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GASTRORETENTIVE DRUG DELIVERY SYSTEM-An Overview

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ABSTRACT

Gastric emptying is a complex process and makes the performance of the drug delivery systems uncertain. In order to avoid this variability, efforts have been made to increase the retention time of the drug-delivery systems for more than 12 h. The floating or hydrodynamically controlled drug delivery systems are useful in such application. The present review addresses briefly about the floating drug delivery systems. Gastroretentive drug delivery systems provide drug delivery at the controlled rate and prolong the retention of dosage forms in gastrointestinal tract. In this review we will discuss the various aspects of the gastroretentive systems. These studies begin with the introduction to the gastroretentive systems along with advantages and factors controlling gastric retention of dosage forms have been discussed. Afterwards the discussion about the requirements for development of gastroretentive drug delivery systems and suitable and unsuitable drugs candidates are briefly explained. At the end, the polymers and the different other substances used in formulating hydro dynamically balanced, raft, muco-adhesive, floating, high density and magnetic systems of gastroretentive drug delivery systems are described. Various gastroretentive dosage forms of the different drugs and polymers utilized in them are presented in this review.

INTRODUCTION

Gastroretentive system ensures that the dosage form remains within the gastric region for the longer duration of time. This provides the advantage that the gastric retention time (GRT) for such drug is improved in comparison to conventional dosage and also the minimum effective concentration of drug remains maintained in systemic circulation for longer duration. Oral controlled release [CR] dosage forms have been developed for the past three decades due to their considerable therapeutic advantages. [1]

Classification of different Gastroretensive drug delivery system

Gastroretensive drug delivery system is broadly categorized into two types

A. Non-Floating System

B. Floating Drug Delivery System (FDDS)

Non-floating system is further divided into:

1. High Density (Sinking) Drug Delivery System
2. Bioadhesive or Mucoadhesive System
3. Magnetic System
4. Swelling/ Expanding Systems

Floating Drug Delivery System (FDDS) Floating drug delivery system can be divided into:

1. Effervescent System

I) Volatile Liquid Containing Systems

a) Intragastric floating gastrointestinal drug delivery
b) Inflatable gastrointestinal drug delivery system
c) Intragastric osmotically controlled drug delivery system

II) Gas Generating Systems

a) Floating capsules
b) Floating pills
c) Floating systems with ion exchange resins

2. Non Effervescent System

a) Hydrodynamically balanced system
b) Microbaloons or hollow microspheres
c) Alginate beads
d) Microporous compartment
e) Raft systems
f) Superporous hydrogel

FDDS [Floating drug delivery system] or hydrodynamically controlled systems are low-density systems that float over the gastric contents because of their sufficient buoyancy and remain buoyant in the stomach for prolonged period of time without affecting the gastric emptying rate. [2] The drug is released slowly from the floating system at a desired rate. The residual system is removed from the stomach after the release of drug. According to buoyancy retention principle, a minimal gastric content is needed to allow the proper achievement of the buoyancy; however, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. [3] Prolonging of gastric residence time enhance drug release duration of drug along with better bioavailability. [4,5] Since the past 3 decades, many approaches to gastroretentive drug delivery system have been developed, including floating, magnetic system, [6] unfoldable, expandable or swellable system, [7] muco-adhesive, [8] sedimentation, susperporous hydrogel system [9]. The application of floating systems is greatly employed for delivery of drug with reduced bioavailability due to low absorption in the upper gastrointestinal tract. The floating system improves the bioavailability by keeping the dosage form at the absorption site. [10]

Floating matrix tablets belong to sustained release drug delivery system that is designed to float on gastric fluids for longer period of time usually by the mechanism of swelling or generating CO_2 gas and release the drug for prolonged period of time. Gastroretensive drug delivery systems are designed to prolong the residence time of drug in the GIT. This approach can be utilised for preparation of bilayer tablet having an immediate release layer and a sustained release layer. [11]

Two different technologies have been utilized for development of FDDS based on the mechanism of buoyancy. They are:

- Effervescent floating system, and
- Non- effervescent floating system.

Effervescent floating systems utilize some gas generating agents that include organic acid (e.g. citric acid and tartaric acid) and carbonates (ex. sodium bicarbonate). It is incorporated in the dosage forms to produce carbon dioxide (CO_2) gas, as a result reduces the density of the system and makes it float on the gastric fluid [12].

Advantages of Floating Drug Delivery System [12, 13]

- The GRFDD are suitable for drugs those are better absorbed through the stomach e.g. ferrous salts.
- The GRFDD are advantageous for drugs those are useful for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.
- Administration of a sustained release floating dosage form capsule or tablet will result in dissolution of the drug in gastric fluid.
- Gastric retention is advantageous for the delivery of drugs having narrow absorption windows in the small intestinal region.
- Drugs that are better absorbed from the proximal part of the gastrointestinal tract (GIT) are also suitable as floating drug delivery system.
- Drugs that are degraded by the alkaline pH or are less soluble at the lower part of GIT are also suitable to deliver as floating drug delivery system.
- Drugs those are absorbed due to variable gastric emptying time.
- Local or sustained drug delivery to proximal part of small intestine and the stomach for the treatment of certain conditions like duodenal ulcers.
- Particularly useful for the treatment of *H. Pylori* induced peptic ulcers.

Disadvantages of Floating Drug Delivery System [12, 13]

- Drugs that are unstable in acidic environment and may irritate the stomach lining should not be formulated as gastro retentive systems.
- Gastric retention is not desirable for the drugs that are known to cause gastric lesions, and causes slow release of such drugs in the stomach e.g Non-steroidal anti-inflammatory drugs and Aspirin.
- Furthermore, drugs such as Isosorbide dinitrate, that are well absorbed throughout the GI tract is not beneficial by incorporating into a gastric retention system.
- The floating systems can be questionable for the case of swellable systems in patients with achlorhydria as the swellable system required faster swelling to achieve floating properties.

MECHSNISM OF FLOATING

Gastric Emptying Time (GET) and Motility: GET occurs during both fasting as well as fed states. GET is the time required to pass drug from the stomach to the small intestine. It is the rate limiting step for drug absorption because the intestine is the major site for absorption. In general, bioavailability of the drugs is increased by rapid gastric Emptying. For drugs that degrade in gastric environment, faster onset is required. [14] The drugs which are poorly soluble at alkaline pH and are majorly absorbed from the stomach or proximal part of the intestine their dissolution is promoted by delayed gastric emptying. However, the pattern of motility is distinct in the two states. The inter-digestive series of electrical events takes place during the fasting states which cycle both through the stomach and intestine every 2-3hr. [15]

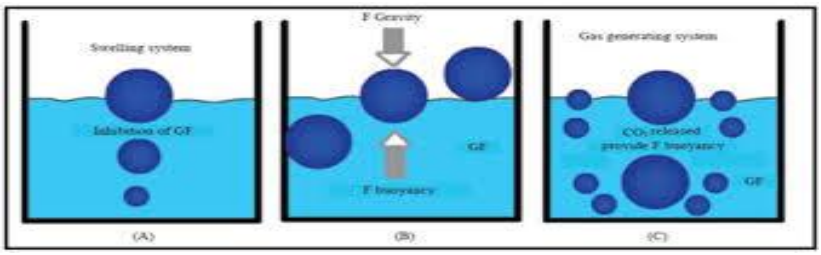


Fig. 1: Mechanism of Floating

Gastric emptying time occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an inter digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myoelectric cycle (IMC) or migrating myoelectric cycle (MIMC) which is dived into four phases as described by Wilson and Ishington.

Phase I: (Basal Phase) This phase lasts from 40 to 60 minutes with concentration.

Phase II: (Pre-Burst Phase) It lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

Phase III (Burst Phase): It lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

Phase IV: It lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

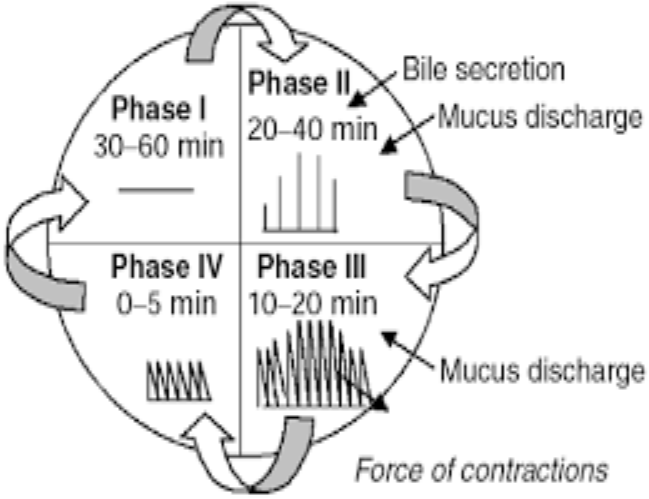


Fig. 2: Motility Patterns in GIT

FACTORS INFLUENCING GASTRIC RETENTION OF DOSAGE FORMS:

The anatomy and physiology of the stomach contain parameters to be considered in the development of gastroretentive dosage forms. Important parameters controlling the gastric retention are as follows:

- **Density of Dosage Forms:** The density of a dosage form affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms which are having density lower than the gastric contents can float to the surface, while high-density systems sink to bottom of the stomach. [7]

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

- **Shape and Size of the Dosage Form:** Shape and size of the dosage forms are important in designing the indigestible single-unit solid dosage forms. [11] Due to the larger size of the dosage form, it will not quickly pass through the pyloric antrum into the intestine. [12] Garg and Sharma [13] reported that tetrahedron- and ring-shaped devices had the better gastric residence time as compared to other shapes. The diameter of the dosage unit is also an important formulation parameter. Dosage forms that are having a diameter of more than 7.5 mm show a better gastric residence time as compared with one having 9.9mm.

- **Single-or multiple- unit formulation:** Food intake and its nature food intake, viscosity and volume of food, caloric value, and frequency of feeding are the factors that have a profound effect on the gastric retention of dosage forms. The presence or absence of food influences the GRT of the dosage form. Usually, the presence of food in the gastrointestinal tract (GIT) improves the gastric retention for a longer period, by allowing its stay at the absorption site. Again, increase in acidity and caloric value slows down GET, which thus improves the gastric retention of dosage forms (Garg et al, 2008) [5].

- **Effect of Gender, posture and Age:** In general, females have slower gastric emptying rates than male partner. The postural effect does not have any significant difference in the mean GRT for individuals in the upright, ambulatory, and supine state. However, in elderly persons, gastric emptying is slowed down. [18] Timmermans et al. [19] studied the effect of buoyancy, posture, and nature of meals on the gastric emptying process using in vivo gamma scintigraphy. In this study, 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) are considered. Then, the floating and non-floating are compared, and it is concluded that, regardless of their sizes, the floating dosage units remained buoyant on the gastric content throughout their residence in the GIT

- **Formulation techniques:** Due to physiological variation in the gastric environment, the aim to achieve retention of drug in the stomach could be fulfilled by modifying drug delivery systems. Thus, various approaches have been used to retain drug in the gastric environment for the longer been used to retain drug in the gastric environment for the longer duration of time.

DIFFERENT APPROACHES FOR DESIGNING OF FLOATING DRUG DELIVERY SYSTEMS (FDDS)

A. Non-effervescent FDDS

- The non-effervescent FDDS works on the mechanism of bioadhesion of the polymer to mucosal layer of GI tract and polymer swelling. The most commonly used excipients for the preparation of non-effervescent FDDS are swellable type hydrocolloids or gel forming polysaccharides, bioadhesive polymers like chitosan and carbopols and matrix forming

polymers like polycarbonates, polymethacrylates, polyacrylates, polystyrenes. One of the approaches in the development of non-effervescent floating dosage forms involves thorough mixing of drug and hydrocolloids that forms gel. After oral administration of such type of the dosage form, it comes in contact with gastric fluids and gets swollen by forming a gelatinous barrier at the surface. The swollen dosage form maintains a proper integrity of shape and has bulk density less than 1.0 g/ml. The air entrapped within the swollen polymer matrix allows the dosage forms to become buoyant. Apart from this, the swollen gel structure acts as a reservoir for the drug and gives prolonged release effect to the dosage forms. The slow release pattern of drug is controlled by mechanism of diffusion due to formation of gelatinous barrier.

Low density floating systems [21]

- These systems are also known as floating drug delivery systems (FDDS) or hydrodynamically balanced systems (HBS). They have a bulk density less than density of gastric fluid, i.e. less than 1 g/cm^3. The specific gravity of gastric fluid is 1.004-1.01g/cm^3 approximately. Thus FDDS remains buoyant in stomach for prolonged period of time without affecting gastric emptying rate and release the drug slowly at desired rate. These are usually single-unit dosage form that contains one or more gel-forming hydrophilic polymers. Polymers such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), hydroxyethyl cellulose (HEC), polyacrylate, polycarbophil, polystyrene, carrageenans, agar or alginic acid are used commonly as excipients to develop these systems.

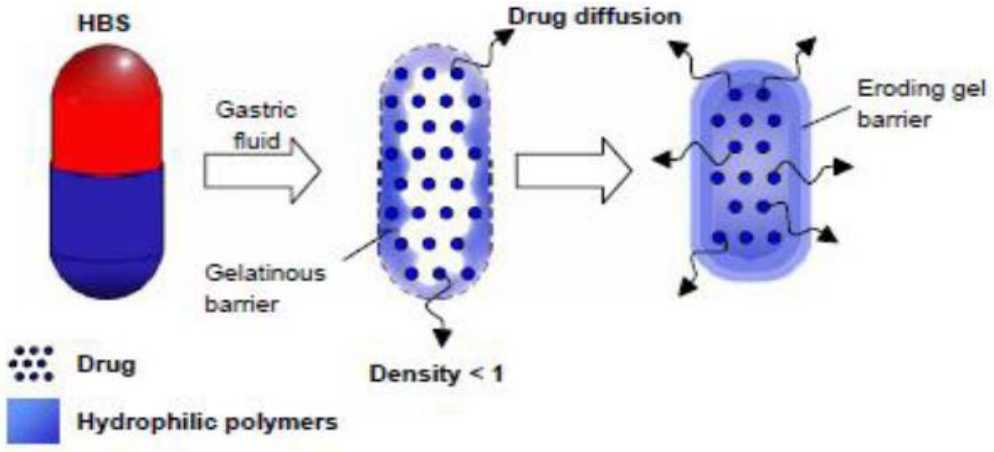


Fig. 3: Schematic diagram of low density floating systems system

Swelling and expanding systems [22]

- After administration of these systems, they swell to an extent which prevents their exit from stomach through pyloric sphincter. As a result of this, the dosage form is retained in stomach for longer period of time. These systems are sometimes called as plug type systems as they usually lodged at the pyloric sphincter. **Sustained and controlled drug release may be achieved by selecting a polymer with the proper molecular weight and swelling properties**

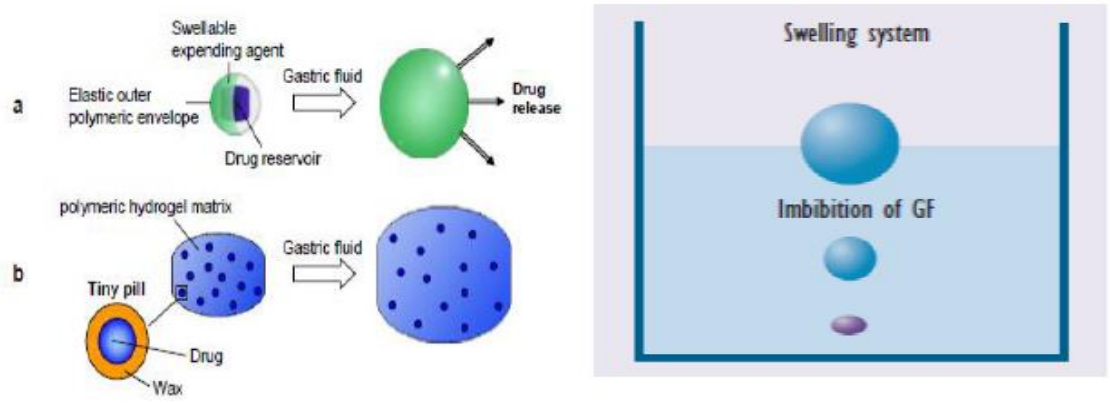
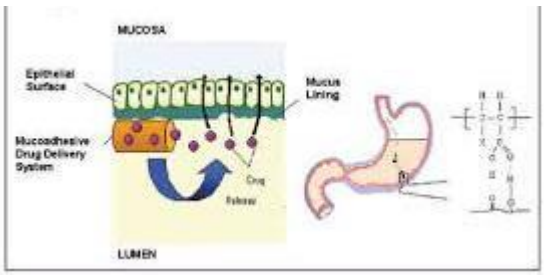


Fig. 4: Schematic diagram of Swelling and expanding systems

Bioadhesive systems [23]

- These systems are used to localize the dosage form within the lumen as well as in cavity of body, to enhance the absorption of drug in site specific manner. Various bioadhesive polymers such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), hydroxyethyl cellulose (HEC), polyacrylate, polycarbophil, polystyrene are used to achieve the effective bioadhesion. These polymers tend to form electrostatic and hydrogen bonds at the mucus membrane and polymer boundary. Rapid hydration usually occurs when it come in contact with the mucous lining of epithelial surface appears to favour adhesion of dosage form.

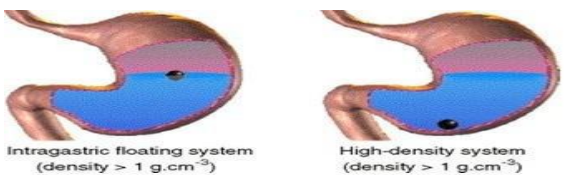


Modified shape systems for gastric retention

- These are non-disintegrating particle having geometric shapes, which usually extruded from polyethylene blends or moulded from plastic elastomer. These systems then enhance the gastric residence time (GRT) depending on the shape, size and flexural modulus of drug delivery system.

High density formulations

- High density formulations have a density greater than that of contents of the stomach. This can be achieved by coating the drug with a heavy inert material such as zinc oxide, barium sulphate, titanium dioxide and iron powder. This type of the dosage forms usually settle in the antrum part of the stomach due to its curvature.

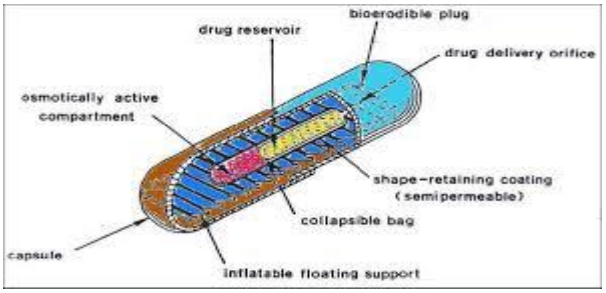


Approaches for delayed release gastric emptying

- This approach usually includes feeding of fatty acid salts or indigestible polymers that change the motility rate of the stomach and decrease the gastric emptying rate.

Microballoon / Hollow microspheres and microparticles

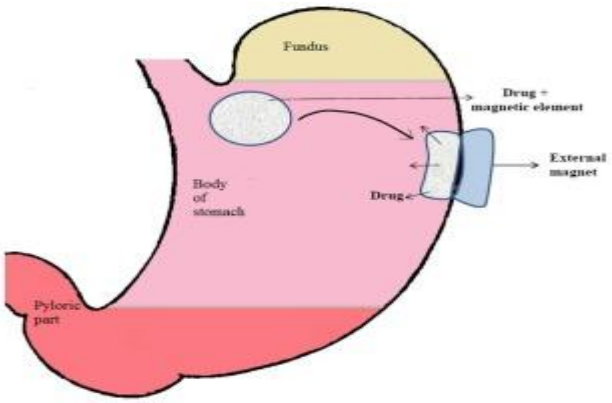
- Hollow microspheres/microballoons are loaded with drugs to enhance the gastric retention time (GRT) of the dosage form those usually prepared by solvent diffusion evaporation or simple solvent evaporation methods. Commonly polymers such as acetate, polycarbonate, cellulose, Eudragit S, agar, calcium alginate, low methoxylated pectin etc are used to develop these systems.



Magnetic systems [24]

- This system is based on a simple principle that the dosage form containing a small internal magnet attracts another magnet which is placed on the abdomen over the position of the stomach and hence increase the gastric residence time of the dosage form.

On the other hand, Rouge and co-workers found that multiple unit dosage forms decreases the inter-subject variability in absorption, which minimizes the probabilities of dose dumping by uniform distribution within the gastric fluids and provides prolong duration of action.



B. Effervescent systems (tablets, capsules and granules) [25]

- These are matrix type systems prepared by using swellable polymers such as polysaccharides, hydroxypropyl methylcellulose or chitosan and various effervescent substances like calcium carbonate, sodium bicarbonate, tartaric acid or citric acid. This dosage form is developed in such a way that, when it comes in contact with gastric fluids in the stomach, CO_2 is liberated and it is trapped in the swollen hydrocolloids. This provides the dosage form to buoyant in gastric fluid. The liberated

carbon dioxide intimately gets mixed within the tablet matrix in case of single layered tablet. The multi-particulate floating reservoir types of drug delivery systems may have double or triple layers. The triple layered tablets are usually prepared, which contains swellable gas generating layer and sustainable approach is utilized in the development of pulsatile or floating drug delivery system based on the effervescent coated core.

- The bilayer dosage form had two layers, first layer consisted of drug, HPMC or cellulose acetate as a sustained release core and second layer consisted of PEG 4000 (4% based on the weight of the second layer), effervescent agents, microcrystalline cellulose or lactose are used as fillers. Sodium bicarbonate and citric acid is usually used as an effervescent agent in a ratio of 1:0.76 in the concentration of 30-50 % of the w/w of the core. The CO_2 is generated by coming in contact with the medium and gets entrapped in the polymeric matrix, which provides buoyancy to the dosage form.

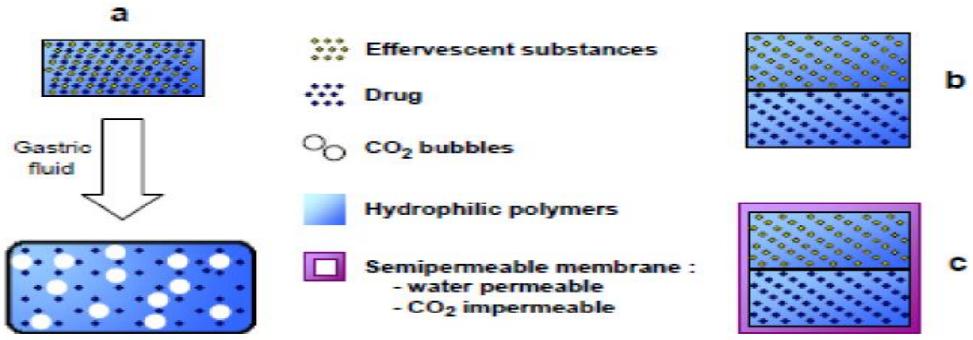


Fig. 5: Schematic representation of gas-generating systems as monolayer drug delivery system

Raft forming system

- Raft forming systems have been mainly used for the delivery of antacids and delivery of drugs for gastrointestinal disorders and infections. The mechanism involved in raft formation dosage form includes the formation of viscous cohesive gel when come in contact with gastric fluids. There each portion of the liquid swells that forms a continuous layer called a raft. This raft floats on gastric fluids due to its low bulk density created by the formation of CO_2 gas. Usually, the system contains a gel forming agent as well as an alkaline bicarbonates or carbonates, which is responsible for the formation of CO_2 to make the system less dense and float on the gastric fluids. The system mainly contains a gel forming agent (e.g. alginic acid), sodium bicarbonate and acid neutralizer, which usually forms a foaming sodium alginate gel (raft) by coming in contact with gastric fluids. Thus the raft formed floats on the gastric fluid which prevents the reflux of the gastric fluids (i.e. gastric acid) into the oesophagus by acting as a barrier between the oesophagus and stomach.

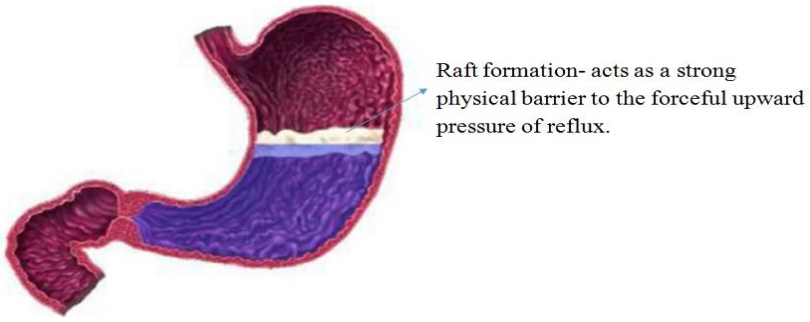


Fig. 6: Raft forming drug delivery system

Programmable drug delivery systems [26, 27]

- Programmable drug delivery system is developed by Farouk Sakrhas for oral administration. It is a new prototype model device (3 cm long and 0.9 cm internal diameter) which usually comprise of a cylindrical shell in the form of oral capsule. Drug is placed in a cylindrical disc made up of slowly eroding polymer and compressed to zero porosity, compressible acid resistant spring, a flexible rubber disc, and a special acid impervious non-permeable rubber ballooning system containing bicarbonate granules. The device contains drug in a slowly eroding matrix in the form of non-digestible oral capsule. It is designed to use an automatically operated geometric obstruction, which keeps the device floating in the stomach and prevents the system from passing to remaining part of GIT. The different grades of HPMC are used to develop the eroding matrix.

Table 1: Polymers and excipients along with their examples that are used in the formulation of gastroretentive dosage forms

S.NO	Structural component	Examples
1	Polymers (Hydrocolloids)	Acacia, Methyl Cellulose, Hydroxyl Propyl Cellulose (HPC), Chitosan, Agar, Gellan gum (Gelrite®)casein, Hydroxyl propyl methyl cellulose(HPMC K4M, K15M, K100M) Bentonite, Sodium carboxy methyl cellulose (CMC), Veegum, Pectin,
2	Inert fatty constitution	Fatty acid long chain alcohol, bees wax ,Gelucires 39/01 and 43/01 fatty acid .
3	Effervescent materials	Tartaric acid-Sodium biocarbonate, Di- SGC (di –sodium glycine carbonate)-Citric acid, Tartaric acid-CG(citroglycine).
4	Fillers	Lactose, Mannitol
5	Retardant of release rate	Talc Di – calcium phosphate, magnesium phosphate, Magnesium stearate
6	Buoyancy enhancing agents	Ethyl cellulose.
7	Material with low density	Polypropelene foam powder (accurel MP 1000

Gastroretentive Tablet manufacturing material & methods:

Methodology Solubility Studies Exactly weighed amounts of drug is repeatedly added to solubility bottles each containing fixed quantity of 0.1M HCl, 6.8 phosphate buffer, and distilled water until the solvent gets saturated. The suspension is agitated at 37 ± 0.5°C for 24 hrs. Aliquots are withdrawn from the suspensions and passed through Millipore filter. The concentration of the drug in each solvent filtrate is

analyzed using Visible spectrophotometer (Perkin Elmer, Massachusetts, USA) at 380 nm The solubility study for each solvent is carried out in triplicate. [29]

Formulation of floating matrix tablet: Sustained release floating matrix tablets are prepared by direct compression method. All the ingredients are dispensed accurately, sifted through 40# mesh screen. Drug is geometrically mixed with diluents followed by addition of the polymer and gas generating agent. Dry mixing is done for 10 minutes and final sifting is carried through 22# mesh screen. Pre-lubrication and lubrication is done for 5 and 2 minutes, respectively. Pre-formulation parameters are evaluated for the blends and then compression is carried out by manual single punching machine (Model: KI-150, Khera Instruments Ltd, New Delhi, India) using 9 mm deep concave punches. The formulated tablets are stored in air tight container at room temperature for further evaluation of the tablet parameters. In all the formulations, polymers concentration is varied from 10 to 50% of the total weight. The composition of various formulations.

Evaluation of Granules Angle of repose: Fixed funnel method is used to measure the flow properties where the granules are poured from funnel walls to form conical heap in which its lower tip is 2-5 cm away from the hard surface. Static angle of repose is measured by using the formula, [28]

Bulk density (BD) and Tapped density (TD): Blend is sieved to ensure free from agglomeration free and is introduced into a calibrated measuring cylinder. The initial volume is observed and then the cylinder is allowed to tap onto a hard surface from 2.5 cm height at 2″ intervals. The tapping is continued to get saturated volume. From the above values, both poured bulk density and tapped density are determined. [29]

Hausner's ratio and compressibility index: Hausner's found that the ratio of tapped volume and poured volume is related to its inter particle friction and can be used as a direct tool for flow property evaluation. Compressibility index is determined by using the formula,

$$Carr's\ index\ (\%) = \frac{TD - BD}{TD} \times 100$$

$$Hausner's\ ratio\ = \frac{TD}{BD}$$

Evaluation of drug Floating Tablets: Thickness and weight variation test randomly selected 6 tablets are subjected for thickness measurements by using Vernier caliper. Average values are calculated and tabulated. To study the weight variation, 10 tablets of each formulation are weighed individually using an electronic balance (Shimadzu, Japan) and the test is performed according to the official method (Indian Pharmacopoeia). [30]

Drug content: To evaluate the drug content, 10 tablets of same weight are selected and crushed using mortar and pestle. Powder equivalent to the average weight of the tablet is weighed and dissolved in 0.1 M HCl and diluted suitably. The concentration of drug in the samples is detected using ultra violet (UV)-visible spectrophotometer. [30]

Hardness and Friability: Six tablets from each formulation are subjected for crushing strength and friability by using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche friabilator (Veego, Mumbai, India), respectively. [29]

***In vitro* buoyancy study:** The *in vitro* buoyancy is determined by observing the floating lag time and the total floating duration (floating capacity). For determining the floating lag time, 0.1 N HCl is taken as the media and three tablets are placed in it. The time required for the matrix tablet to rise from the bottom to the surface of the media for floating is determined. The time is observed visually and recorded using stop watch. [29] For observing the

total floating duration, three individual tablets from each formulation

Swelling index (*SI*): The swelling behaviour of all floating matrix tablet formulations is measured by calculating its weight gain in the dissolution medium under study. The swelling index are determined by placing the tablets in the container of dissolution apparatus maintaining dissolution medium at 37 ± 0.5ºC. After every one hour interval and upto 12 hours, tablet is removed from the dissolution basket and blotted with tissue paper to remove the excess water. The bloated tablets are weighed on the analytical balance (Shimadzu, Ax 120). The experiment is performed in triplicate for each time point and mean with standard deviations are also determined. Swelling index is calculated by using the following formula [30].

$$Swelling\ Index\ (SI) = \frac{Wf - Wi}{Wi} \times 100$$

Where W_f and W_i is called as wet and dry weight of the tablet respectively.

Fourier transform infra-red spectroscopy (FT-IR): The powdered samples of the tablets are mixed thoroughly with previously dried potassium bromide (IR grade) so as to form transparent pellets. The spectral smoothening and baseline correlation procedure are done and then the samples are scanned from 4000 to 400 cm-1 at ambient temperature (Perkin Elmer, Massachusetts, USA). [29]

In vitro dissolution studies Dissolution studies are performed using 900 ml 0.1M HCl with pH 1.2 using paddle method at 100 rotations per minute (rpm) and 37°C. Samples of 10 ml are withdrawn from each basket at periodic time intervals. Equal amount of fresh dissolution media is replaced to maintain the sink condition. [29] The amount of Lornoxicam release in each sample is determined at wavelength of 380 nm using UV-Visible spectrophotometer (Perkin Elmer, Massachusetts, USA).

Curve fitting analysis: Mathematical models such as zero-order, first-order, Higuchi and Peppas kinetics are applied to the observed release profile data to analyze the rate, mechanism, and pattern of the drug release.

***In vivo* methods of evaluation of GRDDS**

Alpha Scintigraphy: It can be used to evaluate *in vivo* buoyancy and *in vivo* release performance of different type of GRDF. In this technology a stable radioisotope like 111In is formulated within the developed system and administered in healthy human volunteers (Google et al., 2008). Major drawbacks with such a technique are associated ionization radiations, limited topographic information, low resolution, and complicated and expensive preparation of radiopharmaceuticals (Wilding et al., 2001).

Radiology: This method includes pre-clinical estimation of gastroretention. In comparison to γ-scintigraphy, radiology is a simpler and cost effective technique. However, limitations regarding exposure to X-rays decline its popularity because for optimum evaluation of buoyancy a high amount of contrasting agent (BaSo4) is generally required (Tanwar et al., 2007b). Radiographs are taken after ingestion of the dosage form, to locate the floating and non-floating (fabricated) dosage forms.

Gastroscopy: This is considered a minimally invasive procedure since it does not require an incision into one of the major body cavities. This technique involves visual inspection of GRDF in the stomach (Klaussner et al., 2003b). Basically it is a type of peroral endoscopy which comprises optic fibers and a video camera. For more detailed information, the evaluated system can be drawn out from the stomach. However, on the other hand the quality of study and

its interpretation are highly dependent on the expertise of the endoscopist. Active uncontrolled bleeding, retained blood in the stomach, and retained food or antacids may also lead to an inadequate study.

Ultrasonography: Ultrasonic waves are used to produce images of body structures. The waves travel through tissues and are reflected back where density differs. The reflected echoes are received by an electronic apparatus that measures their intensity level and the position of the tissue reflecting them. The results can be displayed as still images or as a moving picture of the inside of the body (Hendee, 1994). Most dosage forms do not have sharp acoustic mismatches across their interface with the physiological milieu. Therefore, ultrasonography is not routinely used for the evaluation of FDDS. The characterization included assessment of intra-gastric location of the hydrogels, solvent penetration into the gel, and interactions between the gastric wall and FDDS during peristalsis.

Magnetic resonance imagining (MRI): MRI is a non-invasive diagnostic technology. MRI uses a powerful magnetic field, radio frequency pulses, and a computer to produce detailed pictures of organs, soft tissues, bone, and virtually all other internal body structures. The images can then be examined on a computer monitor, transmitted electronically, and printed or copied to a CD. MRI does not use ionizing radiation (x-rays). In the last couple of years, MRI is shown to be a valuable tool in gastrointestinal research for the analysis of gastric emptying, motility, and intra-gastric distribution of macronutrients and drug models. The advantages of MRI include high soft tissue contrast, high temporal and spatial resolution, as well as a lack of ionizing irradiation. Also, harmless paramagnetic and supra-magnetic MR imaging contrast agents can be applied to specifically enhance or suppress signal of fluids and tissues of interest and thus permit better delineation and study of organs (Dorozynski et al., 2007).

Conventional drug delivery system Vs Gastroretentive drug delivery: When the drug is taken many times a day, conventional drug delivery system retains the concentration of drug in the effective therapeutic range which is necessary for the management of a disease. [20] A successful oral drug delivery system is dependent upon its absorption degree in gastrointestinal tract. So the clue of increasing drug absorption initiated the idea of gastroretentive drug delivery system. [21]

Assimilating apresent medicine into novel drug delivery system can enhance its actions regarding thepatient compliance, 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. [22]

Table 2: Comparison between conventional drug delivery system and gastroretentive drug delivery system.

S.N	Parameters	Conventional drug delivery system	Gastroretentive drug delivery system
1	Patient compliance	Poor	No risk
2	Dose dumping	Risk of dose dumping in higher	No risk
3	Drug having low absorption in small intestine	Not appropriate	Appropriate
4	Not very locally in the stomach	Not very much useful	Much useful
5	Toxicity	Greater susceptibility towards	Low susceptibility

		toxicity	
6	Drugs with poor solubility at higher pH	Not much Beneficial	Much beneficial
7	Drug that undergo degradation in colon	Not much beneficial	Much beneficial
8	Drugs that have fast GIT absorption	Not much beneficial	Much beneficial

Table 3: Drugs suitable for Gastro retention:

S.N	Properties of drug for candidate	Example
1	The drugs having local action in stomach	Misoprostol, antacids, antibiotics.
2	Poorly absorbed drugs both in stomach and in the upper small intestine	Verapamil hydrochloride, diazepam
3	Rapidly absorbed drugs through GIT	Furosemide, levodopa
4	Rapidly absorbed	Amoxicillin
5	Drugs that are unstable and degraded drugs through in the intestinal and large bowel environment are also good candidates for GRDDS.	Captopril.

Drugs unsuitable for Gastroretentive system:

I. Drugs with the very low solubility in acids e.g. Phenytoin etc.
II. Drugs those are unstable in gastric atmosphere e.g. Erythromycin, Esomeprazole, Rabeprazole and Clarithromycin etc.
III. Drugs for specific release in colon e.g. and corticosteroids 5- amino salicylic acid and, etc.

Limitations of Gastroretentive system: High level of fluids in the stomach is required for maintaining buoyancy; float efficient working of dosage form. Not feasible for drugs having solubility or stability problems in gastric fluid. Drugs such as Nifedipine, which is well absorbed. Along the entire GIT and which undergoes significant first-pass metabolism, may not be desirable candidates for gastroretentive system since the slow gastric emptying may lead to reduced systemic bioavailability. Limitation to the applicability of gastroretentive system for drugs that are irritating gastric mucosa.

CONCLUSION:

Gastroretentive system technique may be used for various potential active agents with narrow absorption window, e.g. antiviral, antifungal and antibiotic agents (penicillins, cephalosporins, sulphonamides, quinolones, aminoglycosides and tetracyclines) which are absorbed from very specific regions of GI tract and not much developed due to the lack of appropriate pharmaceutical technologies. In addition, by continual supplying the drug to it is most efficient site of absorption, the dosage form may allow more effective oral use of peptide and protein drugs such as calcitonin, erythropoetin, vasopressin, insulin, low molecular weight heparin, and LHRH. Some of the

unresolved critical issues related to the rational development of gastroretentive system include, the quantitative efficiency of floating delivery systems in the fasted and fed states and the correlation between prolonged GRT and SR/PK characteristics.

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