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Review Article

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GASTRORETENTIVE DRUG DELIVERY SYSTEM- A REVIEW

B. Venkateswara Reddy*, K. Navaneetha, P.Sandeep A. Deepthi.

Department of Pharmaceutics, St.Paul's College of Pharmacy, Turakayamjal village,

Hayath Nagar Mandal, Ranga Reddy Dist-501510, A.P.INDIA.

*Corresponding Author E-mail: **basu.pharmacist@gmail.com**

ABSTRACT

Gastric emptying is a complex process and makes the in vivo performance of the drug delivery system uncertain. In order to avoid this fickleness, efforts have been made to increase the retention time of the dosage form, one such approach is the development to gastroretentive drug delivery system. Gastroretentive drug delivery system (GRDDS) is a type of novel drug delivery system which can remain in the stomach for prolonged period of time and there by increases gastric residence time of drugs, and also improves the bioavailability of drugs. These systems are widely used for the site specific delivery of drugs for the treatment of gastrointestinal diseases and disorders. Gastroretentive drug delivery systems are divided into several approaches like floating, hydrodynamically balanced systems, bioadhesive systems, swelling systems, high density systems, expandable systems etc, which are discussed in detail in the present review.

Keywords: Bioadhesive systems, bioavailability, expandable systems, gastric residence, high density systems.

INTRODUCTION:

Oral route is the most desired, convenient and preferred method of administering the drug for its systemic effect due to its ease of administration, low cost of therapy and patient compliance. Oral route of administration has received more attention in the pharmaceutical field because of more flexibility in the designing of dosage form than the other routes of drug delivery[1]. The release of drug from the delivery system may be by diffusion, dissolution or by combination of both mechanisms in a desired and controlled manner. One main prerequisite for the oral performance of the drug delivery system is that drug should have good absorption throughout the gastrointestinal tract (GIT) [2].

This approach of oral drug delivery of drugs has several physiological difficulties such as inability to restrain and locate the controlled drug delivery system

within the desired region of the gastrointestinal tract due to variable gastric emptying and motility[3].

Gastroretentive drug delivery system (GRDDS) is a type of novel drug delivery system which can remain in the stomach for prolonged period of time and there by increases gastric residence time of drugs, and also improves the bioavailability of drugs[4, 5].

Advantages of gastro retentive drug delivery system[6]:

1. The gastroretentive systems are advantageous for the drugs that are primarily absorbed through the stomach, e.g. ferrous salts, antacids.
2. The gastro retentive systems are advantageous for the drugs that are meant for local action in the stomach. e.g. antacids.
3. When there is a vigorous intestinal movement and a short transit time such as in certain type of diarrhea, poor absorption is expected. Under such conditions it may is advantageous to retain the drug in stomach to get a relatively better response.
4. GRDDS improves patient compliance by decreasing dosing frequency.
5. Bioavailability variations because of fluctuations in plasma drug concentration are avoided and a desirable plasma drug concentration is maintained by continuous drug release.
6. Therapeutic effect of the drugs with short half-life can be enhanced.
7. Drugs which are unstable in intestinal pH can be formulated as GRDDS.
8. Enhanced absorption of drugs which solubilizes only in stomach.
9. There is no risk of dose dumping.
10. Avoidance of gastric irritation, because of sustained release effect, and uniform release of drug through the delivery system.
11. Administration of prolonged release gastro retentive dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid by which the drug would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from the dosage forms if it remains in solution form, even at the alkaline pH of the intestine.

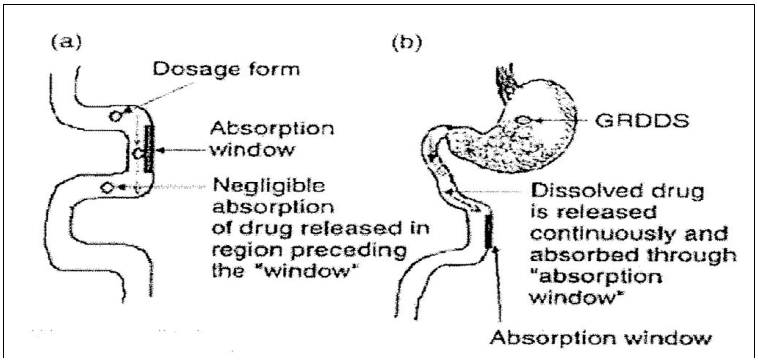

Fig.1. Drug absorption (a) Conventional dosage forms, (b) Gastroretentive drug delivery systems

Disadvantages[7]:

1. These systems require sufficiently high levels of stomach fluids, for the system to float and to work efficiently.
2. It is not suitable for drugs with stability problem in stomach.
3. Drugs which undergo extensive first pass metabolism are not suitable candidates.
4. Drugs with irritant effect also limit the applicability.
5. Drugs which undergo equal absorption throughout all the regions and sites of gastrointestinal tract are not desired candidates.
6. Drugs which are less soluble at acidic pH of the gastric fluids are not suitable for gastro retention.

Drug candidates suitable for Gastroretentive drug delivery system[8]:

a. Drugs which act primarily in the stomach. E.g. antacids.
b. Drugs that are primarily absorbed from the stomach. E.g. amoxicillin
c. Drugs that are poorly soluble at alkaline pH. E.g. verapamil, diazepam, etc.
d. Drugs with a narrow window of absorption. E.g. levodopa, cyclosporine, etc.
e. Drugs which are rapidly absorbed from the GIT. E.g. tetracycline
f. Drugs that degrade in the colon. E.g. ranitidine, metformin, etc.
g. Drugs that disturb normal colonic microbes. E.g. Antibiotics against Helicobacter pylori.

Drug candidates unsuitable for gastroretentive drug delivery system[9]:

a. Drugs that have very limited acid solubility e.g. phenytoin etc.
b. Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
c. Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc.

Factors controlling gastric retention of drugs[10]:

The factors which are to be considered during the development of gastro retentive drugs are

Physiological factors:

a. Size of dosage form: Dosage forms having greater diameter than the diameter of pyloric sphincter remain in the gastric region as these cannot move away along with the gastric contents into intestine nor they can be affected by the gastric emptying.
b. Shape of dosage form: Round or spherical or ring shaped dosage forms are considered to be better in comparison to other shapes.
c. Density: The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach. Dosage form with density lesser than 1.0 gm/ cm^3 is required to exhibit floating property.

Biological factors:

a. Age: Gastric retention time is longer in geriatric patients, while it is lower in neonates and children when compared to normal adults.
b. Gender: Gastric retention time in male (3-4 hours) is less than the female (4-6 hours).
c. Fed or unfed state: Gastric retention time is less during fasting conditions as the gastric motility increases during fasting conditions.
d. Feed frequency: Higher the frequency of taking food, longer will be the gastro retention time.
e. Nature of meal: Higher the amount of fatty acids and other indigestible polymers lesser the gastric retention time due to alteration in gastric motility.
f. Concomitant drug administration: Administration of certain drugs along with gastric motility enhancers or depressants, greatly affect gastric retention time and hence absorption of stomach specific absorbing drugs.
g. Disease state: Gastric disease conditions like diabetes, Crohn's disease etc alters the Gastric retention time.

Approaches for gastro retention[11]:

To improve the retention of an oral dosage form in the stomach various approaches have been developed, it includes floating systems and non floating systems. Floating systems includes effervescent systems and non effervescent systems, these systems have the bulk density lower than the gastric fluid and remain floating and releases the drug slowly in a desired rate. Non floating systems include bioadhesive systems, swelling systems, high density systems, expandable systems, raft forming systems, magnetic systems which utilize different mechanisms to prevent the exit of drugs through pyloric sphincters.

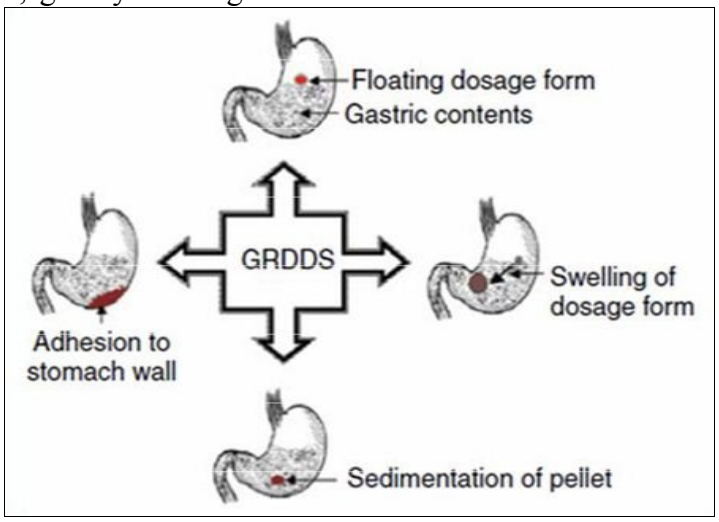

Fig.2. Approaches for gastro retention

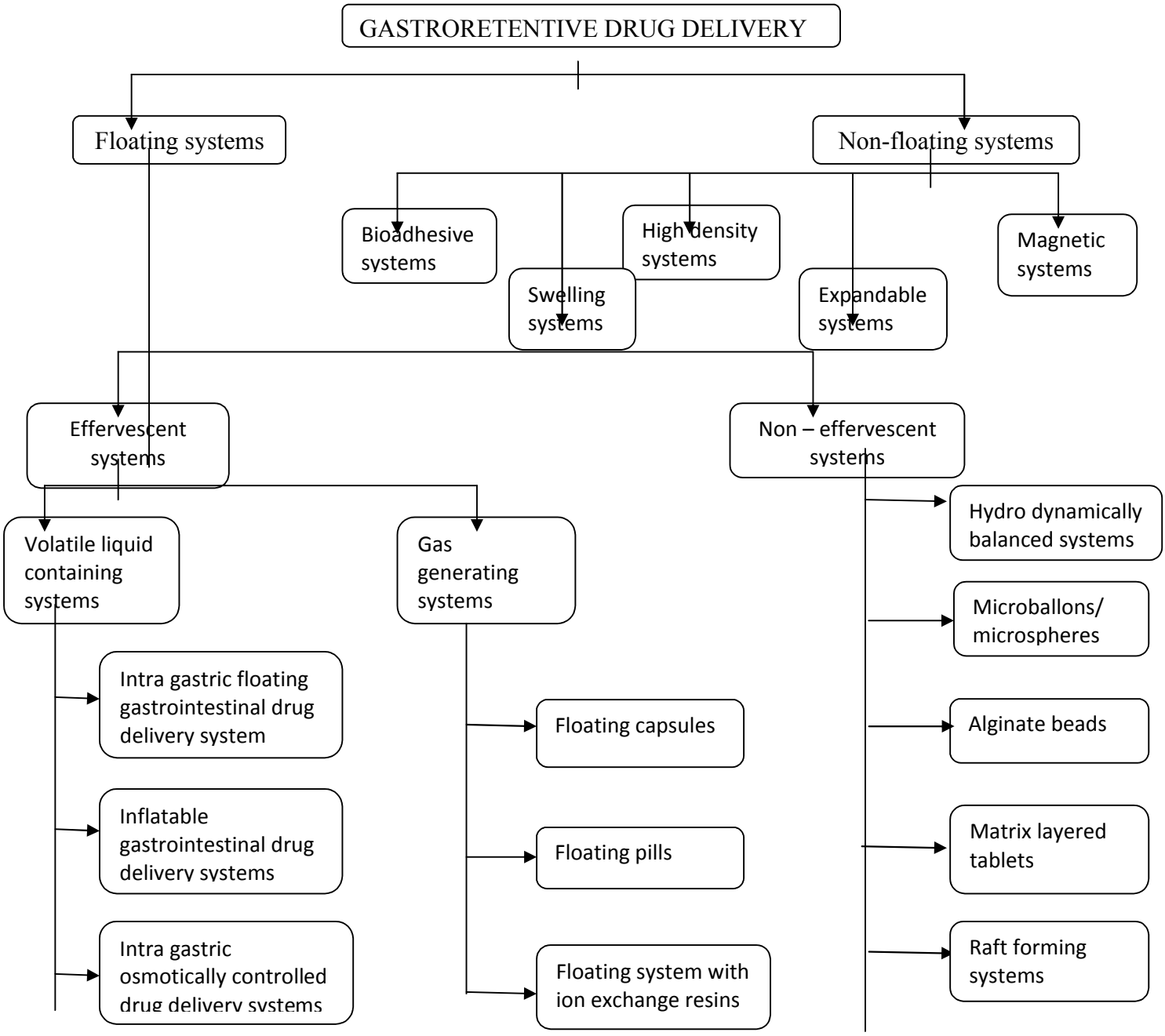

Fig. 3: Flowchart showing different approaches for gastroretentive drug delivery systems

Floating drug delivery systems (FDDS) [12]:

These are the low density systems having the bulk density less than the gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. When the drug delivery system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. This results in increased gastro retention time and a

better control of fluctuations in the plasma drug concentration.

Based on the buoyancy mechanism, floating systems are classified as follows

A. Effervescent systems

B.Non effervescent systems

A. Effervescent systems[5]:

These dosage forms are developed in such a way that, when they come in contact with gastric juices in the stomach , carbon dioxide gas is released due the reaction between sodium bicarbonate, citric acid and tartaric acid and is trapped in the swollen hydrocolloids. This provides buoyancy to the dosage form there by making it to float on the gastric fluids. These systems may also contain liquids which gasify and evaporates at body temperature by which the specific gravity decreases and causes the dosage form to float.

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These effervescent systems have been further classified into different types:

1) **Volatile liquid containing systems[13]:**

These are further classified as

a) Intragastric floating gastrointestinal drug delivery systems: These systems are made to float in the stomach because of the floating chamber, which may be filled with air or vaccum or harmless gas, and the drug reservoir is encapsulated inside a micro porous compartment. This micro porous compartment has pores on the top and bottom surfaces, where as the peripheral walls of the reservoir compartment were completely sealed to prevent any physical contact of the undissolved drug with the walls of the stomach

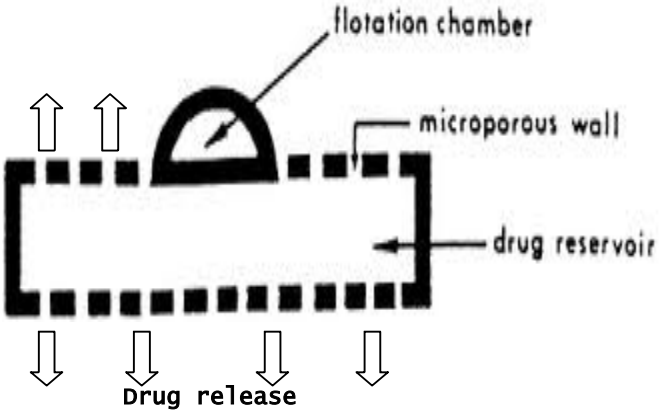

Fig.4. Intragastric floating gastrointestinal drug delivery system

b) Inflatable gastrointestinal drug delivery system: These systems consist of inflatable chamber with liquid ether that gasifies at body temperature making the chamber to inflate in the stomach. This inflatable chamber contains a drug reservoir which is encapsulated in a gelatin capsule. After oral administration, the capsule dissolves and releases the drug reservoir together with the inflatable.

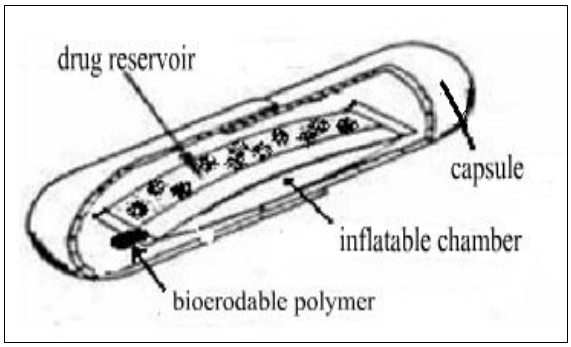

Fig.5. Inflatable gastrointestinal delivery system

c) Intragastric osmotically controlled drug delivery system:

It consists of osmotic pressure controlled drug delivery device and an inflatable support in a biodegradable capsule. On reaching the stomach, inflatable capsule disintegrates and releases the osmotically controlled drug delivery. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. Osmotic pressure controlled drug delivery device consists of two components i.e. drug reservoir compartment and osmotically active compartment. The drug reservoir compartment is enclosed in a pressure responsive collapsible bag, which is impermeable to vapour and liquid and it contains a delivery orifice. The osmotically active compartment consists of a semi permeable membrane which encloses osmotically active salt. This device on reaching the stomach absorbs water from the gastro intestinal fluids through the semi permeable membrane into the osmotically active compartment and dissolves the osmotically active salt and creates the osmotic pressure. The pressure developed acts on the collapsible bag which forces the drug reservoir compartment to activate the release of drug in the solution form through the delivery orifice. After the predetermined period of time the biodegradable plug in the floating support erodes and deflates the support, which is then emptied from the stomach.

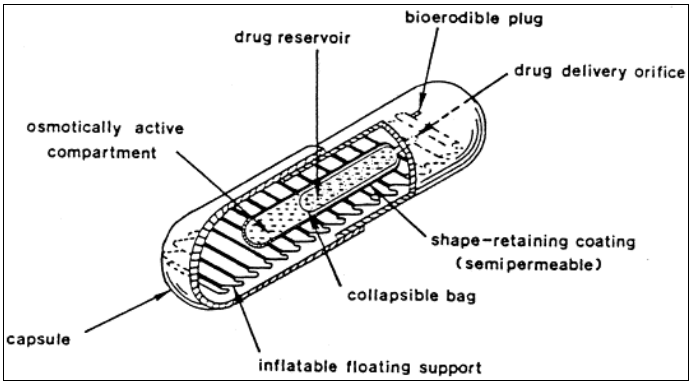

Fig.6. Intragastric osmotically controlled drug delivery system

2. **Gas generating systems[14]:** In these systems floatability is achieved by generation of gas bubbles. Carbon dioxide is generated in situ by incorporation of carbonates or bicarbonates, which react with acid, either the natural gastric acid or co-formulated as citric or tartaric acids. The gas generated makes the systems to float on the gastric fluids and releases the drug at a predetermined rate. These are of different types

a. Floating capsules: Floating capsules are prepared by filling a mixture of sodium alginate and sodium bicarbonate, these float due to the generation of carbon dioxide which gets trapped in the hydrating gel network on exposure to an acidic environment.

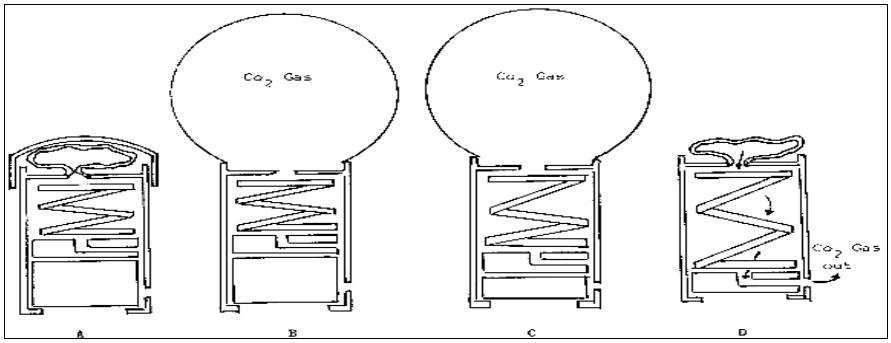

Fig.7. Diagrammatic sketch of the device representing its operation mechanism.(A,B,C,D.) (A) Intact device; (B) device at the beginning of drug release; (C) device with half drug-polymer compact eroded; and (D) device after complete drug–polymer erosion and evacuation of entrapped carbon dioxide (inflated balloon).

b.Floating pills:

These systems consist of two layers, inner effervescent layer containing sodium bicarbonate and tartaric acid and the outer swellable polymeric membrane. The inner layer is further divided into two sub layers to avoid physical contact between sodium bicarbonate and tartaric acid. When this pill is immersed in buffer solution at 37 °C, it settles down at the bottom and buffer solution enters into the effervescent layer through the outer swellable membrane. Swollen pills or balloons are formed due the generation of carbon dioxide as a result of reaction between sodium bicarbonates and tartaric acid. The carbon dioxide generated is entrapped within the delivery system making the device to float. These systems were found to float completely within 10 minutes and have good floating ability independent of pH, viscosity of the medium and the drug is released in a controlled manner.

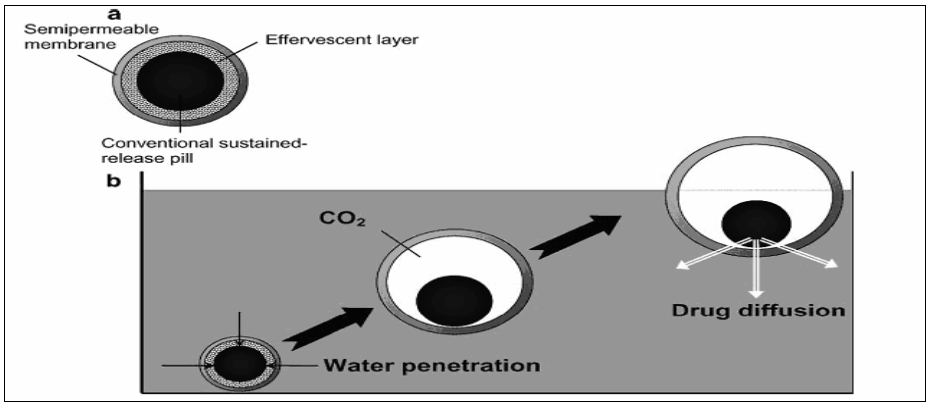

Fig.8. Floating pills a) The penetration of water into effervescent layer leads to a CO2 generation and makes the system to float (b) Mechanism of floatation

C. Floating systems with ion exchange resins:

These systems are formulated by using ion exchange resin that is loaded with bicarbonate by mixing the beads with sodium bicarbonate solution .These loaded beads were then surrounded by a semi permeable membrane to avoid the sudden loss of carbon dioxide. Upon coming in contact with gastric contents there is an exchange of chloride and bicarbonate ions resulting in generation of carbon dioxide thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads, which releases the drug at a predetermined.

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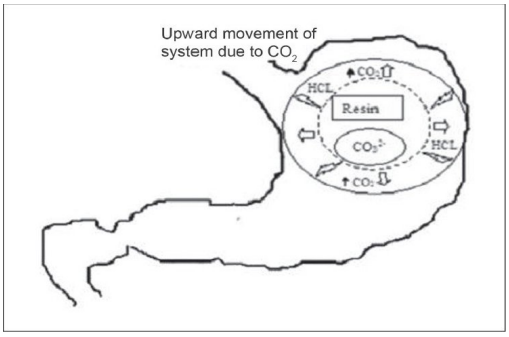

Fig.9. Floating systems with ion exchange resins

B .Non effervescent systems[15]:

Non effervescent drug delivery systems are those which upon swallowing swells via imbibitions of gastric fluids to an extent that it prevents their exit from the stomach. These systems may also be referred to as 'plug-type systems' since they have the tendency to remain lodged near the pyloric sphincter. Different types of non effervescent systems are

a. **Hydrodynamically balanced systems (HBS):** HBS are also called as 'colloidal barrier systems' these systems contains drug along with the gel forming hydrocolloids. When the

capsules containing the drug-hydrocolloid mixture comes in contact with the gastric fluids, the capsule shell dissolves and the mixture swells to form a gelatinous barrier, which imparts buoyancy in gastric fluids for a prolonged period of time due to the continuous erosion of the surface. This allows water penetration in to the inner layers maintaining surface hydration and buoyancy to the dosage form. This gel barrier controls the rate of fluid penetration into the device and consequent release of drug from the system.

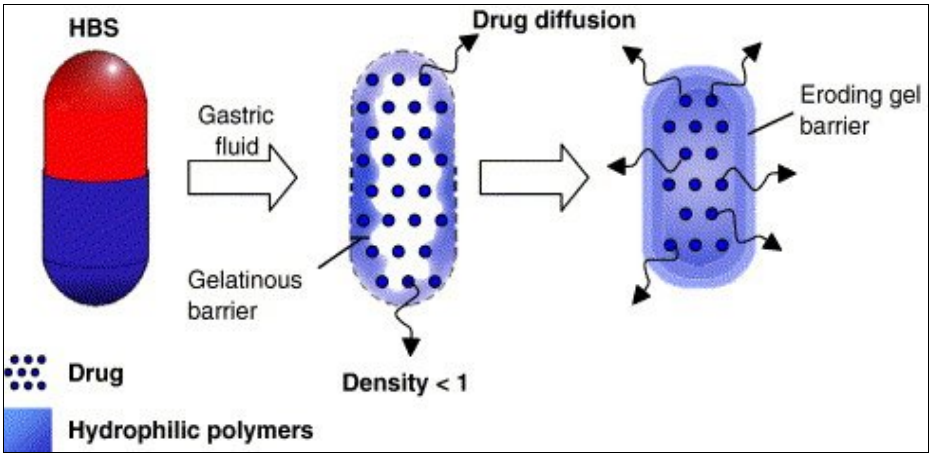

Fig.10. Hydrodynamically balanced systems

b. **Micro balloons / hollow microspheres**[16]: Micro balloons/ hollow microspheres are the low density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. These systems contain outer polymer shell loaded with drug. When they come in contact with gastric fluid the gel formers, and polymers hydrate to form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microspheres. These are considered as one of the most promising buoyant systems as they possess the unique advantage of multiple unit system as well as better floating properties because of central hollow space inside the microspheres.

c. **Alginate beads:** These are the freeze-dried calcium alginate beads of approximately 2.5 mm diameter prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which helps in floating of the system on the gastric contents. Due to the porous nature these can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, and these floating

beads shows a prolonged residence time of more than 5.5 hours.

d. **Matrix layered tablets[17]:** These are the dosage forms which contain gel forming hydrocolloids which make the delivery system to float on the gastric contents. These may be single layered, bi layered and tri layered.

i. Single layered matrix tablets are obtained by intimate mixing of drug with gel forming hydrocolloids which swells in contact with gastric fluids and maintains bulk density less than gastric fluids.

ii. Bi layered tablets contain one immediate release layer and one sustained release layer. Immediate release layer releases the initial dose of drug and the sustain release layer absorbs the gastric fluids and produces the bulk density of less than that of GI fluids and remain in stomach for an extended period of time.

iii. Tri layered tablets consists of immediate release layer, sustained release layer and the gas generating layer, which helps the system to float.

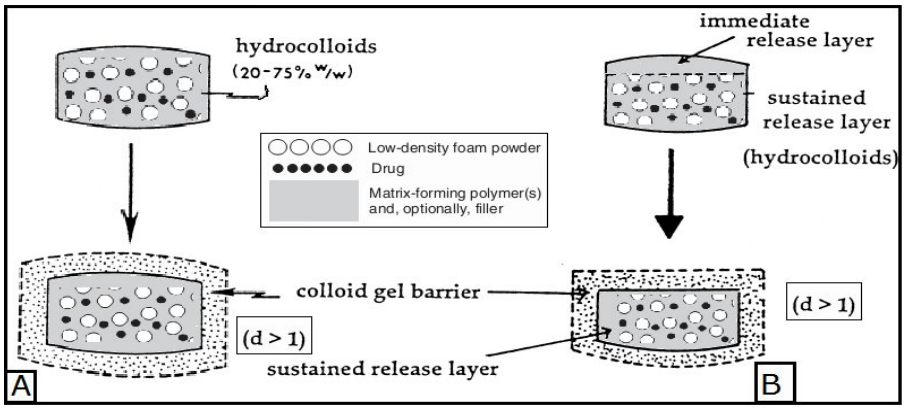

Fig.11. A) Single layer floating tablet; B) Bilayer floating tablet

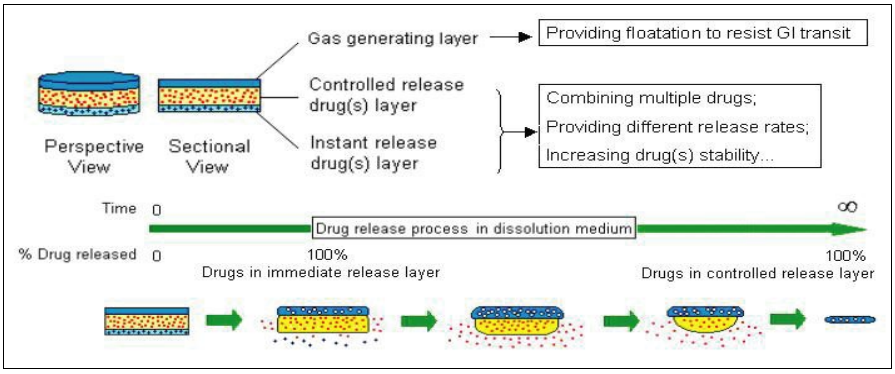

Fig.12. Tri layer floating tablet

e. **Raft forming systems[3]:** These systems contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of carbon dioxide to make the system less dense and float on the gastric fluid. The mechanism involved in the raft formation includes the formation of viscous cohesive gel on contact with gastric fluids, where in each portion of the liquid swells forming a continuous layer called as raft. This raft floats on gastric fluids and prevent the reflux of the gastric contents into esophagus by acting as a barrier between stomach and esophagus, thus these systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders.

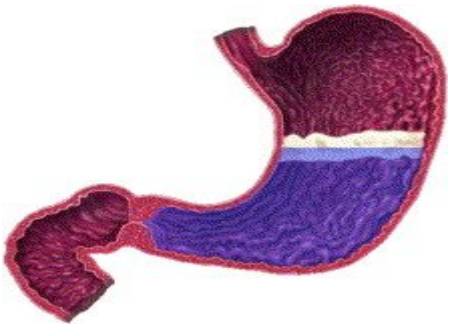

Fig.13. Barrier formed by the raft forming system

Non Floating drug delivery systems[18]:

These are the drug delivery systems which do not float but remain in the stomach for prolonged period of time. Different mechanism have been used to retain the device in the stomach which includes

A. **Bioadhesive systems:** The term bioadhesion is defined as adhesion of the delivery system to biological surface i.e. mucus and/or mucosal surface. Bioadhesive systems adhere to the mucosa of the stomach and remain in intimate contact with the membrane for longer period of time and hence retains in the stomach for its prolonged release. Bioadhesive polymers are used to formulate these systems.

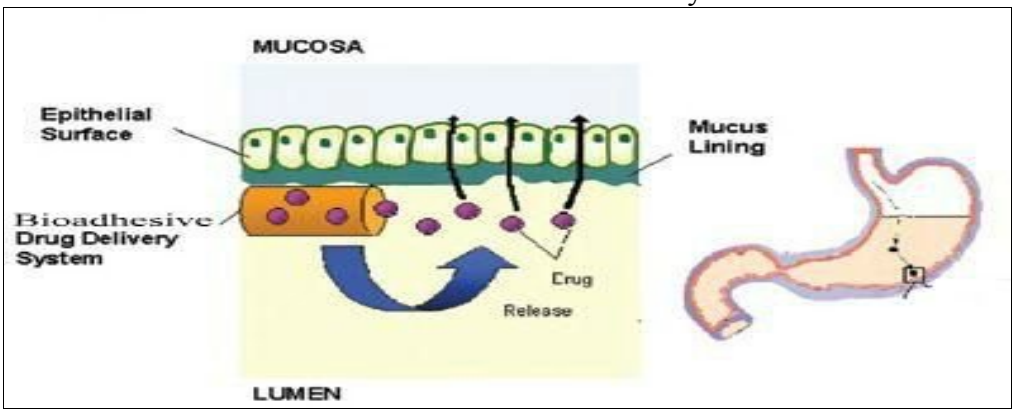

Fig.14. Bioadhesive drug delivery system

B. **Swelling system:** Gastro retentivity of the dosage form can be enhanced by increasing its size above the diameter of the pylorus. Thus, these delivery system are formulated with swellable polymers which upon entering the stomach causes these polymers to swells to an extent the device cannot pass through the pyloric sphincter leading to the retention of the delivery device in stomach.

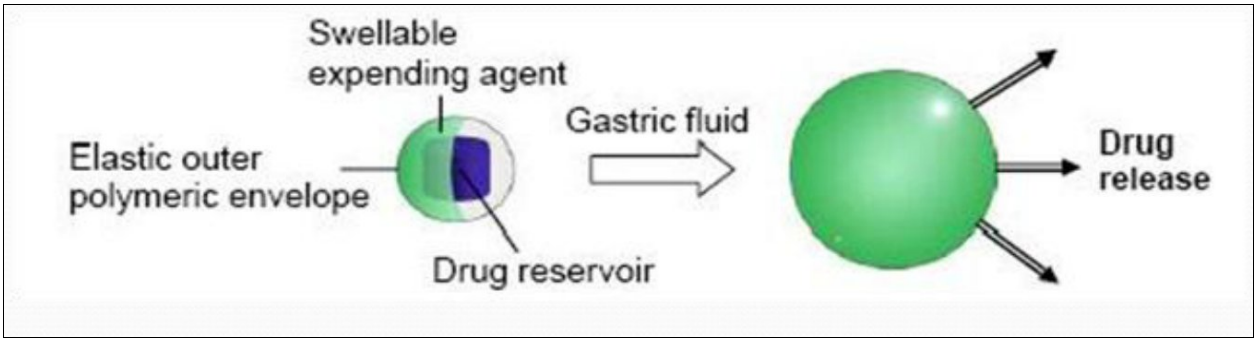

Fig.15. Swelling system

C. **High density systems:** These are the systems which have the density greater than the density of the gastric fluids as a result these systems sinks to the bottom of the stomach, thus retains in the stomach for prolonged period of time. These are usually formulated by coating the drug on heavy inert materials like zinc oxide, titanium dioxide, iron powder etc.

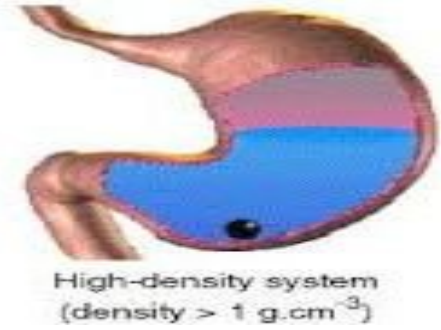

Fig.16. high density system

D. **Expandable / unfolded systems[19, 20]:** In these systems the size of the delivery system is increased beyond the diameter of pylorus there by the gastro retentivity of the dosage form is achieved. Thus expandable or unfolded drug delivery systems were developed. These dosage forms are usually small enough to be swallowed. In the stomach after coming in contact with the gastric fluids, they get expanded to a larger size so that gastric retention is achieved. In these systems compressed systems are placed in the carriers such as capsules and then administered, upon contact with gastric fluid, these systems get unfolded into the forms which can retain in the stomach for longer time.

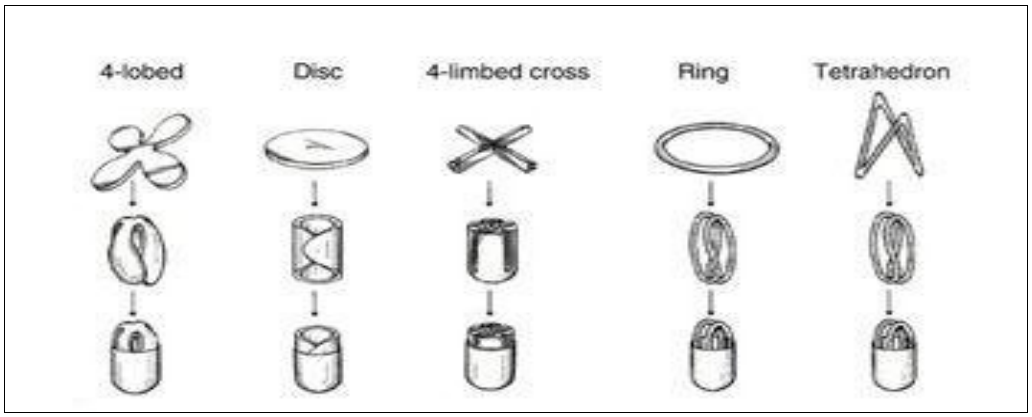

Fig.17. various types of unfolded drug delivery systems

E. **Magnetic systems:** These are designed in such a way that the dosage form contains a small internal magnet. After the administration of the dosage for, a small magnet is placed on the abdomen over the position of the stomach. By this technique the dosage form with an internal magnet is retained in the stomach region until the external magnet remains.

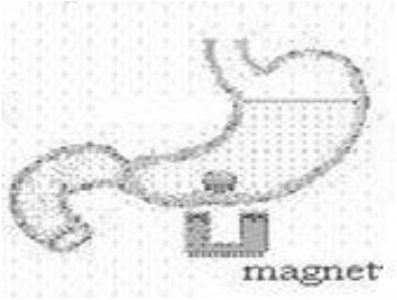

Fig.18. Magnetic systems

CONCLUSION:

Stomach is the major site for absorption of most of the drugs, but due to variation in the gastric emptying rate, these drugs passes through the stomach without being absorbed and resulted in varied absorption pattern. Due to the advances in the pharmaceutical technology various delivery systems have been developed which retains the delivery system within the stomach up to the predetermined period of time, thereby enhancing the absorption of drugs. Gastro retentive drug delivery system has emerged as an efficient tool in enhancing the bioavailability of drugs and to optimize the delivery of drugs having narrow absorption window and low solubility. Delayed gastric emptying rates and buoyancy principles, appear to be the very effective approach to the modulation of controlled oral drug delivery. Since the interest in this area has dramatically increased in the past few years it is likely that it leads to the development of successful dosage forms.

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