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A Review: Gastro Retentive Drug Delivery Systems

Mr.Tangade Abhay*1, Mr.Somani Shravan*[2], Mr. Rode Abhijit*[3], Ms.Gulve Karishma*[4]
Pratibhatai Pawar College Pharmacy, Shrirampur

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ABSTRACT:
GRDDs are an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper GIT for local or systemic effect.
Gastro retentive dosage forms (GRDFs) are being used for a very long time to improve therapy with several important drugs. GRDFs greatly improve the pharmacotherapy of the stomach by releasing the drug locally and thus result in a high concentration of the drug at the gastric mucosa which can be sustained over a longer duration of time. GRDFs enable prolonged and continuous release of the drug to the upper part of the Gastrointestinal tract (GIT) and this significantly extends the duration of drug release and improves the bioavailability of drugs that have a narrow therapeutic window, by this way they prolong dosing interval and increase compliance of the patient. The purpose of this paper is to briefly describe gastro retentive drug delivery (GRDD), factors related to GRDD, its advantages, and disadvantages, and emphasis is given over its significance over conventional forms of drug deliveries.
Keywords: Gastro retentive, floating, gastric, bioavailability.

I. INTRODUCTION:

Gastro retentive drug delivery systems are a type of system that prolongs the residence of the administered drug in the gastric region for several hours thereby the bioavailability and solubility of challenging drugs may get enhanced, and improves patient compliance. Gastric emptying delaying conceptual mechanisms of mucoadhesion, flotation, and sedimentation supports the gastro retentive drug delivery systems1. Thereby gastro retentive drug delivery systems enhance the absorption of drugs in the gastrointestinal tract drug by improving the contact time with the small intestinal mucosa. Gastric retention-based drug delivery systems in turn provide newer therapeutic possibilities and substantial benefits for researchers. Gastro retentive drug delivery systems may reduce drug wastage. Gastro retentive drug delivery systems offer a controlled drug delivery profile with effective plasma drug concentration, reducing dosing frequency and minimizing plasma fluctuations. Drugs suitable for gastro retentive drug delivery formulations include drugs that have low absorption in the lower part of the GIT, are unstable, poorly soluble at alkaline pH, have a short half-life, and show local activity at the upper part of the intestine. Due to the sustained/controlled release effect gastro retentive drug delivery formulations minimizes the mucosal irritation which may provide a desired plasma drug concentration and prevent drug fluctuations without causing dose dumping. Unstable drugs can also be delivered by this approach. The various approaches utilized in gastro retentive drug delivery systems include extended gastric residence time, low-density (floating), high-density (sinking), expandable (swelling), and mucoadhesive systems.

A better understanding of the anatomy and physiology of the stomach (specifically proximal stomach- fundus and body; and the distal stomach-antrum and pylorus) plays a crucial role in the successful development of the gastro retentive dosage form. The critical factors which affect the gastro-retentive drug delivery systems are the size/shape/density of gastro-retentive formulations, caloric density, factors associated with patients, etc. The passage through the pyloric antrum can be prevented by an increase in the size of the dosage form. The lower density of gastro-retentive drug delivery formulations than that of gastric fluids flavors the floating capacity of the gastro-retentive formulations. The caloric density of the ingested food increases the gastro-retentive property, herein the gastric emptying rate also gets affected by the gastro-retentive formulations. The other factors related to the patient such as gender, age, illness, and emotional state also influence the delivery of gastro retentive formulations. Diseases conditions as Parkinson's disease and diabetes also influence the gastric emptying rate.

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Anatomy And Physiology Of Stomach

The Gastrointestinal tract is essentially a tube about nine meters long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx), esophagus, stomach, small intestine (consisting of the duodenum, jejunum, and ileum) and large intestine (consisting of the cecum, appendix, colon, and rectum). The wall of the gastrointestinal tract has the same general structure throughout most of its length from the esophagus to the anus, with some local variations for each region. The stomach is an organ with a capacity for storage and mixing. The antrum region is responsible for the mixing and grinding of gastric contents.

The inter-digestive motility pattern is commonly called the 'migrating motor complex' ('MMC') and is organized in cycles of activity and quiescence.

Each cycle lasts 90–120 minutes and consists of four phases. The concentration of the hormone motilin in the blood controls the duration of the phases. In the inner digestive or fasted state, an MMC wave migrates from the stomach down the GI tract every 90–120 minutes. A full cycle consists of four phases, beginning in the lower esophageal sphincter/gastric pacemaker, propagating over the whole stomach, the duodenum, and the jejunum, and finishing at the ileum. Phase III is termed the 'housekeeper wave' as the powerful contractions in this phase tend to empty the Stomach of its fasting contents and indigestible debris. The administration and subsequent ingestion of food rapidly interrupt the MMC cycle, and the digestive phase is allowed to take place. The upper part of the stomach stores the ingested food initially, where it is compressed gradually by the phasic contractions. The digestive or fed state is observed in response to meal ingestion. It resembles fasting Phase II and is not cyclical, but continuous, provided that the food remains in the stomach. Large objects are retained by the stomach during the fed pattern but are allowed to pass during Phase III of the inner digestive MMC. It is thought that the sieving efficiency (i.e. the ability of the stomach to grind the food into smaller sizes) of the stomach is enhanced by the fed pattern or by the presence of food.

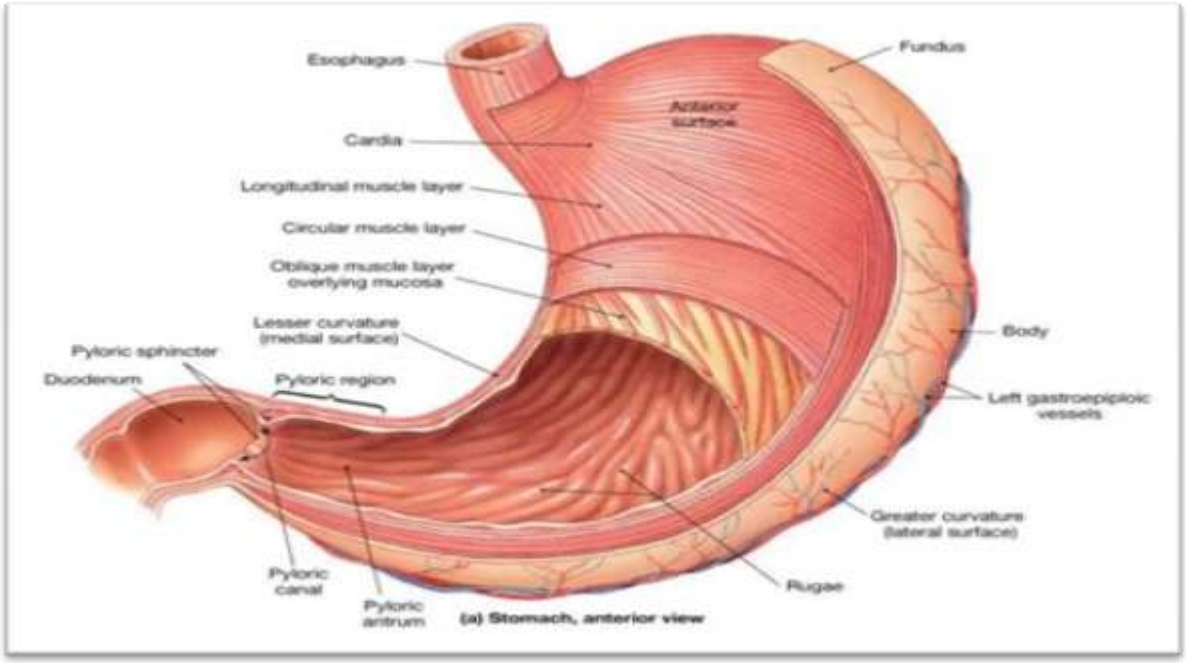

Fig 1. Structure of Stomach

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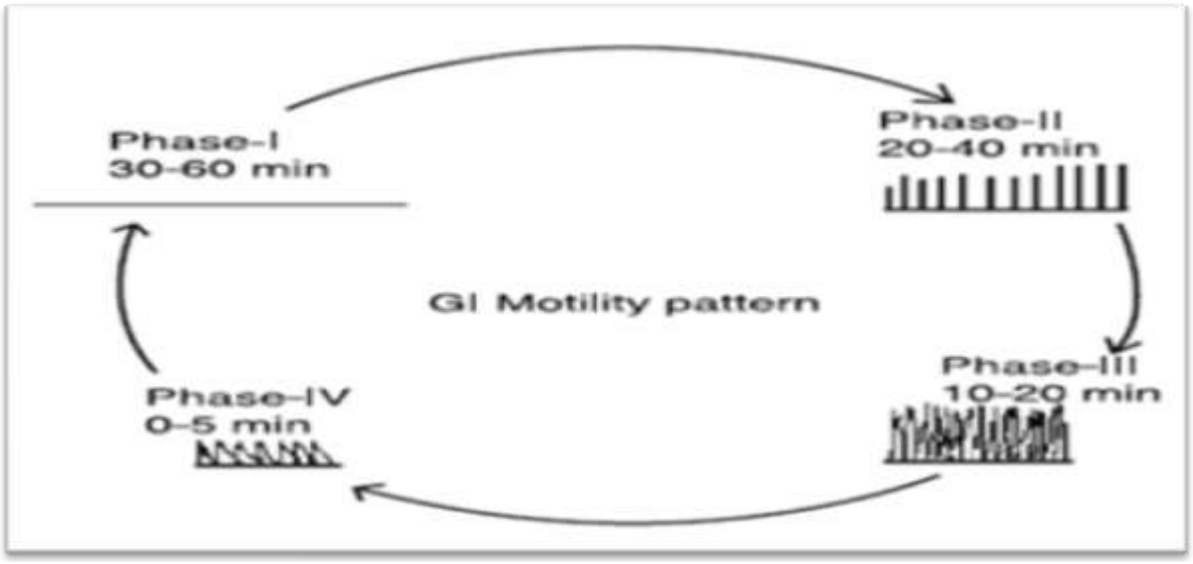

Fig 2. Phases of Gastric Cycle

NEED FOR GRDDS:

- Conventional oral delivery is widely used in the pharmaceutical field to treat diseases. However, conventional delivery had many drawbacks and the major drawback is non-site specificity.
- Some drugs are absorbed in specific sites only. They require release at a specific site or a release such that the maximum amount of drug reaches the specific site.
- The pharmaceutical field is now focusing on such drugs which require site specificity.
- Gastro-retentive delivery is one of the site-specific delivery for the delivery of drugs either in the stomach or intestine. It is obtained by retaining dosage form in the stomach and the drug is released in a controlled manner to the specific site either in the stomach, duodenum, or intestine.

FACTORS CONTROLLING GASTRIC RETENTION OF DOSAGE FORMS

The stomach anatomy and physiology contain parameters to be considered in the development of gastro retentive dosage forms. To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm. The most important parameters controlling the gastric retention time (GRT) of oral dosage forms include density, size, and shape of the dosage form, food intake and its nature, caloric content and frequency of intake, posture, gender, age, sex, sleep, body mass index, physical activity and diseased states of the individual (e.g. chronic disease, diabetes, etc.) and administration of drugs with impact on gastrointestinal transit time for example drugs acting as anticholinergic agents (e.g. atropine, propantheline), Opiate(e.g.codeine) and prokinetic agents(e.g.metclopramide, cisapride.).The molecular weight and lipophilicity of the drug depending on its ionization state are also important parameters.

The density of dosage forms

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 the bottom of the stomach. Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm/ cm3 is required to exhibit floating property.

Shape and size of the dosage form

The shape and size of the dosage forms are important in designing indigestible single-unit solid dosage forms. The mean gastric residence times of nonfloating dosage forms are highly variable and greatly dependent on their size, which may be large, medium, or small units. In most cases, the larger the dosage form the greater will be the gastric retention time (GRT) due to the larger size of the dosage form would not allow this to quickly pass through the pyloric antrum into the intestine. Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm. Ring-shaped

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and tetrahedron-shaped devices have a better gastric residence time as compared with other shapes.

Food intake and its nature

Food intake, viscosity and volume of food, caloric value, and frequency of feeding have a profound effect on gastric retention of dosage forms. The presence or absence of food in the gastrointestinal tract (GIT) influences the gastric retention time (GRT) of the dosage form. Usually, the presence of food in the gastrointestinal tract (GIT) improves the gastric retention time (GRT) of the dosage form, and thus, the drug's absorption increases by allowing it to stay at the absorption site for a longer period. Again, an increase in acidity and caloric value shows down gastric emptying time (GET), which can improve gastric retention of dosage forms. Effect of gender, posture, and age.

Generally, females have slower gastric emptying rates than males. The effect of posture does not have any significant difference in the mean gastric retention time (GRT) for individuals in the upright, ambulatory, and supine states. In the case of elderly persons, gastric emptying is slowed down.

ADVANTAGES OF GRDDS

1. The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT by this gastro-retentive drug delivery approach in comparison to the administration of gastro-retentive drug delivery. There are several different factors related to the absorption and transit of the drug in the gastrointestinal tract (GIT) that act concomitantly to influence the magnitude of drug absorption.
2. For drugs with a relatively short half-life, the sustained release may result in flip-flop pharmacokinetics and also enable reduced frequency of dosing with improved patient compliance.
3. They also have an advantage over their conventional system as they 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 employment because their bulk density is lower than that of the gastric fluids.
4. gastro retentive drug delivery can produce prolong and sustained release of drugs from dosage forms that avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to the stomach and small intestine.
5. The controlled, slow delivery of drug form gastro retentive dosage form provides sufficient local action at the diseased site, thus mini mixing eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable effects of side effects.
6. gastro retentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration-dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for a drug with a narrow therapeutic index.
7. gastro retentive drug delivery can minimize the counter activity of the body leading to higher Drug efficiency.
8. Reduction of fluctuation in drug concentration makes it possible to obtain improved selective receptor activation.
9. The sustained mode of drug release from Gastroretentive doses form enables the extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes.

DISADVANTAGES OF GRDDS

1. Unsuitable for drugs with limited acid solubility. E.g. Phenytoin.
2. Unsuitable for drugs that are unstable in an acidic environment. E.g. Erythromycin.
3. Drugs that irritate or cause gastric lesions on slow release. E.g. Aspirin & NSAIDs. 4. Drugs that absorb selectively in the colon E.g. Corticosteroids.
4. Drugs that absorb equally well through GIT. E.g. Isosorbide, dinitrate, Nifedipine.
5. Floating drug delivery systems require a high fluid level in the stomach to float and work effectively.

SUITABLE DRUG CANDIDATES FOR GASTRO RETENTION:

Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous, controlled manner. Drugs delivered in this manner have a lower level of side effects and provide their therapeutic effects without the need for repeated dosage with a low dosage frequency. Sustain release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustain release prolongs the contact time of the agent in the stomach or in the upper part

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of the small intestine, which is where absorption occurs and contact time is limited under normal condition, Example. the material passes through the small intestine in as little as 1-3 hrs.

In general, appropriated candidate CRGRDF is molecules that have poor colonic absorption but are characterized by better absorption, properties at the upper part of GIT:

- Narrow absorption window in GIT, E.g. Riboflavin and Levodopa.
- Primarily absorbed from the stomach and upper part of GIT, for Example, Calcium supplements, Chlordiazepoxide, and Cinnarizine.
- Drugs that are locally in the stomach, for Example. Antacids and Misoprostol.
- Drugs that degrade in the colon, for Example. Ranitidine HCl and Metronidazole.
- Drugs that disturb normal colonic bacteria, for Example. Amoxicillin trihydrate.

GOOD CANDIDATES FOR GASTRO RETENTIVE DRUG DELIVERY SYSTEM

Sr.No	Drug & Category	Bioavailability
1	Verapamil Calcium channel blocker	20-35%
2	Nifedipine Calcium channel blocker	45-65%
3	Omeprazole Proton pump inhibitor	35-60%
4	Atenolol Antihypertensive	40-50%
5	Propranolol Antihypertensive	4-26%
6	Verapamil Antihypertensive	18-35%
7	Diltiazem Calcium channel blocker	40%
8	.Lidocaine Local anaesthetic	35%
9	Clarithromycin Antibiotic	50%
10	Ramipril ACE inhibitor	28%

DRUGS THAT ARE UNSUITABLE FOR GRDDS

1. Drugs that have very limited acid solubility e.g. Phenytoin etc.
2. Drugs that suffer instability in the gastric environment e.g. Erythromycin, Rabeprazole, Clarithromycin, Esomeprazole, etc.
3. Drugs intended for selective release in the colon e.g. 5-amino salicylic acid and corticosteroids etc.

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APPROACHES TO ACHIEVE GASTRIC RETENTION

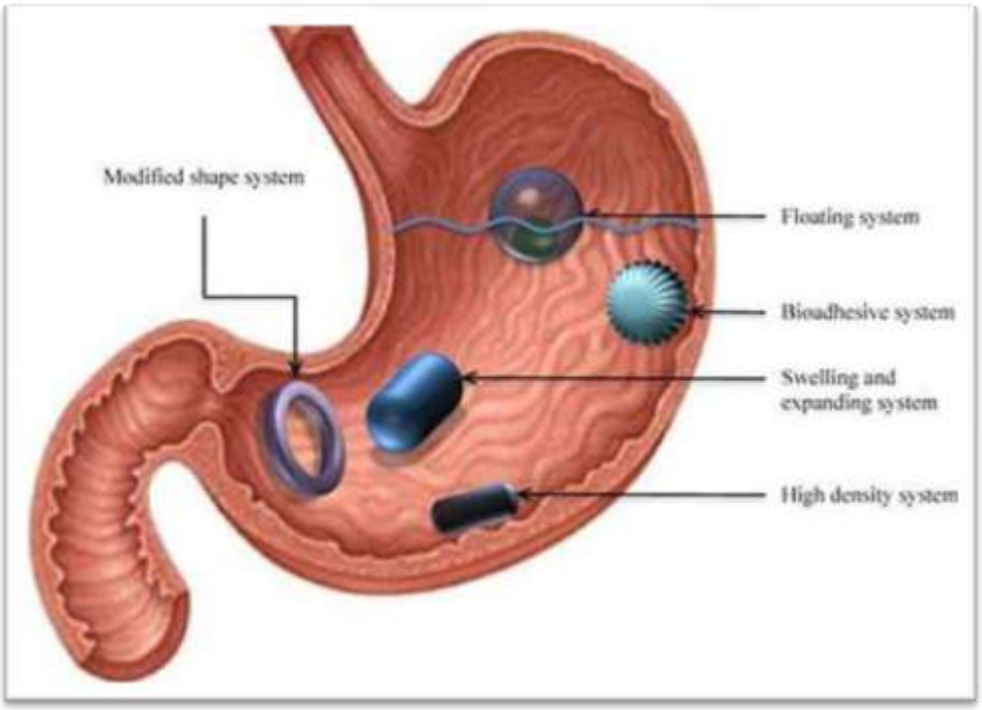

Fig 3. Approaches Of GRDDS

High-density (sinking) system or non-floating drug delivery system

This approach involves the formulation of dosage forms with a density that must exceed the density of normal stomach content (~ 1.004 gm/cm3). These formulations are prepared by coating the drug on a heavy core or mixed with inert materials such as iron powder, barium sulfate, zinc oxide, titanium oxide, etc. The materials increase density by up to 1.5- 2.4 gm/cm3. A density close to 2.5 gm/cm3 seems necessary for significant prolongation of gastric residence time. But, the effectiveness of this system in human beings was not observed and no system has been marketed. Floating drug delivery systems

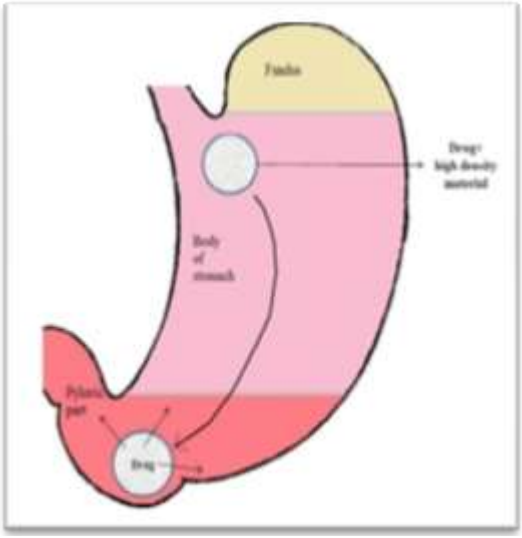

Fig 4. High Density (Sinking) System

Floating drug delivery systems are one of the important approaches to achieving gastric retention to obtain sufficient drug bioavailability. This delivery system is desirable for drugs with an absorption window in the stomach or the upper small intestine. This has a bulk density less than gastric fluids and so remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly

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at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increased gastric retention time (GRT) and better control of the fluctuation in plasma drug concentration. The major requirements for a floating drug delivery system are :

- It should release contents slowly to serve as a reservoir.
- It must maintain specific gravity lower than gastric contents (1.004 – 1.01 gm/cm3).
- It must form a cohesive gel barrier.

The inherent low density can be provided by the entrapment of air (e.g. hollow chambers) or by the incorporation of low-density materials (e.g. fatty materials or oils, or foam powder). The following approaches have been used for the design of floating dosage forms of single and multiple-unit systems. Recently a single-unit floating system was proposed consisting of polypropylene foam powder, matrix-forming polymers, drugs, and filler. The good floating behavior of these systems could be successfully combined with accurate control of the resulting drug release patterns. Single-unit dosage forms are associated with problems such as sticking together or being obstructed in the gastrointestinal tract (GIT) which may produceirritation. On the other hand, multiple-unit floating systems may be an attractive alternative since they have been shown to reduce the inter- and intra- subject availabilities in drug absorption as well as to lower the possibility of dose dumping. Various multiple-unit floating systems like air compartment multiple-unit system, hollow microspheres (micro balloons) prepared by the emulsion solvent diffusion method, microparticles based on low-density foam powder, beads prepared by emulsion gelatine method, etc. can be distributed widely throughout the GIT, providing the possibility of achieving a long-lasting and more reliable release of drugs. Based on the mechanism of buoyancy two distinctly different technologies, i.e. non-effervescent and effervescent systems have been utilized in the development of a floating drug delivery system.

Non-effervescent Systems

Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable cellulose-type hydrocolloids, polysaccharides, or matrix-forming polymers like polyacrylate, polycarbonate, polystyrene, and polymethacrylate. In one approach, the intimate mixing of the drug with gel-forming hydrocolloid results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methylcellulose (HPMC) polyacrylates, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide, and polycarbonates. This system can be further divided into the sub-types:

Hydrodynamically balanced systems:

Sheth and Tossounian first designated these 'hydrodynamically balanced systems'. These systems contain drugs with gel-forming hydrocolloids meant to remain buoyant on the stomach content. These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. Hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (Nam), polycarbophil, polyacrylate, polystyrene, agar, carrageenan's or alginic acid are commonly used excipients to develop these systems. The polymer is mixed with drugs and usually administered in a hydrodynamically balanced system capsule. The capsule shell dissolves in contact with water and the mixture swells to form a gelatinous barrier, which imparts buoyancy to a 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 the dosage form. The incorporation of fatty excipients gives low-density formulations reducing erosion. Mopar LP®, based on the system was marketed during the 1980s. Effective drug deliveries depend on the balance of drug loading and the effect of the polymer on its release profile.

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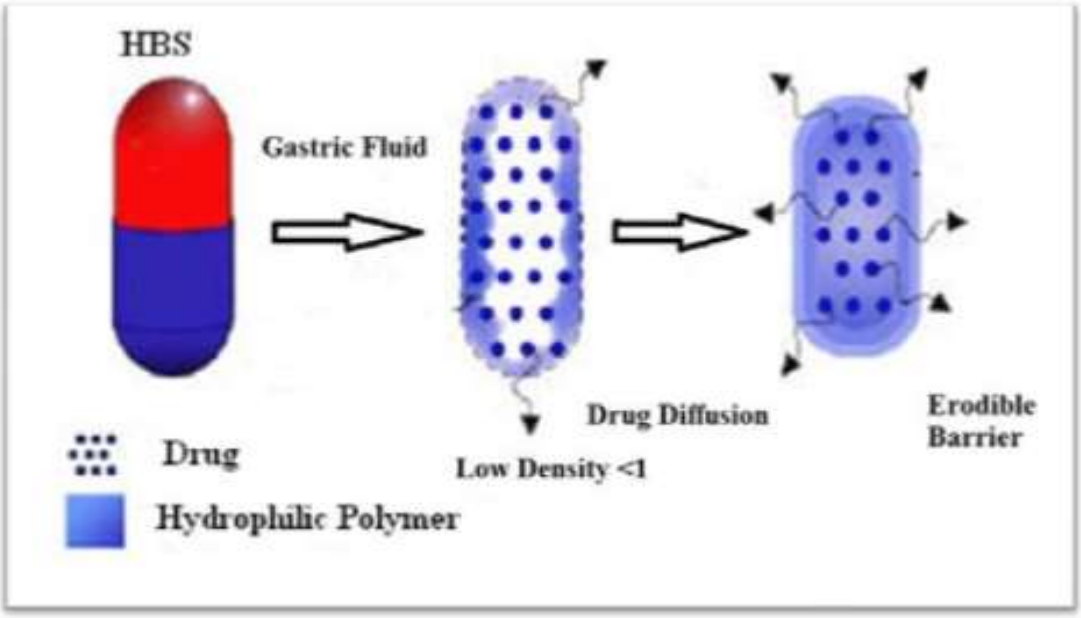

fig 5. Hydrodynamically Balanced Systems

Several strategies have been tried and investigated to improve the efficiencies of the floating hydrodynamically balanced systems.

Micro balloons / Hollow microspheres:

Micro balloons / hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion/evaporation methods to prolong the gastric retention time (GRT) of the dosage form. Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar, low methoxylated pectin, etc. Buoyancy and drug release from dosage form are dependent on the number of polymers, the plasticizer polymer ratio, and the solvent used for formulation. The micro balloons floated continuously over the surface of an acidic dissolution media containing surfactant for >12 hours. At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of a multiple-unit system and good floating.

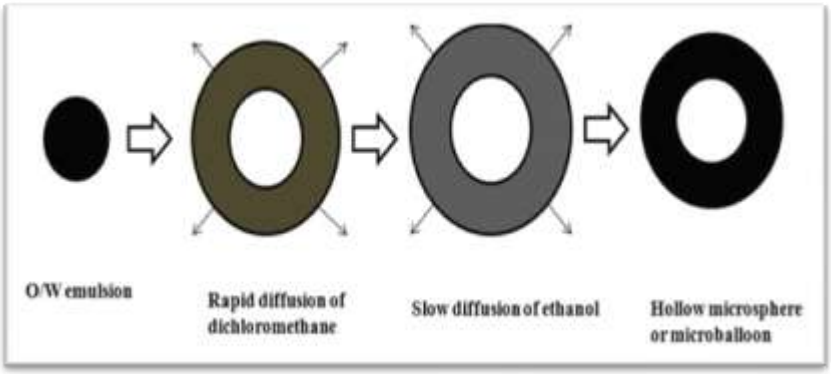

Fig 6. Formulation Of Floating Hollow Microsphere Or Micro balloon

Alginate beads: Talukdar and Fasih recently developed a multiple-unit floating system based on cross-linked beads. They were made by using Ca2+ and low methoxylated pectin (anionic polysaccharide) or Ca2+ low methoxylated pectin and sodium alginate. In this approach, sodium alginate solution is generally dropped into an aqueous solution of calcium chloride and causes the precipitation of calcium alginate. These beads are then separated and dried by air convection and

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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) by more than 5.5 hrs.

Microporous compartment system:

This approach is based on the principle of the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the device were completely sealed to present any direct contact of the gastric surface with the undissolved drug. In the stomach the floatation chamber containing entrapped air causes the delivery system to float in the gastric fluid. Gastric fluid enters through the aperture, dissolves the drug, and causes the dissolved drug to continuously transport across the intestine for drug absorption.

Effervescent (gas-generating) systems:

Floatability can be achieved by the generation of gas bubbles. These buoyant systems utilize matrices prepared with swellable polymers such as polysaccharides (e.g. chitosan), and effervescent components (e.g. sodium bicarbonate, citric acid, or tartaric acid). The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1 . In this system carbon dioxide is released and causes the formulation to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating dosage forms that generate gas (carbon dioxide) when ingested, floating mini capsules with a core of sodium bicarbonate, lactose, and polyvinyl pyrrolidone (PVP) coated with hydroxypropyl methylcellulose (HPMC), and floating system based on ion exchange resin technology, etc. A bilayer or multilayer system has also been designed. Drugs and excipients can be formulated independently and the gas-generating material can be incorporated into any of the layers. Further modifications involve coating the matrix with a polymer that is permeable to water, but not to carbon dioxide. The main difficulty of these formulations is finding a good compromise between the elasticity, plasticity, and permeability of the polymers.

Bioadhesive or Mucoadhesive drug delivery systems:

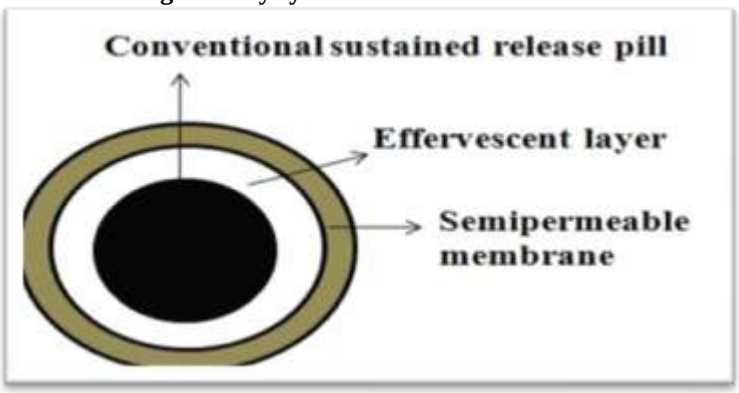

Fig 7. Effervescent (Gas Generating) Systems

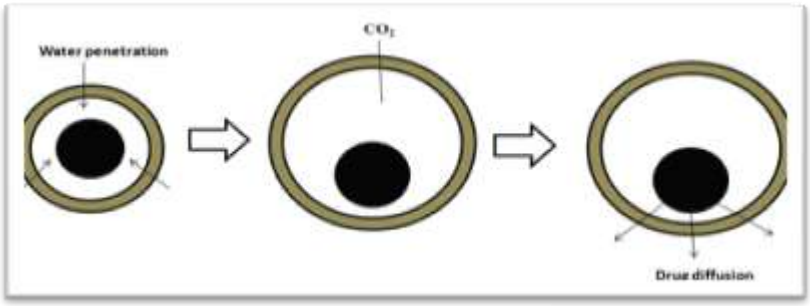

Fig 8. DrugRelease From Effervescent (Gas-Generating) Systems

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Bioadhesive drug delivery systems are used as a delivery devices within the human to enhance drug absorption in a site-specific manner. In this approach, bioadhesive polymers are used and they can adhere to the epithelial surface in the stomach. Thus, they improve the prolongation of gastric retention. The basis of adhesion is that a dosage form can stick to the mucosal surface by a different mechanism. These mechanisms are:

1) The wetting theory is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucous layers.
2) The diffusion theory proposes the physical entanglement of mucin strands the flexible polymer chains, or interpenetration of mucin strands into the porous structure of the polymer substrate.
3) The absorption theory, suggests that bio adhesion is due to secondary forces such as Vander Waal forces and hydrogen bonding.
4) The electron theory proposes attractive electrostatic forces between the glycoprotein mucin network and the bioadhesive material.

Materials commonly used for bio adhesion are poly acrylic acid, chitosan, cholestyramine, sodium alginate, hydroxypropyl methylcellulose (HPMC), sucralfate, tragacanth, dextrin, polyethylene glycol (PEG) and polylactic acids, etc. Even though some of these polymers are effective at producing bioadhesives, it is very difficult to maintain them effectively because of the rapid turnover of mucus in the gastrointestinal tract (GIT).

Expandable, unfold able and swellable systems:

A dosage form in the stomach will withstand gastric transit if it is bigger than the pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, their configurations are required to develop an expandable system to prolong gastric retention time (GRT):

1) a small configuration for oral intake,
2) an expanded gastro retentive form, and
3) a final small form enabling evacuation following drug release from the device.

Thus, gastro retentivity is improved by the combination of substantial dimension with high rigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach. Unfoldable and swellable systems have been investigated and recently tried to develop an effective gastro-retentive drug delivery. Unfoldable systems are made of biodegradable polymers. They are available in different geometric forms like tetrahedrons, rings, or planner membranes (4 - label disc or 4 - limbed cross form) of bio-erodible polymer compressed within a capsule that extends into the stomach. Swellable systems are also retained in the gastrointestinal tract (GIT) due to their mechanical properties. The swelling usually results from the osmotic absorption of water and the dosage form is small enough to be swallowed by the gastric fluid. Expandable systems have some drawbacks like problematical storage of much easily hydrolyzable, biodegradable polymers relatively short-lived mechanical shape memory for the unfolding system most difficulty to industrialize, and not being cost-effective. Again, permanent retention of rigid, large single-unit expandable drug delivery dosage forms may cause brief obstruction, intestinal adhesion, and gastropathy.

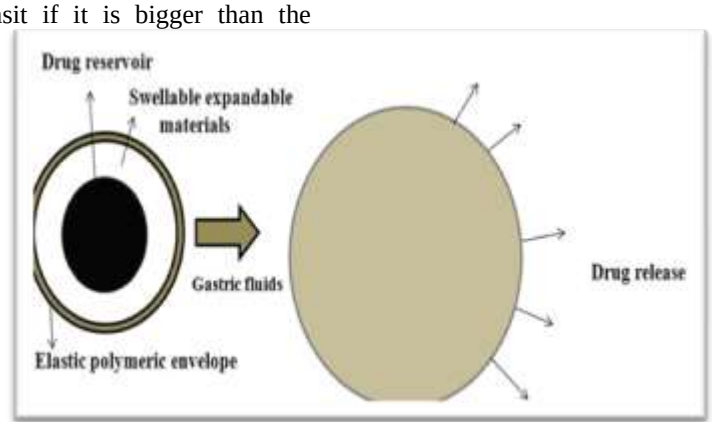

Fig 9. Drug Release From Swellable Systems

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Super porous hydrogel systems:

These swellable systems differ sufficiently from the conventional types to warrant separate classifications. In this approach to improve gastric retention time (GRT) super porous hydrogels of average pore size >100 micro miter, 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 the sufficient mechanical strength to withstand the pressure of gastric contraction. This is advised by the co-formulation of hydrophilic particulate material.

Magnetic Systems:

This approach to enhancing 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 the magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance.

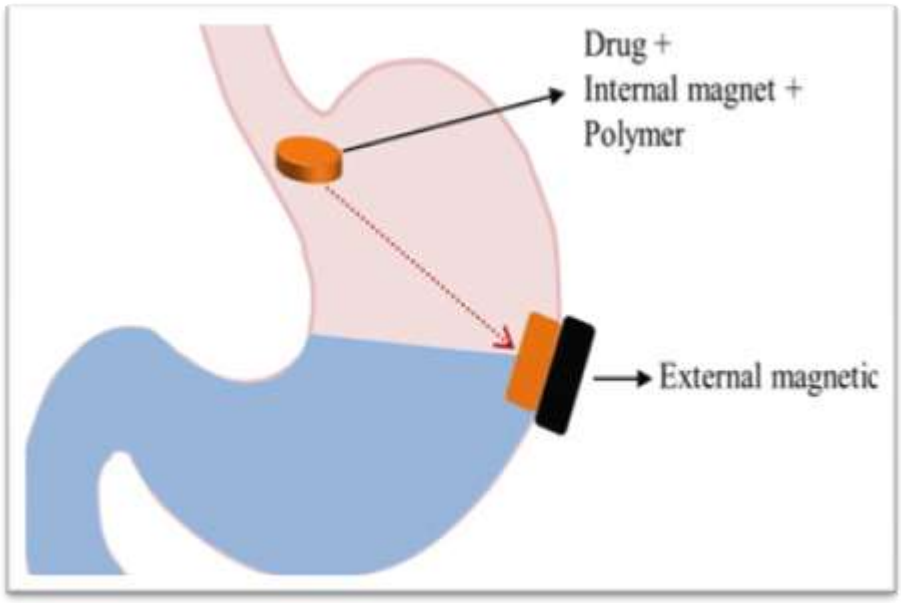

Fig 10. Magnetic Systems

EVALUATION PARAMETER OF GASTRO RETENTIVE DRUG DELIVERY SYSTEM

Floating system:

6 stage dissolution test apparatus is used. 0.1N, 900 ml HCl is used as dissolution media. The time required to emerge on the surface of the medium (Floating lag time) and the Total duration of floating time are measured.

In-vitro studies are done at a temperature of 370C for the duration as specified (approx. 8 hours).

Mucoadhesive system:

Bio-adhesive strength is measured. Cellophane membrane is used, similar to the mucosa of the stomach, or intact mucosa from rabbit is taken.

When mucosa is there bioadhesive polymer sticks to it and the force required to separate is measured. The force required to separate gives a measure of the strength of the polymer.

Swellable system:

We check the water uptake. Water uptake gives an idea of the swelling index. We also check Weight, diameter, and increase in thickness. The dissolution test is done using 0.1N Hal as dissolution fluid.

Swelling index (S.I) = (Wt. - W0 / W0) X 100 Wt. = Final weight after water uptake.

Micro balloons:

Furrier transforms infrared spectroscopy (FTIR) analysis:

The FTIR analysis was done for the analysis of drug-polymer interaction. FT-IR spectra of Pure Drug, Eudragit RS 100, HPMC, and floating micro

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balloons were recorded using Shimadzu 8700 FTIR spectrophotometer.

Micromeritics:

The prepared micro balloons were characterized for micropolitics properties, such as particle size, bulk density, tapped density, compressibility index, and flow properties.

Morphology:

The dried micro balloons were coated with a gold film under a vacuum using a sputter coater. The surface part of micro balloons was observed under scanning electron microscopy (Joel JSM-1600, Tokyo, Japan).

Floating behavior:

Fifty milligrams of the floating micro balloons were placed in simulated gastric fluid (pH 1.2, 100 ml) containing 0.02 w/v% Tween 20. The mixture was stirred at 100 rpm in a magnetic stirrer. After 6h, filtration recovered the floating and the settled portion of micro balloons separately. The micro balloons were dried and weighed. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

Buoyancy (%) = WFP / (Wf + Ws) × 100 Where Wf and Ws are the weights of floating and settled micro particles respectively.

In-vitro release study:

The drug release rate from micro balloons was determined using a USP XXIII basket-type dissolution apparatus. A weighed amount of hollow microspheres equivalent to 20 mg of the drug was filled into a capsule (# 3) and placed in the basket. Simulated gastric fluid (SGF, pH-1.2) (900 ml) containing Tween 20 (0.02 w/v %) was used as the dissolution medium and maintained at 37± 0.5° C at a rotation speed of 100 rpm.

Perfect sink conditions prevailed during the drug release studies. 5ml sample was withdrawn at each 1h interval, passed through a 0.5µm membrane filter (Millipore), and analyzed spectrophotometrically at 296 nm to determine the concentration of the drug present in the dissolution medium. The initial volume of the dissolution fluid was maintained by adding 5 ml of fresh dissolution fluid after each withdrawal. All experiments were conducted in triplicate.

Stability Study:

In the prepared floating micro balloons, the best formulation was selected on basis of buoyancy and the percentage of drug released. The selected formulation was placed in borosilicate screw-capped glass containers and stored at different temperatures (27±2°C), oven temperature (40±2°C), and in the refrigerator (5-8°C) for 90 days. The samples were assayed for drug content (drug entrapment) at regular intervals.

The future with industrial-focused perspectives of gastro-retentive drug delivery systems includes the development of novel gastro-retentive drug delivery formulations by overcoming the drawbacks associated with oral drug delivery. The Pharmacotherapy of disease states and assessment of fed and fasted condition should be considered during development strategies. The scope of scaling up the technology should be also considered to improve the marketability of gastro-retentive drug delivery formulations.

RECENT ADVANCES IN STOMACH-SPECIFIC FLOATING DOSAGE FORMS:

Sungthongjeen et al have prepared floating multilayer coated tablets based on gas formation. The system consists of a drug-containing core tablet coated with a protective layer (hydroxypropyl methylcellulose), a gas-forming layer (sodium bicarbonate), and a gas-entrapped membrane, respectively. Eudragit RL 30D was chosen as a gas-entrapped membrane due to its high flexibility and high water permeability.

The obtained tablets enabled to float due to the CO2 gas formation and the gas entrapment by a polymeric membrane. The effect of formulation variables on floating properties and drug release was investigated. The floating tablets using directly compressed cores had a shorter time to float and faster drug release than those using wet granulated cores. The increased amount of a gas-forming agent did not affect the time to float but increased the drug release from the floating tablets

while increasing the coating level of gas entrapped membrane increased the time to float (more than 8 hours) and slightly retarded, but sustained drug release. Rajnikanth et al have developed a floating in situ gelling system of clarithromycin (FIGC) using gallant as gelling polymer and calcium carbonate as a floating agent for potentially treating gastric ulcers, associated with Helicobacter pylori (Pylori). Gellan-based FIGC was prepared by dissolving varying concentrations of gallant in deionized water, to

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which varying concentrations of the drug and sucralfate were dispersed well. The addition of sucralfate to the formulation significantly suppressed the degradation of clarithromycin at low ph. FIGC showed a significant antiH. pylori effect than that of clarithromycin suspension. The in situ gel formulation with sucralfate cleared Pylori more effectively than the formulation without sucralfate. In addition, the required amount of clarithromycin for eradication of Pylori was found to be less from FIGC than from the corresponding clarithromycin suspension. It was concluded that prolonged gastrointestinal residence time and enhanced clarithromycin stability resulting from the floating in situ gel of clarithromycin might contribute better to the complete clearance of H. pylori than the corresponding clarithromycin suspension.

GASTRO RETENTIVE PRODUCTS AVAILABLE IN MARKET

Brand Name	Drug
Cifran OD	Ciprofloxacin
Madopar	L-DOPA and Benserazide
Valrelease	Diazepam
Topalkan	Aluminum -magnesium antaci
AlmagateFlatCoat	Aluminum -magnesium antacid
Liquid Gavison	Aluminium hydroxide,
Conviron	Ferrous sulfate
Liquid Gavison	Alginic acid , Sodium bicarbonate

PATENTS IN THE GASTRO RETENTIVE DRUG DELIVERY SYSTEM

The patents in gastro-retentive drug delivery systems include various approaches in which Vishwanath Sudhir Nande patented technology of novel gastro-retentive drug delivery system comprising inert core, polymers, and plasticizer that floats for an extended period over the simulated physiological fluids owing to its low density. Hassan Mohammad; 2013 patented a technology-based pharmaceutical product for retention in the stomach comprising a sheet of hydratable polymer that will not pass out of the stomach. It has been reported that gastro retentive floating drug formulation comprising at least one functionalized natural and/or synthetic calcium carbonate-comprising mineral and at least one pharmaceutically active ingredient and at least one formulating aid wherein said functionalized natural or synthetic calcium carbonate is a reaction product of natural or synthetic calcium carbonate with carbon dioxide and one or more acids, wherein the carbon dioxide is formed in situ by the acid treatment and/or is supplied from an external source.

Futurepe Perspectives Of The Gastro Retentive Drug Delivery System

The future with industrial-focused perspectives of gastro-retentive drug delivery systems includes the development of novel gastro-retentive drug delivery formulations by overcoming the drawbacks associated with oral drug delivery. The Pharmacotherapy of disease states and assessment of fed and fasted condition should be considered during development strategies. The scope of scaling up the technology should be also considered to improve the marketability of gastro-retentive drug delivery formulations.

II. CONCLUSION:

It may be concluded that gastro retentive drug delivery offers various potential advantages for a drug with poor bioavailability due to its absorption being restricted to the upper gastrointestinal tract (GIT) and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability. Due to the complexity of pharmacokinetics and pharmacodynamics parameters, in vivo studies are required to establish the optional dosage form for a specific drug. Another promising area of research for a gastro retentive drug delivery system is the eradication of Helicobacter pylori, which is now believed to be a causative bacterium of chronic gastritis and peptic ulcers. Although this microorganism is highly sensitive to many antibiotics, its complete eradication requires a high concentration of antibiotics to be maintained within gastric mucosa for a prolonged period. An

important feature to take into account is stomach physiology. An important parameter is a time when the drug is taken (during or apart from the meal). Developing an efficient gastro retentive dosage form is a real challenge to pharmaceutical technology. Indeed, the drug delivery system must remain for a sufficient time in the stomach, which is not compatible with its normal physiology. All these gastro retentive drug delivery systems (high density, floating, expandable or unfoldable or swelling, super porous, bioadhesive, magnetic systems, etc.) are interesting and present their advantages and disadvantages. Now, a lot of work is running to develop different types of gastro retentive delivery systems for various drugs. In the future, it is expected that they will become of increasing importance, ultimately leading to improved efficiencies of various types of pharmacotherapies.

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