



## REVIEW ON NOVEL APPROACHES OF GASTRORETENTIVE DRUG DELIVERY SYSTEM

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### ABSTRACT

The aim of writing this article on gastroretentive drug delivery systems (GRDDs) is to compile the recent literature with special focus on different gastroretentive approaches. They have recently become leading methods in the field of site-specific oral administered controlled release drug delivery in the upper GIT for local or systemic effects. Afterwards, we have reviewed various gastroretentive approaches, i.e. High density (sinking), floating, bio- or mucoadhesive, expandable (Swellable), unfoldable, super porous hydrogel, magnetic system and alginate beads system. Gastroretentive dosage forms (GRDFs) are being used from a very long time to improve therapy with several important APIs. GRDDs greatly improves the pharmacotherapy of stomach by releasing the drug locally, thus result in high concentration of drug at gastric mucosa which can be sustained over a long period of time. The duration of release drug and improve bioavailability of drugs that have narrow window, by this way they prolong dosing interval and increase compliance of the patient. Finally, the factors related to GRDDs, its advantages, disadvantages, and emphasis are given over its conventional form of drug delivery in detail.

**KEYWORDS:** Introduction, Anatomy and Physiology of GIT, Advantages & disadvantages of GRDDs, Suitable candidate for the GRDDs, Approaches of GRDDs.

### 1. INTRODUCTION

Orally administration of drug is the most convenient and generally used method for the drug delivery to the systemic circulation. They have recently been of increasing interest in pharmaceutical field to achieve therapeutic advantages, such as ease of dosing, patient compliance many others. This route has many physiological problems including a gastric emptying rate that varies from person to person, a brief gastrointestinal transit time (8 to 12 hours), and the existence of an absorption window in the upper part of small intestine for different types of drugs.<sup>[1]</sup>

These problems have prompted researchers to design a new drug delivery system which can easily stay in the stomach for prolonged period of time, which can provide therapeutic effective plasma drug concentration for a maximum period. Drugs that are easily absorbed from GIT and have short half-lives ( $T_{1/2}$ ) are eliminated quickly from the systemic circulation. Frequent dosing of these types of drug is required to achieve therapeutic effect. To avoid this, the development of oral sustained release formulations is an attempt to release the drug into the gastrointestinal tract (GIT) and maintain drug concentration in the systemic circulation.<sup>[2]</sup>

Gastroretentive drug delivery system can improve the controlled delivery of drugs that have a high absorption

window by continuously releasing the drug for a longer period before it reaches to the absorption site.<sup>[3]</sup> This is sometimes valid for achieving therapeutic efficacy of drug that is absorbed from the proximal part of the gastro intestinal tract or less soluble or degraded by alkaline pH.<sup>[4]</sup>

GRDDs are beneficial for such drugs by improving their bioavailability, increases the duration of drug release, improves the drug solubility that are less soluble in a high pH (i.e. weakly basic drugs like Domperidone, papaverine and many others) and increases the duration of drug release, prolonged gastric retention time (GRT) in the stomach could be a big advantage for local action in the upper small intestine for the treatment of peptic ulcer. Apart from these advantages, this system offers various pharmacokinetics advantages like maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in the therapeutic levels.<sup>[4, 5, 6]</sup>

It is an approach of target site-specific drug release in the upper gastro intestinal tract (GIT) for systemic effects. GRDDs easily remain in the stomach for longer time significantly prolong the GRT (gastric retention time) of drugs.

The controlled gastric retention of dosage forms may be achieved by the mechanism of.<sup>[7]</sup>

- Sedimentation
- Flotation
- Mucoadhesion
- Expansion
- Modification in shape etc.

## 2. DIFFERENCE BETWEEN GASTRORETENTIVE DDs AND CONVENTIONAL DDs.<sup>[7]</sup>

When the drug is taken orally many times in a day, conventional DDs retains the concentration of drug in the

effective therapeutic range which is essential for the management of a disease. A successful drug delivery system is dependent on its absorption degree in the GIT. So the clue of increasing drug absorption initiated the idea of GRDDs.<sup>[8]</sup>

Assimilating a present medicine into novel drug delivery system can increase its actions concerning the patient adherence, efficacy and safety. The development of the new drug delivery system came into being due to the need of proficient delivery of drug to the patient with lesser side effect.<sup>[9]</sup>

Table1. Difference between grdds and cdds<sup>[10]</sup>

S.No.	Parameters	Gastroretentive DDs	Conventional DDs
1.	Patient compliance	better patient compliance	Bad patient compliance
2.	Drugs with poor absorption in small intestine	appropriate	Not appropriate
3.	toxicity	Low susceptibility	Greater susceptibility towards toxicity.
4.	Drugs having fast absorption through GIT	Very much beneficial	Not much beneficial
5.	Dose dumping	risk of dose dumping is low	Risk of dose dumping is higher
6.	Drugs acting locally in stomach	much advantageous	Not much advantageous
7.	Drugs that undergo degradation in colon	Very much advantageous	Not much advantageous
8.	Drugs with poor solubility at higher pH	Much useful	Not very much useful

## 3. ANATOMY AND PHYSIOLOGY OF THE GASTROINTESTINAL TRACT.

The gastrointestinal tract can be divided into three main regions i.e.

- 1). Stomach
- 2). Small intestine- duodenum, jejunum and ileum
- 3). Large intestine

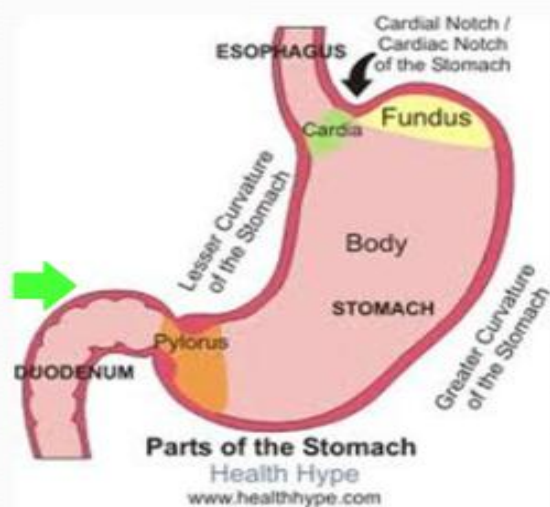


FIGURE1. Anatomy of gastrointestinal tract<sup>[11]</sup>

The GIT functions to take in nutrients and eliminate waste by such physiological process as secretion, motility, absorption, digestion & excretion. The stomach is a 'J' shaped enlargement of the GIT which can be divided into four anatomical regions; cardia, fundus, body and antrum. The main function of the stomach is to store and mix food with gastric secretions before emptying its load through the pyloric sphincter into the small intestine at a controlled rate. When empty, the stomach occupies a volume of about 50ml, but this may increase to as much as 1L when full. The wall of GIT (from stomach to large intestine) has the same basic arrangement of tissues. The different layers, from outside to inside, comprising serosa, longitudinal muscle, intramuscular plane, circular muscle, submucosa, muscularis mucosae, lamina propia and epithelium.<sup>[12]</sup>

### 3.1 PHYSIOLOGY OF THE GASTROINTESTINAL TRACT:

Anatomically the stomach is divided into 3regions;

- Fundus,
- Body and
- Antrum pylorus.

The proximal part is made of fundus and body acts as a reservoir for undigested material whereas the antrum is the main site for mixing motions and acts as a pumping machine for gastric emptying by propelling actions.

Gastric emptying occurs during the fasting and fed states. The pattern of motility is however distinct in the 2 states.

### 3.2 GASTROINTESTINAL DYNAMICS

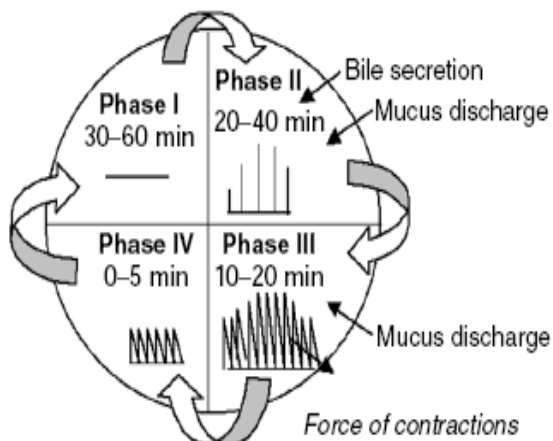
During the fasting state an interdigestive series of electrical events take place, which cycle through both

stomach and intestine every 2 to 3 hours. This is called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into four phases. These four phases are described in table 2.<sup>[13]</sup>

**TABLE2. Phases of migrating myoelectric complex.**

S.No.	Phase	Phase name	Description	Avg. time period
1	Phase I	Basal phase	Period of no contractions	30-60 mins
2	Phase II	Preburst phase	Period of intermittent contractions	20-40 mins
3	Phase III	Burst phase	Period of regular contraction at the maximal frequency that migrate distally	10-20 mins
4	Phase IV	transit phase	Period of transition between burst phase and basal phase	0-5 mins

After the ingestion of a mixed meal, the pattern of contractions changes from fasting to that of feeding state. This is also called as digestive motility pattern and comprises of continuous contractions as in phase 2 (pre-burst phase) of fasting state. These contractions result in reduced size of food particles (to less than 1mm), which are propel towards the pylorus in a suspension form. During the feeding state onset of MMC (migrating myoelectric complex) is delayed resulting in slowdown of gastric emptying rate<sup>[14]</sup>. The studies determining gastric emptying rate revealed that orally administered controlled released dosage forms are subjected to complications that of short gastric residence time and unpredictable gastric emptying rate.

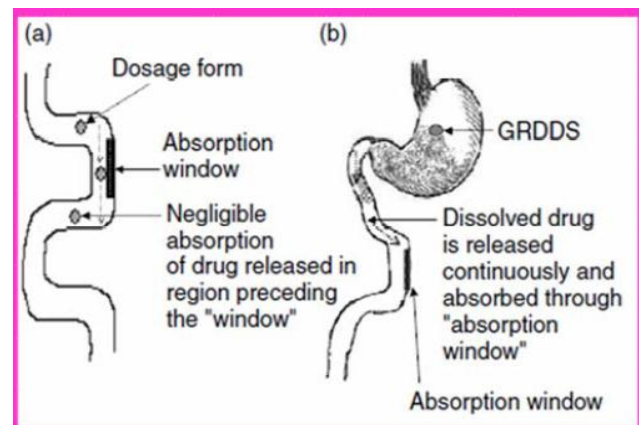


**Figure2. A schematic representation of the interdigestive motility pattern, frequency of contraction forces during each phase, and average time period for each period.**

### 4. DRUGS THOSE ARE SUITABLE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEM

- Drugs that are absorbed from the stomach (levodopa, furosemide).
- Acting locally in stomach (antacids, antiulcer)

- Are poorly soluble at an alkaline pH (diazepam, salbutamol)
- Degrade in colon (captopril, ranitidine, metronidazole)
- Narrow window of absorption.



**Figure 3: Absorption window.**

### 5. FACTORS CONTROLLING GASTRIC RETENTION OF DOSAGE FORMS

The stomach anatomy and physiology contain parameters to be considered in the development of gastroretentive dosage forms.<sup>[6]</sup>

**5.1 PARTICLE SIZE:** To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm.<sup>[15]</sup>

**5.2 DENSITY:** The density of a dosage form also affects the 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.<sup>[16]</sup> Both positions may isolate the dosage system from the pylorus. A density of less than 1.0 gm./cm<sup>3</sup> is required to exhibit floating property of the drug.<sup>[5, 17, 18]</sup>

**5.3 SIZE AND SHAPE OF THE DOSAGE FORM:**

Shape & size of the dosage forms are important in designing indigestible single unit solid dosage forms. Size should be greater than 7.5 mm in diameter<sup>[18]</sup> and Ring and tetrahedron devices with flexural modulus of 22.5-48 KSI (keto pound/inch) shows 90-100% GRT (gastric retention times).<sup>[17, 19]</sup>

**5.4 FOOD INTAKE AND ITS NATURE:** Food intake, volume, viscosity of food, caloric value 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 it is allowed to stay at the absorption site for a maximum period.<sup>[20]</sup>

**5.5 EFFECT OF GENDER, AGE & POSTURE<sup>[21]</sup>**

- **GENDER:** females have shorter GRT than males.
- **AGE:** Age > 70 shows longer GRT.
- **POSTURE:** varies between spine and upright ambulatory states.

**5.6 NATURE OF THE DRUG:** Drugs with impact on gastro intestinal transit time e.g. codeine and pharmacokinetic agents e.g. metoclopramide cisapride increases gastro retention time (GRT).<sup>[22]</sup>

**5.7 OTHER FACTORS<sup>[22]</sup>**

- The molecular weight and lipophilicity of the drug depending on its ionization state are important parameter.
- Caloric content and frequency of food intake, sex, sleep, body mass index, physical activity.
- Diseased state of a person (e.g. chronic disease, diabetes etc.)
- Administration of drugs having an impact on gastrointestinal transit time for example drugs acting as anticholinergic agents like atropine, propantheline, Opiates like codeine and prokinetic agents like metoclopramide, cisapride.<sup>[18]</sup>

**6. ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEM**

**6.1 BIOAVAILABILITY ENHANCEMENT:** The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT by this gastroretentive drug delivery system.<sup>[23]</sup>

**6.2 ENHANCED FIRST-PASS BIOTRANSFORMATION:** In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes cytochrome P450, in

particular (CYP3A4) in a sustained manner, rather than by a bolus input.<sup>[24]</sup>

**6.3 PATIENT COMPLIANCE:** drugs acting locally in the stomach, drugs which degrade in the colon and those having rapid absorption through GIT are formulated by use of this system. This site-specific drug delivery reduces undesirable side effects. It improves patient compliance.<sup>[5]</sup>

**6.4 FREQUENCY OF DOSING:** for drugs with relatively short half-life, sustained release may enable reduced frequency of dosing with improved patient compliance.

**6.5 REDUCED FLUCTUATIONS OF DRUG CONCENTRATIONS:** gastroretentive dosage forms minimize the fluctuation of drug concentrations and effects. This feature is of special importance for drug with a narrow therapeutic index. Reduction of fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.<sup>[25]</sup>

**6.6 MINIMIZED ADVERSE ACTIVITY AT THE COLON:** Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamics aspect provides the rationale for GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

**6.7 SITE SPECIFIC DRUG DELIVERY:** This controlled, slow delivery of drug form gastroretentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable effects.<sup>[26]</sup>

**6.8 ADVERSITIES OF GASTRIC RETENTION TIME (GRT):** They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because their bulk density is lower than that of the gastric fluids.

**6.9** Gastroretentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency.

**6.10** The sustained mode of drug release from Gastroretentive doses form enables extension of the time over a critical concentration and thus enhances

the pharmacological effects and improves the chemical outcomes.

**6.11** Gastroretentive drug delivery can cause prolong and sustain release of drugs from which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.

### 7. DRUGS THOSE ARE UNSUITABLE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEM.<sup>[6]</sup>

- drugs having limited acid solubility (phenytoin)
- drugs are instable in gastric conditions (erythromycin)
- extensive first pass metabolism
- drugs intended for selective release in the colon (5-amino salicylic acid)

**TABLE3.** Commonly used drug in formulation of gastroretentive dosages forms.<sup>[4, 27]</sup>

DOSAGE FORM	DRUGS	Ingredients
FLOATING BEADS	<u>Mosapride</u>	Sodium alginate, HPMC
FLOATING TABLETS	Acetaminophen, acetylsalicylic acid, ampicillin, amoxicillin tri-hydrate, atenolol, captopril, <u>cinnerzine</u> , <u>chlorpheniramine</u> maleate, ciprofloxacin, <u>diltiazem</u> , <u>flurouracil</u> , <u>isosorbidedinitrate</u> , <u>sotalol</u> , theophylline, verapamil, famotidine.	HPMC K4M, Sodium bicarbonate
FLOATING CAPSULES	Furosemide, <u>nicardipine</u> , misoprostol, propranolol, <u>dipyridamole</u> .	NaCl, HPMC K4M
FLOATING MINITABLETS	Furosemide	Ethyl cellulose, HPMC K100
FLOATING MICROSPHERES	Ranitidine, aspirin, <u>griseofulvin</u> , p-nitro aniline, ibuprofen, <u>terfenadine</u> , <u>tranilast</u> .	Eudragit RLPO, eudragit L100-55, ethyl cellulose
FLOATING GRANULES	Diclofenac sodium, indomethacin, prednisolone, <u>Diltiazem HCL</u>	<u>Gelucire</u> 43/01, <u>Glyceryl monosterate</u> , <u>Methocel</u> K4M, ethyl cellulose
Pellet	Theophylline	HPMC E15LV, PEG 6000, MCC, Eudragit (RL30D, NE 30D)
POWDER	different basic drugs	-

**Table4.** Gastroretentive products available in the market.<sup>[27, 28]</sup>

BRAND NAME	ACTIVE INGREDIENT(s)
Cifran OD <sup>®</sup>	Ciprofloxacin
Madopar <sup>®</sup>	L-DOPA and Benserazide
Valrelease <sup>®</sup>	Diazepam
Topalkan <sup>®</sup>	Aluminium-magnesium antacid
AlmagateFlatCoat <sup>®</sup>	Aluminium-magnesium antacid
Liquid Gavison <sup>®</sup>	Aluminium hydroxide
Conviron	Ferrous sulphate
Cytotec <sup>®</sup>	Misoprestal

### 8. APPROACHES TO ACHIEVE GASTRIC RETENTION

Certain factors should be considered during development of gastroretentive dosage form. They include retention in the stomach according to the clinical demand, convenient intake, and ability to load substantial amounts of drugs with different physicochemical properties and release them in controlled manner, preferably in the stomach. Various approaches have been pursued to increase the retention of an oral dosage form in the stomach including floating systems, swelling and expanding system, super porous hydro gel, magnetic systems, and high density systems and delayed gastric emptying devices.

**8.1 HIGH DENSITY SINKING SYSTEM:** These systems with a density of about 3 g/cm<sup>3</sup> are retained in the antrum part of the stomach and are capable of withstanding its peristaltic movements. The only major drawbacks with such systems is that it is technically difficult to manufacture such formulations with high amount of drug (>50%) and to achieve a density of about 2.8 g/cm.<sup>[24, 29, 30]</sup>

**8.2 LOW DENSITY FLOATING SYSTEM:** Floating systems are low-density systems are those which have sufficient buoyancy to float over the gastric contents and

remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased GRT and reduces fluctuation in plasma drug concentration. FDSS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Most of the floating systems

are single-unit, such as the HBS and floating tablets. These systems are unreliable and irreproducible in prolonging residence time in the stomach when orally administered. On the other hand, multiple-unit dosage forms appear to be better suited since they are claimed to reduce the inter-subject variability in absorption and lower the probability of dose-dumping.<sup>[31]</sup>

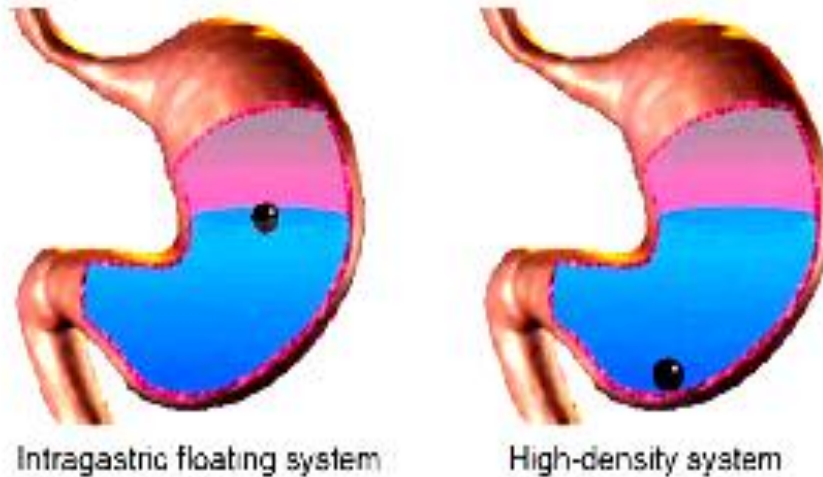


IMAGE4. High density sinking and low density floating system.

Table5. Difference between high and low density systems.

S.No.	HIGH DENSITY SINKING SYSTEM	LOW DENSITY FLOATING SYSTEM
1.	Density of pellets/tablets > density of stomach fluid and should be at least 150g/ml.	Density of pellets/tablets < density of stomach fluid and should be < 1g/ml
2.	Drugs can be coated or mixed with heavy nontoxic materials. e.g. barium sulphate, titanium dioxide etc.	Low bulk density systems. Designed in such a manner that it floats in gastric fluid and release the drug slowly for a longer period of time.
3.	High density systems.	Also known as hydrodynamic balanced system**.

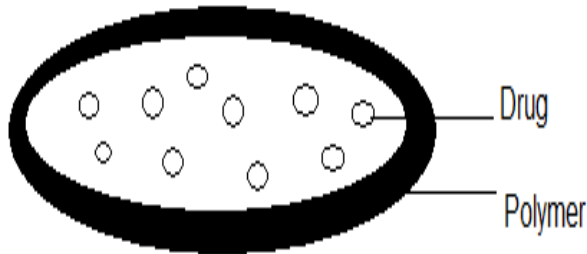
\*\*[**HYDRODYNAMIC BALANCED SYSTEM:** These systems contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. These are single-unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxypropyl methylcellulose (HPMC), hydroxethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polycarboxiphil, polyacrylate, polystyrene, agar, carrageenans or alginic acid are commonly used excipients to develop these systems. The polymer is mixed with drugs and usually administered in hydrodynamically balanced system capsule. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period. Because, continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form].

**8.3 NON-EFFERVESCENT SYSTEMS:** This system, after swallowing, swells via imbibing gastric fluid to an

extent that it prevents its exit from the stomach. These systems may be referred to as the 'plug-type systems' since they have a tendency to remain lodged near the pyloric sphincter. The air trapped by the swollen polymer confers buoyancy to these dosage forms. They maintain relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier. The gel structure acts as a reservoir for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier. Commonly used excipients in non-effervescent FDSS are gel-forming or highly Swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene.<sup>[5, 39]</sup>

**8.3.1 COLLOIDAL GEL BARRIER SYSTEM:** These are designated as "HBS". They contain drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. They prolong GRT and maximize the amount of drug that reaches its absorption sites in the

solution form for ready absorption. These systems incorporate a high level of one or more gel-forming highly soluble cellulose type hydrocolloid, matrix forming polymer such as polycarbophil on coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface. The air trapped by the swollen polymer confers buoyancy to these dosage forms.



**IMAGE5. Intra-gastric floating tablet releasing drug via colloidal gel barrier**

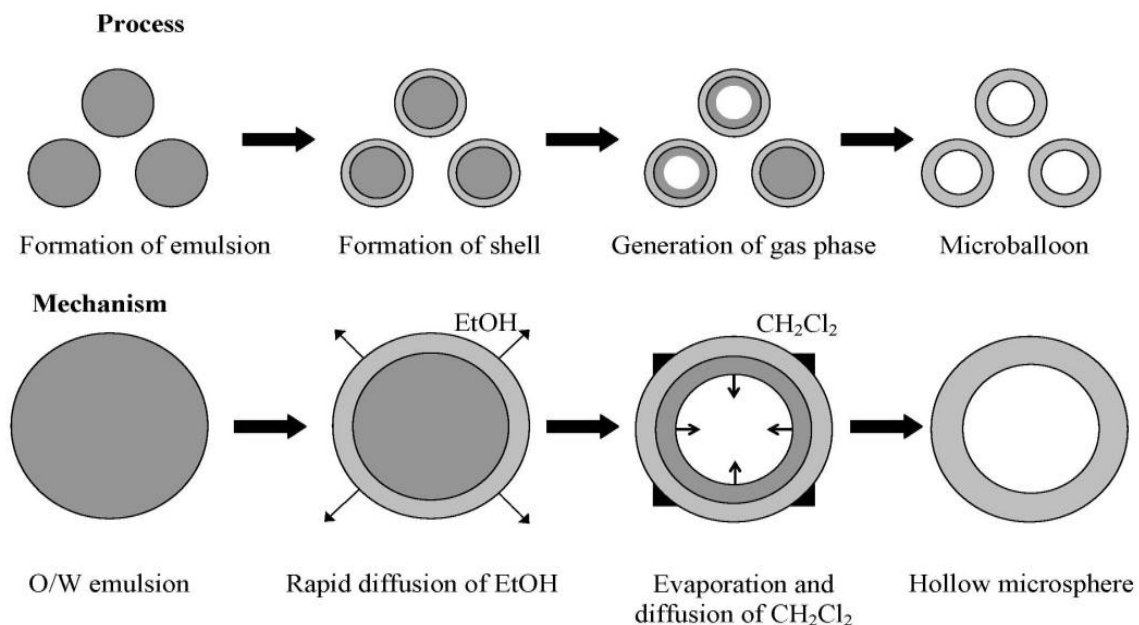
**8.3.2 MICROPOROUS COMPARTMENT SYSTEM:** Drug reservoir is encapsulated inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with an un-dissolved drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric

content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.<sup>[27,42]</sup>

**8.3.3 ALGINATE BEADS:** In this approach, generally sodium alginate solution is dropped into aqueous solution of calcium chloride and causes the precipitation of calcium alginate. These beads are then separated and dried by air convection and freeze drying, leading to the formulation of a porous system, which can maintain a floating force for over 12 hrs. These beads improve gastric retention time (GRT) more than 5.5 hrs.<sup>[5,41]</sup>

#### 8.3.4 HOLLOW

**MICROSPHERES/MICROBALLONS:** Hollow microspheres loaded with drug in their outer polymer shell were prepared by a novel emulsion solvent diffusion method.<sup>[37]</sup> The solution of the drug and an enteric acrylic polymer is poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40°C. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed in the internal cavity in the microsphere of the polymer with drug. The Microballons floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 h.<sup>[38]</sup>



**IMAGE6: Formulation of Microballons.**

**8.3.5 EXPANDABLE, UNFOLDABLE AND SWELLABLE SYSTEM:** These type of dosage forms, which after swallowing, swells to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a longer period of time. These systems may be named as 'plug type systems',

since they exhibit the tendency to remain lodged at the pyloric sphincter if that exceed a diameter of approximately 12-18mm in their expanded state.<sup>[19]</sup> The balance between the extent and duration of swelling is maintained by the degree of cross linking between the polymeric chains. A high degree of cross – linking

retards the swelling ability of the system maintaining its physical integrity for prolonged period. [43, 44, 45]

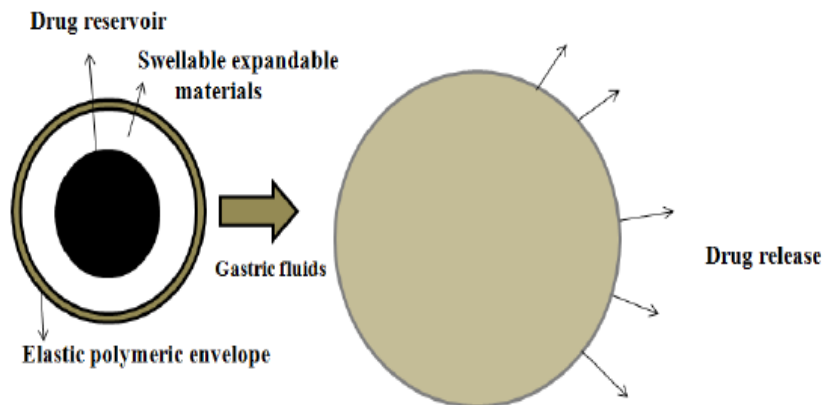


IMAGE7. Swellable system.

**8.3.6 MAGNETIC SYSTEM:** This approach to enhance the gastric retention time (GRT) is based on the simple principle that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance. [32,40, 41]

**8.3.7 SUPER POROUS HYDROGEL SYSTEM:** Super porous hydrogel (SPH) was originally developed as a novel drug delivery system to retain Drugs in the gastric medium. Super porous hydro gel composites have a combination of a high swelling rate and a ratio of more than 100 times the original weight of the dried matrix with substantial mechanical strength. These systems should instantly swell in the stomach and maintain their integrity in the harsh stomach environment, while releasing the pharmaceutical active ingredient. In this approach to improve gastric retention time (GRT) super porous hydrogels of average pore size >100 micro metre, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores. They swell to a large size (swelling ratio: 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is advised by co-formulation of hydrophilic particulate material. [33, 34, 35]

**8.3.8 BIO/MUCOADHESIVE SYSTEM:** Bio/Mucoadhesive systems bind to the gastric epithelial cell surface, or mucin, and extend the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membrane. The concept is based on the self-protecting mechanism of the GIT. The epithelial adhesive properties of mucin are well known and have been applied to the development of GRDDS through the use of bio/Mucoadhesive polymers. The adherence of the delivery system to the gastric wall increases residence time at a particular site, thereby improving bioavailability. A bio/Mucoadhesive substance is a natural or synthetic polymer capable of

adhering to a biological membrane (bio adhesive polymer) or the mucus lining of the GIT. They must be nontoxic and non-absorbable, form non-covalent bonds with the mucin-epithelial surface. [36, 48]

#### Various mechanisms of adhesion are

**Wetting theory,** ability of bio adhesive polymers to spread and cause intimate contact with mucin layers.

**Diffusion theory,** physical entanglement of mucin strand with soluble polymer or interpenetration of mucin strand into structure of polymer.

**Absorption theory,** bio adhesion is due to secondary forces such as Vander walls forces and Hydrogen binding.

**Electronic theory,** proposes attractive electrostatic forces between glycoprotein mucin network and bio adhesive material.

**BIOADHESIVE POLYMERS ARE USED:** PAA, chitosan, sodium alginate, HPMC, Sucralfate, Tragacanth, Dextrin, and PEG.

**LIMITATION:** Bio adhesion is difficult to maintain due to rapid turnover of mucin in GIT.

## 9. CONCLUSION

Based on the literature surveyed, it can be concluded that GRDDs offers various advantages for drugs with poor bioavailability. Drug absorption in the gastro intestinal tract is a highly variable process and prolonging the gastric retention of the dosage form extends the time for drug absorption. The control of gastro intestinal transit of orally administered dosage forms using GRDD systems can improve the bioavailability of drugs that exhibit site specific absorption. GRDDs also provide an additional advantage for drugs that are absorbed primarily in the upper segment of GIT, i.e., stomach, duodenum and jejunum. Different approaches for GRDD are studied each having their own advantages and disadvantages.



Due to unpredictability of human GIT development of efficient GRDFs is a real challenge to pharmaceutical technology as the drug delivery system must remain for a sufficient time in the stomach which is not compatible with normal physiology. In the future it can be easily assumed that GRDD systems will become more popular in terms of delivering drug to the systemic circulation with improving efficiency of various type of pharmacotherapy.

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