric blood supply have restrictions on how antimicrobial medications can access the location. It's possible that H. pylori has developed resistance to widely-used antibiotic substances. Traditional formulations might not stay in the stomach for a long time, thereby antimicrobial medicines are unable to reach the specific infection site in sufficient quantities or in their fully active forms. Because of this, it is crucial to create drug delivery methods that not only address the drawbacks of traditional formulation vehicles but also deliver antimicrobial agents to diseased cell lines. Antimicrobial drugs are thought to be more successful at eliminating H. pylori when absorbed into the mucus through the mucus layer rather than the basolateral membrane (from blood). For more efficient H. pylori eradication, researchers have concentrated on creating novel dds that might stay in the stomach for a long duration. (68-70).

**Polyelectrolyte coated multilayered liposomes (nanocapsules):**

For the total eradication of H. pylori, Jain P et al. produced polyelectrolyte coated with multilamellar liposomes. The formulations have an impact on the benefits of vesicular and particulate carriers. In order to create the formulation, liposomes were used as the core and alternate coatings of polyanion (poly(acrylic acid, PAA) and polycation (poly(allylamine hydrochloride, PAH) were used. The polyelectrolyte-based multilayered system (nanocapsules), which provided longer drug release in simulated gastric fluid when compared to standard liposomes, is perfectly adapted for formulation against H. pylori infection in the abdomen. The formulation's successful in-vitro

activity and binding propensity were suggested by tests on cultured H. pylori that included agglutination, adhesion, and in situ adherence assays. A study on the in-vivo clearance of pathogens using a mouse model infected with H. pylori was conducted. Considerable H. pylori infections were shown to be controlled by the new delivery technique.

**Floating in situ gelling system**: Amoxicillin and clarithromycin floating in situ gelling systems premised on gellan gum were created by dissolving different concentrations of the gum in deionized water with sodium citrate, the drugs, and calcium carbonate as a gas producing agent (71,72). This technique required less amoxicillin and clarithromycin to eradicate H. pylori than the matching simple suspensions did. For addressing H. pylori infections, floating systems—which include gas-generating systems and non-effervescent systems—have been employed most frequently. (73).

**Vaccine delivery systems (gastric-retention by mucoadhesive):**

The inadequacy of antibacterial drug therapy to inhibit reinfection and the rise in resistance strains are its two main downsides, and they are what are motivating researchers to create a vaccine to restrict this infection (74). Immunization against pathogens that enter the body through mucosal membranes is provided by mucosal vaccination. Mucosal vaccination has many benefits, including greater patient acceptance, simple delivery, minimal cost (trained workers are not necessary), and a reduced chance of unfavorable needle-borne illnesses (AIDS, etc.). Moreover, vaccination of mucosal surfaces may increase mucosal immunity, which is present not only at the vaccination spot but also at distant mucosal epithelia (75,76). By destroying the pathogen at the point of entrance, it may also be able to avert infection. (77). Since chitosan can loosen up tight junctions and encourage paracellular transport of antigen via mucosa, it is appropriate for mucosal vaccination. (78,79).

**Nanoparticles:**

The primary goal of nanoparticles and muco-penetrating formulations was to completely eradicate H. pylori, which had deeply colonised the lining of the stomach. The nanoparticles can both adhere to surfaces and allow medications to pass through to the mucous layer (80). In order to create pH-responsive chitosan/heparin nanoparticles, heparin solution is added to a chitosan solution and appropriately stirred by magnetic stirring at ambient temperatures. The nanoparticles appeared to be stable at pH 1.2–2.5, having a particle size of 130–300 nm, and a positive surface charge, enabling them to guard against harmful gastric acids for a medication that had been integrated. Nanoparticles cling to cell-cell junctions, enter them, and interact with them natively to drastically reduce H. pylori infections (81,82). H. pylori infection can be treated with proprietary gastric retention formulations now on the market.

Marketed products used to cure the *H. pylori* infection using floating formulations given below table 5.

**Table 5:** Trading-wise products used to treat *H. pylori* infection

| S.No | Product name | API | Type of delivery system |
|---|---|---|---|
| 1 | Amalgate Float Coat | Amphojel- Mylanta Antacid | Gastroretentive dosage form. |
| 2 | Topalkan | Amphojel- Mylanta Antacid | Effervescent Gastroretentive liquid alginate preparation. |
| 3 | Cifran OD | Ciprofloxacin (1 gm) | Gas generating FDDS |
| 4 | Liquid Gaviscone | Aluminium hydroxide | Colloidal gel preparation |
| 5 | Cyrotech | Misoprostol | Bilayer floating capsule technology |

**EVALUATION PARAMETERS FOR GRDDS:**

In vitro estimation of floating formulations are used to predict the in-vivo execution. The various analytical parameters for floating dosage forms includes calculation of tensile strength of tablet, weight variation, friability, drug content, etc. for the determination of floating behavior of the formulation, the parameters for evaluation used are floating lag time and total floating duration, buoyancy force is utilised to estimate the buoyancy capacity of the floating dosage form. In addition, swelling rate, water uptake capacity, and gel strength of the polymer used in the dosage form can also be evaluated for a minimum of 8hrsin order to ensure the floating mechanism, drug release, and gel strength**.** The different *invitro* evaluation parameters for different GRDDS are described as follows.

**I. Evaluation methods of gastroretentive tablets:**

1. **Weight variation (**83,84**):** The formulated tablet was weighed to ensure that the tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit.

2. **Hardness (**83,84**): T**ransportation and handling before usage, the tablets show resistance to shipping or any type of breaking and this depends on its resistance. The hardness of each batch of tablet was checked by using Pfizer hardness tester. The hardness was measured in terms of $kg/cm^2$. Six tablets were chosen randomly and tested for hardness. The average hardness of six determinations was recorded.

3. **Friability (**83,84**):** This evaluation parameter is used to determine any resistance shown by the tablets to freight or any type of damage under the conditions of storage, transportation and handling before their use. Friability is the percentage loss in weight of tablets due to some mechanical action on the surface of the tablet. If any defect like chipping, capping or cracking is detected in the tablets, then that batch should be rejected.

4. **Dimensions:** Tablet dimensions include tablet thickness and the diameter of the tablet. They must have uniform thickness and diameter. The manufacturer normally states these. Thickness and diameter of a tablet were measured using vernier calipers. These values were checked and used to adjust the initial stages of compression**.**

5. **Content uniformity studies:** This is done to determine the actual amount drug substances present in the formulation. For this, the ratio of absorbance for the sample and the pure drug is calculated. Five tablets were taken and crushed in a pestle mortar to fine powder and then an amount equivalent to 40 mg was taken in a 100ml standard flask. This powder was then dissolved in 0.1N Hydrochloric acid and the volume was made up with 0.1N Hydrochloric acid solution. Then it was mixed properly and filtered through Whatman filter paper. The filtered solution was diluted appropriately and the drug content was determined by using the UV-VIS Spectrophotometer at wavelengths 200 nm and 400 nm. The percent drug content was calculated by comparing the standard with the prepared formulation.
6. **In-vitro dissolution test:** *In-vitro* dissolution test is performed by using USP apparatus II (paddle).

The In-vitro dissolution test for GRDDS tablets was performed by using USP XXIII type-II apparatus (Paddle). 900 ml of gastric fluid was used as the dissolution medium at room temperature 37±0.5°C. At specific intervals of time, 5 cc of the sample were taken out using a cannula with a pre-filter. The equal amount of fresh dissolution medium was added to the volume that was removed at each interval. The drug release from the dosage form was determined by calculating the absorbance (λmax) by make use of UV spectrophotometer after proper dilutions. Repeat the process in triplicate (n=3).

Since the container is large and the paddles are at bottom, so the paddle force acting on the dosage form is much less. So therefore, the dosage form does not rotate properly and hence may not give prosperous outcomes. Same problem exists with the swellable dosage form, as they contain hydrogels, so they may adhere to the walls of container or the paddle and does not gives prosperous outcomes.

To forestall such issues, different kinds of changes are made in the dissolution set up. These changes are described below –

1. To forestall the sticking of the formulation at vessel or paddle and to further enhance the motion of formulation, strategy recommended is to maintain the paddle at the surface and not in depth of the dispersion medium (85).
2. Gastroretentive unit can be made completely lowered, by joining few little, free, non-responding material around the formulation. In any case, this strategy can hinder three-dimensional swelling of some formulations and furthermore influences the release of the drug.
3. Another change is to keep the floating unit completely lowered under the ring or mesh assembly and keeping the paddle above the ring giving better force for motion of unit.
4. Another way is to keep the formulation in between two rings or sieves.
5. Change in dispersion vessel that is indented at some location above the base and mesh is kept on indented protrusions, giving more regions for the formulation.

6. In spite of the different changes done to obtain reproducible outcomes.

**II. Floating behaviors:**

1. **Buoyancy delay Time:** The time taken by the formulation to float over the surface of the dispersion medium, after putting it in the dissolution medium. This evaluation parameter can be included in dissolution testing.
2. **Floating Time:** This test is done in SGF (Simulated Gastric Fluid) at a temperature of at $37^0$C. Retention time is the time in which the formulation floats continuously over the dispersion medium.
3. **Relative density:** It can be measured by the method of displacement and benzene can be used as the displacement medium.

**III. Net End product:** The major parameters for determining buoyancy are bulk density and floating time but density alone is not enough to calculate buoyancy as density changes with changes in the resultant weight of the formulation with respect to course. For example, a matrix tablet containing bicarbonate floats in the medium by the generation of gas and its entrapment in the polymer matrix. After some time, drug is released by the erosion of the outer layer of the polymer matrix. This leads to the change in the end product weight of the formulation.

**IV. Swelling systems:**

1. **Swelling Index:** Thereafter submerging the swelled-up formulation into the Simulated Gastric Fluid at $37^0$C, the formulation is removed on a regular basis, and the changes in size are assessed in terms of a gradual rise in tablet thickness/diameter.
2. **Water Uptake:** It measured the swellable matrix's swelling potential indrectly. Here, the formulation is taken out at regular time interval and the change in weight of the formulation is measured with different time.

**Water uptake, WU = (Wt – Wo) * 100 / Wo**

Where, **Wt** = weight of dosage form at time t and **Wo** = initial weight of dosage form.

**V. In vivo method:**

1. **X-Ray method (**86-88): This method is becoming very popular in order to evaluate the gastroretentive dosage forms. It helps to locate dosage form in the GIT and by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Here the inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays.

2. **Gamma-Scintigraphy** (86-88): Gamma - Emitting radioisotopes compounded into CR-DFs has become the state-of-art for evaluation of gastroretentive formulation in healthy volunteers. A small amount of a stable isotope e.g., Sm, is compounded into DF during its preparation.
3. **Gastroscopy** (86-88): It includes oral endoscopy, along with the use of strand optic and computer display. This method is used to see the result of prolonged stay of the dosage form in the gastric environment on a screen. Also, the dosage form may be removed from the gastric area for further investigation.
4. **Ultrasonography** (86-88): Supersonic waves deliberate substantially different acoustic impedances across interface enable the imaging of some abdominal organs. Most DFs don't have sharp acoustic mismatches across their interface with the physiological environment. Thus, this method is not used regularly for doing the evaluation of the dosage form. The evaluation involves the assessment of intragastric location of the hydrogels, penetration of the solvent into the gel and interactions between the gastric wall and dosage form during peristalsis.
5. **Magnetic marker monitoring (**86-88**):** In this method, the formulation is marked magnetically by putting iron fines into it. The imaging is done by using very sensitive bio-magnetic measurement equipment. The main benefit of this technique is that it is radiation free and less hazardous.
6. **13C Octanoic acid breath test (**86-88**):** In this method, 13C Octanoic acid is involved in the gastroretentive system. In stomach due to chemical reactions, octanoic acid liberates $CO_2$ gas which comes out in breath. The important Carbon atom which will come in $CO_2$ is replaced with 13C isotope. So, time upto which $13CO_2$ gas is observed in breath can be considered as gastric retention time of dosage form. As the dosage form moves to intestine, there is no reaction and no $CO_2$ release. So, this method is cheaper than other.

7. **Magnetic resonance imagining (MRI)**: MRI is a scintigraphy diagnostic technology. This technology uses a powerful magnetic-flux, pulse packet frequency, 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.

Commercially Available Marketed Products of GRDDS (89): are given table 6.

**Table 6:** Trading-wise available products of Floating Formulations

| Sl No | Trademark Name | API | Formulation | Dose | Indications | Company |
|---|---|---|---|---|---|---|
| 1 | Cifran OD | Ciprofloxacin | Tablet | 500mg | Systemic treatment of infections | Ranbaxy, India |
| 2 | Liquid Gavison | Al hydroxide and Mg carbonate | Liquid | 95mg and 358 mg | respectively Antacid Glaxo. | Smith Kline, India. |
| 3 | Madopar | Levodopa and Benserazide | Capsule | 100mg and 25mg | Parkinson's disease. | Roche Products, USA. |
| 4 | Glumetza | Metformin Hydrochloride | Tablet | 500mg and 1000mg | Type 2 diabetes | Depomed, Canada. |
| 5 | Valrelease | Diazepam | Capsule | 15 mg | Anxiety disorders, alcohol withdrawal symptoms, muscle spasms. | Hoffmann- LaRoche, USA. |
| 6 | Topalkan | Aluminium & Magnesium antacid. | Liquid alginate | -- | Antacid | Pierre Fabre Drug, France. |
| 7 | Cyotec | Misoprostol | Bilayer capsule | 100mcg/200 mcg | Used with non-steroidal anti-inflammatory drug to prevent gastric ulcers. | Pharmacia, USA |
| 8 | Conviron | Ferrous sulphate | Colloidal gel | -- | Antianaemic | Ranbaxy, India. |
| 9 | Oflin OD | Ofloxacin | Tablet | 400mg | Genito urinary, respiratory, gastro intestinal, skin and soft tissue infections. | Ranbaxy, India. |

**FUTURE ASPECTS OF GRDDS:**

The major obstacles for the pharmaceutical industry for the research and designing of the conventional dosage form are their gastric residence time (GRT), especially for some drugs whose absorption occurs at the upper area of the colon. Many researchers have been done for GRDDS using a single approach system and their development of has helped to overcome the problems of conventional dosage forms but a lot of work is still required to be done. Different floating delivery technologies have been developed and are found to be effective but they have limitations. The problem is the discrepancy in residence time, mainly in the fasted and fed states. So, a suitable technique of GRDDS should be designed that can conquer the restrictions of one technique. Utilizing blended techniques might be helpful for limiting the fluctuation of GRT (combinations like muco-adhesive and high-density systems, effervescent systems, muco-adhesive and floating systems, etc.). Additionally, these combination formulations are low affected by the biological state of the gastric and may assure delayed gastric emptying. In this manner, the future aspects of GRDDS should be centered around these combination approaches so as to extend the gastrocolic retention of formulations even in fasted state.

Another significant viewpoint for the improvement of GRDDS is to comprehend the impacts of process variables and formulation on the CQA (Critical Quality Attributes) of GRDDS like floating force, floating behavior, muco-adhesive time and strength, gel strength, swelling ability, friability, etc. Also, selecting an appropriate polymer for the formulation of dosage forms is another aspect (90).

Some Gastroretentive technologies like the magnetic systems have not been widely examined. So, these systems require future work centered around the clinical possibility to indicate their pragmatic applications in humans. Magnetic system can be used in combination with superporous hydrogel system, as the dosage form will swell and cover bigger volume and with the help of the external magnet it can be located. Hence, the advancement of technology provides accurate estimation tools that can help predict and correlate the timing of stomach emptying and the entry of medication into the GIT (91-93).

It is important to evaluate gastroretentive formulations on an individual basis since the physiological and chemical nature of API and additives, types and composition of different polymers, medicament dose, and fabricated may be based on the product description (94). Other significant characteristic to boost up gastroretentive system is to know the influence of formulation and process variables on the CQA of GRDDS. It is important to understand the behavior of polymer and its role in preparation, as it is essential for the rational development of the floating formulation. Also, the strength of the polymer used is equally crucial for developing

these products. The quality by design (QbD) method may be useful in this situation for examining how formulation and process variables affect the crucial quality attributes of GRDDS. The understanding and control of the production process have undergone significant change as a result of the adoption of the QbD technique in the pharmaceutical business, significantly reducing the risk of product failure.

Some of the GRDDS such as magnetic systems have not been studied broadly. These formulations' clinical studies have not yet been fully documented. Therefore, the practical applications of magnetic systems in humans should be the focus of their future development. Moreover, by combining the magnetic system with the super porous hydrogel system may assist the extracorporeal magnet to precisely locate the ingested formulation as it swells and occupies a larger volume. The advancement of technologies may provide us with effective analysis tools that may be to forecast and correspondence the gastro-emptying period and passage of the dosage form into the GUT (95).

**Application of Gastro-Retentive Drug Delivery System (**96):

1. Enhance bioavailability: The bioavailability of CR-GRDF is greatly increased in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.
2. First-order kinetics drug delivery: The GRDDS is utilised for dosage form retained in the stomach for longer period for the drug released in the stomach or intestine. In this system dose large in size and passing from the pyloric opening is prohibited. New sustained-release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. Plasma concentration-time curves showed a longer duration for administration (16 hours) in the sustained-release floating capsules as compared with conventional MICARD capsules (8 hours). Similarly, a comparative study between the Madopar HBS and Madopar standard formulation was done it shown the drug was released up to 8 hours in vitro in the former case and the release completed in less than 30 minutes in the latter case.
3. Site–specific drug delivery systems: For medications that are selectively absorbed from the stomach or the closest region of the small intestine, these approaches are very beneficial. The regulated, delayed distribution of the medicine restricts systemic exposure to the drug while providing adequate localized therapeutic levels in the stomach. It lessens the drug's adverse effects on blood circulation. Moreover, site-directed administration device may lower the frequency of dose by extending stomach availability.
4. Absorption enhancement: Medicines with low bioavailability due to site-specific absorption from the upper GIT are likely candidates for developing floating dds, which would maximise their uptake.
5. Reduce unfavourable colon activity. By retaining the medication in the stomach's HBS systems, the portion of medication that reaches the colon is limited. As a conclusion, it could be possible to avert the drug's harmful effects in the colon. For beta-lactam antibiotics, that are primarily assimilated from the small intestine and whose existence in the colon leads to the emergence of pathogenic resistance, this pharmacodynamics feature gives the justification for GRDF formulation.
6. Limit changes in medication concentration. Unlike to immediate release dose forms, controlled-release gastro-retentive dose forms generate blood drug concentrations within a limited range after medication delivery. As a consequence, variations in medication effects are minimiseduj, and undesirable effects that are influenced by concentration and linked to peak levels can be averted. This characteristic is particularly crucial for medications with a restricted therapeutic index.

**CONCLUSION:**

GRDDS provides enhanced bioavailability for different medicaments which are poorly absorbed in the upper part of GIT and also provides a controlled delivery of various drugs. These technologies provide potential benefits for enhancing the therapeutic effectiveness of medicaments are having narrow absorption windows. The future aspects of GRDDS may be centered on the combination approaches of GRDDS to provide enhanced quality of the product. One application of GRDDS is in the treatment of *H. pylori* infection, which also provides a promising zone in pharmaceutical industry and academics. In light of writing, huge numbers of corporations are concentrating on marketing this strategy. The number of products present is a proof of it. We finally conclude that the GRDDS has more opportunities as

commercial products in the market and in filing a patent.

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