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GASTRO RETENTIVE DRUG DELIVERY SYSTEM- A REVIEW

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ABSTRACT

The purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems, and their classification and formulation aspects are covered in detail. This review also summarizes the *in vitro* techniques, *in vivo* studies to evaluate the performance and application of floating systems, and applications of these systems. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form.

INTRODUCTION:

Considerable efforts have been made in the last decades to develop new pharmaceutically viable and therapeutically effective controlled drug delivery systems. Controlled drug delivery usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient. Controlled drug delivery results in optimum therapy, and not only reduces the frequency of dosing, but may also reduce the severity and frequency of side effects.

An approach to oral controlled drug delivery:

An orally administered controlled drug delivery system encounters a wide range of highly variable conditions, such as pH, agitation intensity, and composition of the gastrointestinal fluids as it passes down the G.I. tract.

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Considerable efforts have been made to design oral controlled drug delivery systems that produce more predictable and increased bioavailability of drugs. However, the development process is precluded by several physiological difficulties, like inability to retain and localize the drug delivery systems within desired regions of the G.I. Tract and highly variable nature of gastric emptying process. An important factor, which may adversely affect the performance of an oral controlled drug delivery system, is the G.I. Transit time. The time for absorption in the 0.1. transit in humans, estimated to be 8-10 hrs from mouth to colon, is relatively brief with considerable fluctuation. G.I transit times vary widely between individuals, and depend up on the physical properties of the physiological conditions of the gut. This variability may lead to bioailabi1ity and times to achieve peak plasma levels. Determinants of G.I. transit is the residence time in the stomach. Most of the drugs are well absorbed from all the regions of the G.I. tract, while some are absorbed only from specific areas, principally due to their low permeability or solubility in the intestinal tract, their chemical instability, the binding or the drug to the gut contents, as well as to the degradation of the drug by microorganisms present in the colon. Therefore, in instances

where the drug is not absorbed uniformly over the G.I. tract, the rate of drug absorption may not be constant in spite of the drug delivery system delivering the drug at a constant rate into the G.I. fluids. More particularly, in instances where a drug has a clear cut "absorption window," i.e., the drug is absorbed only from specific regions of the stomach or upper parts of the small intestine; it may not be completely absorbed when administered in the form of a typical oral controlled drug delivery system. This is due to the relatively brief gastric emptying time in humans, which normally averages 2-3 hrs through the major absorption zone. It may cause incomplete drug release from the dosage form at absorption sites leading to diminished efficacy of the administered dose. It is apparent that for a drug having such an "absorption window," an effective oral controlled drug delivery system should be designed not only to deliver the drug at a controlled rate, but also to retain the drug in the stomach for a long period of time. For this drug, increased or more predictable availability would result if controlled release systems could be retained in the stomach for extended periods of time. It is suggested that compounding narrow absorption window drugs in a unique pharmaceutical dosage form with gastro retentive properties would enable an extended absorption phase of these drugs. After oral administration, such a dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastro intestinal tract. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of controlled release dosage forms for these drugs. Gastric retention dosage forms would be particularly valuable for drugs (i) That have an absorption window in the stomach or in the upper parts of small intestine (ii) That are locally active in the stomach (iii) That are unstable in the intestinal or colonic environment, and for (iv) Have low solubility at alkaline pH values.

Gastric Emptying Process and Conditions: The process of gastric emptying occurs both during fasting and fed states: however, the pattern of motility differs markedly in the two states. In the fasted state, it is characterized by an inter digestive series of electrical events that cycle both through the stomach and small intestine every 2-3 hrs. This activity is called the inter digestive myoelectric cycle or migrating myoelectric complex (MMC), which is often divided into four consecutive phases. As described by Wilson and Washington.

Phase I is a quiescent period lasting from 40 to 60 mm with rare contractions.

Phase II is a period of similar duration consisting of intermittent action potentials and contractions that gradually increase in intensity and frequency as the phase progresses.

Phase III is a short period of intense, large regular contractions lasting from 4 to 6 mm. It is this phase, which gives the cycle the term. "Housekeeper wave", since it serves to sweep undigested materials out of the stomach and down the small intestine. As phase III of one cycle reaches the end of the small intestine, phase III of the next cycle begins in the duodenum.

Phase IV is a brief transitional phase that occurs between phase Ill and phase I of two consecutive cycles. The motor activity in the fed state is induced *5-10* mm after ingestion of a meal and persists as long as food remains in the stomach, It consists of regular and frequent contractions. These contractions are not as severe as those in the third phase of fasted motility pattern.

Requirements:

To achieve gastro retention, a dosage form must satisfy the following requirements.

- One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and constant grinding and churning mechanism.

- It must resist premature gastric emptying and once the purpose has been served, it should be removed from the stomach with ease.

FACTORS AFFECTING GASTRIC RESIDENCE TIME OF FDDS

a) Formulation Factors

Size of Tablet: Retention of floating dosage forms in stomach depends on the size of tablets. Small tablets are emptied from the stomach during the digestive phase, but large ones are expelled during the house keeping waves. Floating and non floating capsules of 3 different sizes having a diameter of 4.8 mm (small units), 7.5 mm (medium units), and 9.9 mm (large units), were formulated and analyzed for their different properties. It was found that floating dosage units remained buoyant regardless of their sizes on the gastric contents

throughout their residence in the gastrointestinal tract, while the non floating dosage units sank and remained in the lower part of the stomach. Floating units away from the gastroduodenal junction were protected from the peristaltic waves during digestive phase while the non floating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase.

Density of Tablets :Density is the main factor affecting the gastric residence time of dosage form. A buoyant dosage form having a density less than that of the gastric fluids floats, since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period. A density of less than 0.1mg/ml i.e. less than that of gastric contents has been reported. However, the floating force kinetics of such dosage form has shown that the bulk density of a dosage form is not the most appropriate parameter for describing its buoyancy capabilities.

Shape of tablets: The shape of dosage form is one of the factors that affect its gastric residence time. Six shapes (ring tetrahedron, cloverleaf, string, pellet, and disk) were screened in-vivo for their gastric retention potential. The tetrahedron (each leg 2cm long) rings (3.6 cm in diameter) exhibited nearly 100% retention at 24 hr.

Viscosity grade of polymer: Drug release and floating properties of FDDS are greatly affected by viscosity of polymers and their interaction. Low viscosity polymers (e.g., HPMC K100 LV) were found to be more beneficial than high viscosity polymers (e.g., HPMC K4M) in improving floating properties. In addition, a decrease in the release rate was observed with an increase in polymer viscosity.

b) Idiosyncratic factors

Gender: Women have slower gastric emptying time than do men. Mean ambulatory GRT in meals (3.4±0.4 hours) is less compared with their age and race-matched female counterparts (4.6± 1.2 hours), regardless of the weight, height and body surface.

Age : Low gastric emptying time is observed in elderly than do in younger subjects. Intra subject and inter subject variations also are observed in gastric and intestinal transit time. Elderly people, especially those over 70 years have a significantly longer GRT.

Posture:

i) Upright position : An upright position protects floating forms against postprandial emptying because the floating form remains above the gastric contents irrespective of its size l4. Floating dosage forms show prolonged and more reproducible GRTs while the conventional dosage form sink to the lower part of the distal stomach from where they are expelled through the pylorus by antral peristaltic movements.

ii) Supine position : This position offers no reliable protection against early and erratic emptying. In supine subjects large dosage forms (both conventional and floating) experience prolonged retention. The gastric retention of floating forms appear to remain buoyant anywhere between the lesser and greater curvature of the stomach. On moving distally, these units may be swept away by the peristaltic movements that propel the gastric contents towards the pylorus, leading to significant reduction in ORT compared with upright subjects.

Concomitant intake of drugs: Drugs such as prokinetic agents (e.g.. metoclopramide and cisapride). Anti Cholinergics (e.g., atropine or propantheline), opiates (e.g., codeine) may affect the performance of FDDS. The co-administration of G.I motility decreasing drugs can increase gastric emptying time.

Feeding regimen : Gastric residence time increases in the presence of food, leading to increased drug dissolution of the dosage form at the most favorable site of absorption. A GRT of 4-10 hrs has been reported after a meal of fats and proteins.

Absorption window:

The G.I. tract offers a varied environment capable of affecting the absorption of per orally administered drugs. Anatomical features, physiological phenomenon, and nature of' gastrointestinal milieu contribute these changes. This can lead to the variations in intestinal permeability of drug molecules, resulting in the phenomenon of "absorption window" as shown fig. no. 1, where in the drug is preferentially absorbed only from a particular region of the G.I. tract. Physicochemical and/or physiological factors are responsible for the formation of absorption window for certain classes of drugs.

Various Factors for absorption window: Physico-chemical factors:

pH-dependent solubility and stability: A drug experiences a Ph range of 1-8 across the G.I. tract, and needs to be in solubilised and stable form to successfully cross the biological membrane. Most of the drugs are passively absorbed, in their un-ionized form and the extent of ionization at different pH values in different regions of G.I tract can significantly alter the absorption profile. pH dependent solubility, stability and ionization by changing the physical properties of the drug in different portions of the G.I. tract, can lead to regional variability in absorption of drugs.

Physiological factors:
(a). Mechanism of absorption: Per orally administered drugs are absorbed both by passive diffusion as well as by non-passive means of absorption. Drugs absorbed by active and facilitated transport mechanisms show higher regional specificity due to the prevalence of these mechanisms only in a particular region of G.I. tract.

(b). Metabolic enzymes: Presence of certain enzymes in a particular region of G.I. tract can also lead to regional variability in absorption of drugs that are substrates to those enzymes; Intestinal metabolic enzymes principally, phase one metabolizes like cytochrome P-450 are abundantly present in the intestinal epithelium. Their activity decreases longitudinally along the small intestine, with the levels rising slightly from the duodenum to the jejunum and then declining in the ileum and colon. This non-uniform distribution of cytochrome P-450 causes regional variability in the absorption of drugs that are substrate to these enzymes.

Gastric Retention System: Gastric Retention System is a device, which resides in the confines of the stomach over a prolonged period of time (prolonging the residence time) for the purpose of Providing .a platform for controlled release of biologically active agents. The system releases the active agent to be absorbed or released from the stomach to be absorbed in the Upper parts of the small intestine. In particular it allows for less frequent dosing of active agent than with immediate release formulations or sustained release formulations that are not gastric retention dosage forms. In other applications the frequency of dosing may be the same, but the gastric retention dosage forms will beneficially alter the absorption profile of the active agent from that available with immediate release formulations. This may result in increased bioavailability of the active agent with reduced side effects. Over the last three decades, various approaches have been pursued to prolong the residence time of an oral dosage form in the stomach. These methods include floating systems, Swelling and expanding systems , Bio adhesive systems, Modified-shape system, High-density systems , Other gastric emptying devices.

Floating Drug Delivery Systems or Hydrodynamically Balanced Systems (HBS): These systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in the gastric retention lime and a better control of fluctuations in plasma drug concentrations. HBS system containing a homogeneous mixture of drug and the hydrocolloid in a capsule, which upon contact with gastric fluid acquires and maintains a bulk density of less than I and there by being buoyant on the gastric contents of stomach until the entire drug was released. Hydro dynamically balanced sustained release tablets containing drug and hydrophilic hydrocolloids, which on contact with gastric fluids at body temperature forms a soft water-impermeable colloid gel barrier on their surface. The drug is slowly released from the surface of the gelatinous mass that remained buoyant on gastric fluids. Hydro dynamically balanced systems are designed to prolong the stay of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form. The success of FIBS capsule as a better system is best exemplified with chlordiazeopoxide hydrochloride. The drug is a classical example of a solubility problem where in it exhibits a 4000 fold difference in solubility going from p^H 3 to 6 (the solubility of chlordiazepoxide hydrochloride is 150 mg/ml and is -0.1 mg/ml at neutral pH).

Swelling and Expanding Systems: One way to retain a dosage form in the stomach is by increasing its size. The stomach discharges its content through the pylorus into intestine. If the dosage form can attain a size larger than that of the pylorus, it can be retained in the Stomach for a long time. Swelling type dosage forms as shown in

fig. nol.4 are such Systems that after swallowing swell to an extent that prevents their exit from the stomach trough the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be referred to as "plug type systems" since they exhibit a tendency to remain lodged at the pyloric sphincter.

Bio adhesive Systems: Bio-adhesive systems are used to localize a delivery device within the lumen and cavity of the body to enhance the drug absorption process in a site specific manner. This approach involves the use of bioadhesive polymers that can adhere to the epithelial surface of the G.I, tract. The proposed mechanism of bioadhesion is the formation of hydrogen and electrostatic bonding at the mucus-polymer boundary. Rapid hydration in contact with the muco-epithelial surface appears to favour adhesion, particularly if water can be excluded at the reactive surfaces. These bioadhesive systems do not seem to be a very feasible solution as this bond formation is prevented by the acidic environment and thick mucus present in the stomach. High turnover of mucus adds to the difficulties in retaining a hioadhesive system at the site. The commonly used mucoadhesive polymers are carboxymethyl cellulose. carhopol. polycarbophil, tragacanth, sodium alginate, gelatin and pectin etc.

Modified Shape Systems: Modified-shape systems are non-disintegrating geometric shapes molded from silastic elastomer or extruded from polyethylene blends, which extend the gastric retention time depending on size, shape and flexural modulus of the drug delivery device.

High Density System: High-density formulations include coated pellets, which have a density greater than that of the stomach contents (~l ,004 g/cm3). This is accomplished by coating the drug with a heavy inert material such as barium sulfate, zinc oxide, titanium dioxide, N iron powder etc. Other delayed gastric emptying approaches of interest include sham feeding of indigestible polymers or fatty acid salts that change the motility pattern of the stomach to a fed state, thereby decreasing the gastric emptying rate and permitting considerable prolongation of drug release. Of these abovementioned approaches, floating drug delivery or hydro dynamically balanced drug delivery systems are given much importance, because of their ease of preparation and reliable and reproducible gastric retentive action.

Gastric Floating Drug Delivery Systems (GFDDS): The various buoyant preparations include tablets, pills, granules, powders, capsules, hollow microspheres (micro balloons) and laminated films. Based on the mechanism of' buoyancy, two distinctly different technologies i.e., non effervescent and effervescent systems have been utilized in the development of GFDDS.

Non Effervescent GFDDS: The approach involved in the formulation of these floating dosage fhrrns is intimate mixing of drug with a gel-forming hydrocolloid, which swells in con act with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. In addition, 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. The most commonly used excipients in this type of GFDDS are gel forming or highly sellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate. polyacrylate, polymethacrylate and polystyrene.

Effervescent GFDDS: These floating drug delivery systems utilize matrices prepared with swellable polymers such as methocel or polysaccharides and effervescent components or matrices_containing chambers of liquid that gasify at body temperature. The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy. A decrease in the specific gravity causes the dosage form to float on the gastric fluids. The carbon dioxide generating components may be intimately mixed within the tablet matrix, in which case a single-layered tablet is produced or a bilayered tablet may be compressed which contains the gas generating mechanism in one hydrocolloid containing layer and the drug in the other layer formulated for a sustained release effect. This concept has also been exploited for floating capsule systems as shown in fig. no1.5

Development and evaluation of GFDD

Formulation development: For the optimum design of a GFDDS, the key step is to understand the principles of G.I. dynamics such as gastric emptying, small intestinal transit, colonic transit43, etc. Acquiring knowledge about the rate and extent of drug absorption from different sites of G.I. tract, and factors that can alter or limit the absorption further aid in designing the type of dosage form that is needed for a particular drug. For instance, with drugs such as sulpiride, furosemide, theophylline and albuterol, which are predominantly absorbed from the upper pan of the G.I. tract, designing a gastric retention dosage form

is a logical strategy for improving and extending their limited oral bioavailability. For the formulation of a hydro dynamically balanced dosage form, three major conditions must be met:

(i) It must have sufficient structure to form a cohesive gel barrier;
(ii) It must maintain an overall density lower than that of gastric contents (reported as 1.004-1.01g/cc) &
(iii) It should dissolve slowly, enough to serve as a 'reservoir' for the delivery system. The task of designing a dosage form to achieve a consistent and controlled residence in the stomach begins with selection of potential excipients that allow the formulation of matrices having sustained delivery characteristics and a bulk density of less than unity. As far as the ideal floating dosage form is concerned, it should have high buoyancy, adequate mechanical strength, excellent acid resistance and a high drug releasing capacity in the stomach. Ideally water-soluble cellulose derivatives are best suited for such purposes.

***In Vitro* and *In vivo* evaluation:** The various parameters that need to be evaluated for their effects on gastric retention time of buoyant formulations can mainly be categorized into following different classes.
* Galenic parameters: diametral size ('cut-off size'), flexibility and density of matrices.
*Control parameters: floating time, dissolution, content uniformity, hardness and &inability.
*Geometric parameters: shape.
*Physiological parameters: age. Sex, posture. Food and bio adhesion. The test for buoyancy and *in vivo* drug release studies are usually carried out in simulated gastric fluid maintained at 37°C. The *in vivo* gastric retentivity of a floating dosage form is usually determined by y-scintigraphy or roentgenography. Studies are done both under fasted and fed conditions using floating and non floating (control) dosage forms. It is also important that both dosage forms are non-disintegrating units, and human subjects are young and healthy.

Advantages of GFDDS:
Sustained drug delivery:

Sustained drug absorption from oral controlled release dosage forms is often limited due *to* short gastric retention time. However, GFDDS remain in the stomach for more hours due to their increased GRT. It has been suggested that due to their low density than the gastric contents and relatively large size they do not pass through the pylorus that has an opening of approximately 0.9-1.9 cm53. It has been observed that major portion of drug releases in the colon rather than stomach in case of modified release capsule. However, prolongation in the GRT may sustain the drug-release behavior.

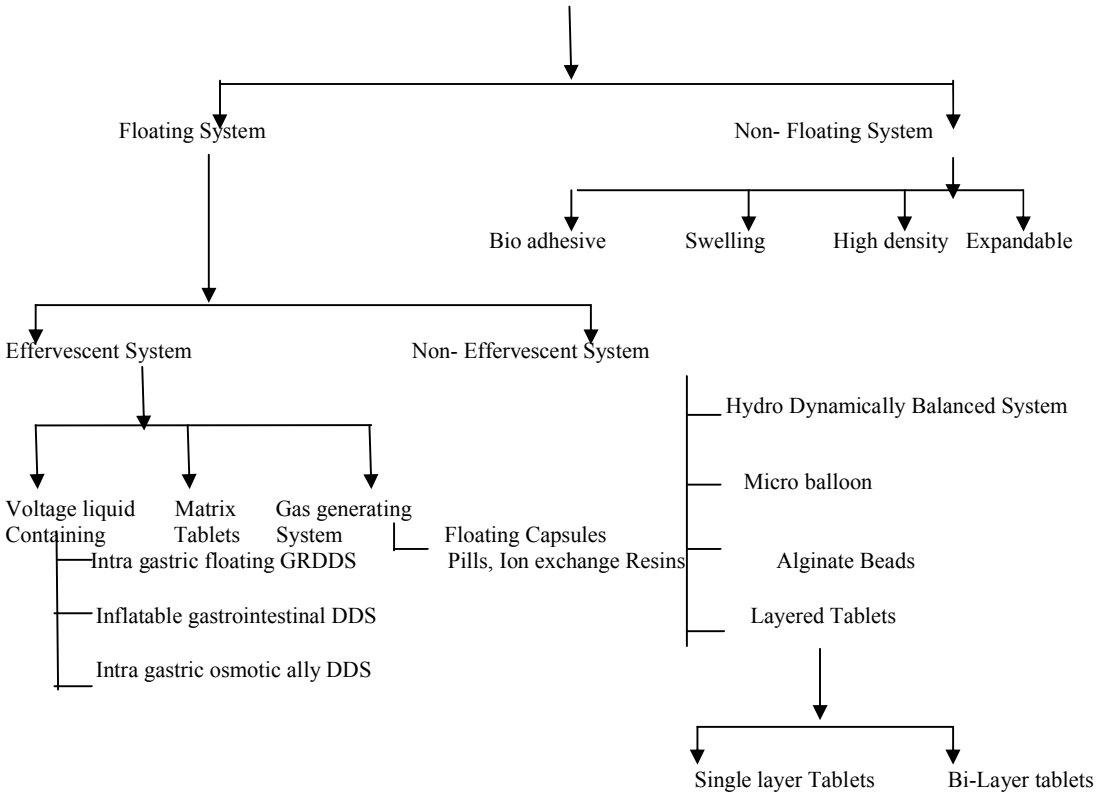
Site specific drug delivery: Drugs having absorption sites in the upper small intestine like furosemide and riboflavin are typically formulated in floating dosage form. It has been reported that absorption of furosemide takes place mainly through stomach followed by duodenum55. This characteristics of furosemide prompted scientists to develop a monolithic floating system, which could prolong the ORT and thereby increase the bioavailability. A bilayer floating capsule has been developed for local delivery of misoprostol to the gastric mucosa for prevention of gastric ulcers caused by non-steroidal anti-inflammatory drugs (NSAID's). Mechanistically, the drug replenishes the GI-protective prostaglandins that are depleted by NSAID's. Therefore, sustained and controlled delivery of misoprostol to the stomach provides sufficient local therapeutic levels vis-a-vis exposure to the drug. This in turn reduces the side effects caused by the presence of the drug in systemic circulation (uterotonic activity) and also retards diarrhea, which is result of combination of intestinal and systemic exposure of drug. Moreover, the prolonged gastric availability of the misoprostol from FDDS also reduces the dosing frequency 5-fluorouracil bearing floating tablets have been successfully evaluated in four patients with stomach neoplasms.

Limitations:

1. The major disadvantage of floating systems is requirement of a sufficiently high level of fluids in the stomach for the drug delivery. However, this limitation can be overcome by coating the dosage form with the help of bio-adhesive polymers that easily adhere to the mucosal lining of the stomach.
2. The dosage form should be administered with a minimum of glass full of water (200-
250 ml).
3. Floating system is not feasible for those drugs that have solubility or stability problems in gastric fluids.
4. The drugs, which are absorbed throughout gastrointestinal tract. which undergo significant first pass metabolism, are not desirable candidates.

5. Some drugs present in the floating system causes irritation to gastric mucosa.

Gastro retentive Drug Delivery System (GRDDS)



Ideal Properties of GRDDS					
Effective Retention in The stomach	Sufficient Drug Loading capacity	Controlled Drug release profile	Full degradation & evacuation after drug release	No effect on gastric motility including emptying pattern	No other local effects

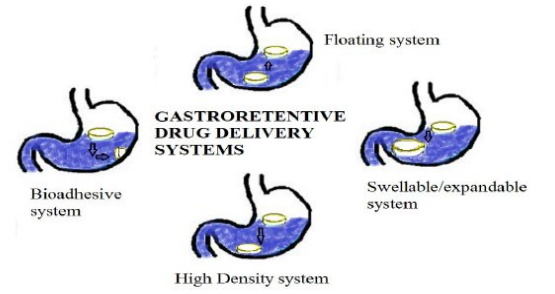
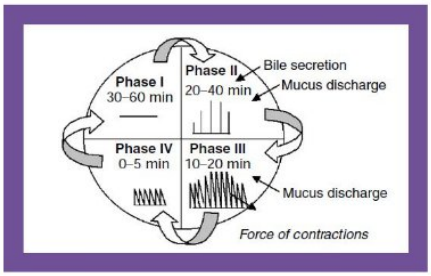


Fig. 1: Figure showing various approaches for gastroretentive drug delivery system



S.no	Dosage Form	Examples of Drugs
1	Microspheres	Aspirin, Grisiofulvin, Pnitroanilline, Ibuprofen, Terfinadine, Tranilast
2	Granules	Diclofenac sodium, Indomethacin, Prednisolone
3	Films	Cinnarizine
4	Powders	Several basic drugs
5	Capsules	Chlordiazepoxide HCl, Diazepam, Furosemide, 1-dopa, Benserazide,Misoprostol, Propranolol HCl, Ursodeoxycholic acid
6	Tablets/pills	Acetaminophen, Acetyl salicylic acid, Amoxicillin, Trihydrate, mpicillin, Atenolol, Isosorbide

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