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A REVIEW ON GASTRORETENTIVE DRUG DELIVERY SYSTEMS

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ABSTRACT

The most convenient method of drug delivery System is oral route which is due to patient's compliance, it's reliability, ease of administration and flexibility of formulation. Gastro retentive drug delivery system has lot of advantages and applications which include significance of prolong gastric residence time of drug and improve bioavailability, reduce drug wastage, enhance solubility of those drugs specifically that are poorly soluble in high ph environment. The another important physiology is that gastro retention facilitate local drug delivery to the stomach & proximal small intestine. This technology has novel approach for those drugs which have narrow absorption window in Gastric intestinal tract. Gastro retentive drug delivery system is designs in such a way that it must retain in stomach for prolonged time & release active drug and hence, thereby provide sustainable and long time input of drug to the upper part of Gastric intestinal tract. Enormous amount of attention has been generated towards this novel technology since, from last few decades owing to their potential usefulness to improve solubility & bioavailability thereby targeting site specific release. Ultimately, enhancing their therapeutic outcome. This technique has a innovative approach for those drugs having narrow absorption window in gastric intestinal tract. Owing to it's reliability, we can consider the significant applicability of gastro-retentive drug delivery in future days.

Keywords: Gastro-retentive drug delivery, Solubility, Gastric residence, Bioavailability.

INTRODUCTION

Development of oral controlled release dosage form quiet few decades ago due to it's considerable merits which include ease of administration patient compliance and it's

flexibility in formulation. Simultaneously, this methodology has several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within desired region of gastric intestinal tract due to variable gastric motility and it's emptying time. The average gastric emptying time is 2-3 hour through stomach and the upper part of intestine which can be resulting in incomplete drug release from the drug delivery system leading to reduced efficacy of administered dose.[1] Therefore, control of placement of drug delivery in a specific region of gastric intestinal tract offers advantage for a variety of important drugs characterized by narrow absorption window & stability complication in gastro intestinal tract.[2]

The dosage form of gastro-retentive drug delivery system may remain in gastric environment for several hour and hence significantly prolong the gastric residence time of drug. Prolong gastric retention results in enhancement of bioavailability, reduction in drug wastage and improvement of poorly soluble drugs. Thus this innovative approach is suitable for local drug delivery to the stomach and proximal small intestine. It facilitates the novel products with suitable therapeutic activity and the numerous benefits for the patient.[3]

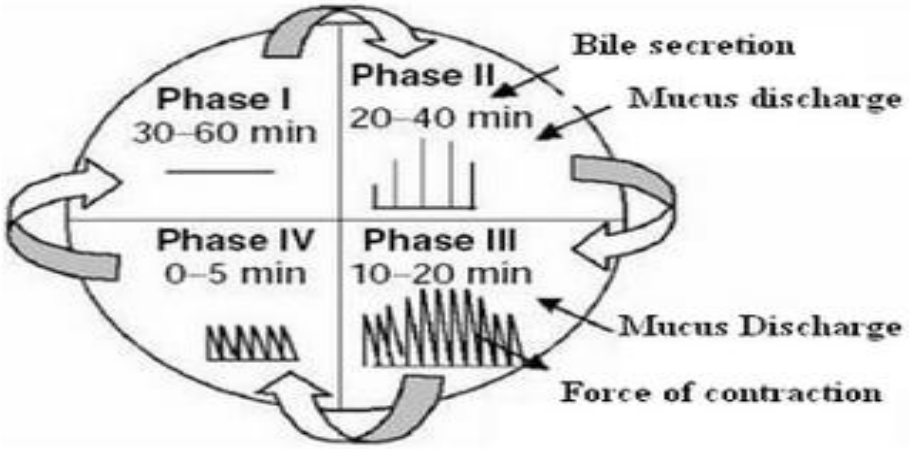

Figure 1: Schematic representation of inter-digestive motility

Need of study[4-9]

1. Low density dosage form causes buoyancy in gastric fluid.

2.Dosage form with high density which is retained at the bottom of stomach.

3.Bioadhesion to stomach mucous.

4.Expansion by swelling to a large size which restricts emptying to the dosage form through the pyrolic sphincter.

5.Concomitant administrations of drugs causes slow motility of gastric intestinal tract.

Physiology of Stomach[10-11]

The Migrating Myloelectric cycle is divided into four phases which described by Wilson and Washington as follows:

1. Phase I: Also known as basal phase lasts from 40 to 60 minutes with rare contractions.

2. Phase II: Also known as preburst phase lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

3.Phase III: Also known as burst phase lasts for 4 to 6 minutes. It includes intense and regular contractions for short period.

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

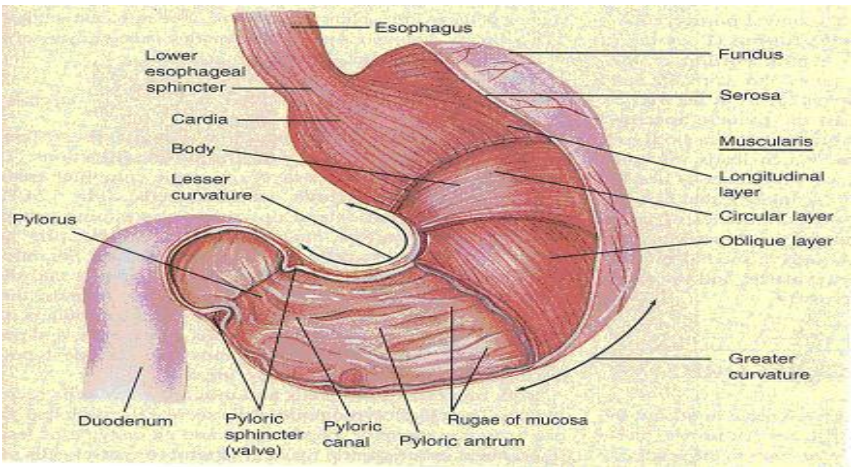

Figure 2: Diagram of human stomach

Advantages[12-13]

- Used in the stomach for local action.
- To treat peptic ulcer.
- Employed for the drug delivery with narrow absorption window in small intestine.
- Dosing frequency reduced.
- Bioavailability of the drug improved
- Applied for those drugs which are unstable in intestinal fluids.
- Maintain the systemic drug concentration within the therapeutic window.
- Site specific drug delivery is possible.

Disadvantages[13]

- It needs high levels of stomach fluids, for the system to float.
- Stability /Solubility problem drugs are not suitable.

- Those drugs which undergo extensive first pass metabolism are not suitable candidates.
- Irritant effect drugs restricts the applicability.

Factors affecting gastric retention[14-16]

1.pH of the stomach

The particle size must be in the range of 1 to 2 mm to pass through the pyloric valve into the small intestine. The stomach ph in fasting state is ~1.5 to 2.0 and in fed state is 2.0 to 6.0.

2.Gastric Emptying

The rate of gastric emptying depends mainly on viscosity, volume, and caloric content of meals. Determination gastric emptying time is possible with nutritive density of meals.

a. **Density:** Dosage forms which have a low density than that of gastric fluid experience floating behavior and therefore gastric retention. A density of <1.0 gm/cm3 needs to exhibit floating property.
b. **Size and shape of dosage unit:** During the digestive phase the smaller units get emptied from the stomach and the larger units during the housekeeping waves in fed conditions.
c. **Food Fed and Unfed State:** Food intake, the nature of the food, caloric content, and frequency of feeding has a profound impact on the gastric retention. The presence/absence of food in the stomach influences the gastric retention of the dosage form.
d. **Gender:** Mean ambulatory gastric retention in males (3.4±0.4 hours) is less as compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.
e. **Age :** People those over 70 years have a significantly longer gastric retention.
f. **Miscellaneous:** Biological factors such as age, body mass index, gender, posture, and diseased states influence gastric emptying the effect of buoyancy, posture, and nature of meals on the gastric emptying process have impact on the gastric emptying rate.

APPROACHES TO ACHIEVE GASTRIC RETENTION

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

The formulation of dosage forms with the density that should exceed density of normal stomach content (~ 1.004 gm/cm3) involve in this technique. Preparations of these formulations by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulphate, zinc oxide and titanium oxide etc [13]. The materials increase

density by up to 1.5- 2.4 gm/cm3. A density near to 2.5 gm/cm3 are essential for specific prolongation of gastric residence time. [19]

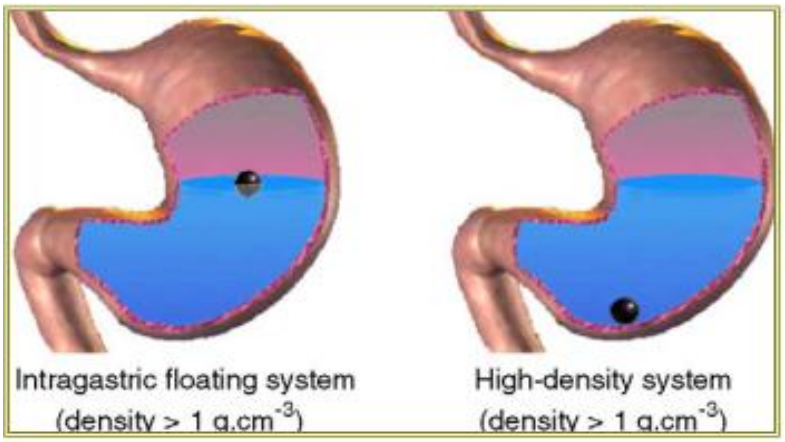

Figure 3: Schematic localization of an intragastric floating and high density system in the stomach.

2.Floating drug delivery systems

Floating drug delivery systems is one of the significant approaches to achieve gastric retention to obtain enough drug bioavailability. [20] This delivery systems is desirable for drugs with an absorption window in the upper small intestine. [21] It has a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and thus, drug is released at desired rate. Residual system is emptied from the stomach after release of drug. Therefore it result in an improved gastric retention time and a better control of the fluctuation in plasma drug concentration.

The major requirements for floating drug delivery system are[13]

• It must release contents at desirable rate to serve as a reservoir.

• It should maintain specific gravity lower than gastric contents (1.004 – 1.01 gm/cm3).

• Cohesive gel barrier should be formed.

3. Hydro dynamically balanced systems

'Hydro dynamically balanced systems' are initially designated by Sheth and Tossounian. [24] These are single-unit dosage form, containing one or more gel-forming hydrophilic polymers.For the development of these systems Hydroxypropyl methylcellulose hydroxethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, polycarbophil, polyacrylate, polystyrene, agar, carrageenans or alginic acid are commonly employed as excipients.[25-26] In hydrodynamically balanced system capsule the polymer is mixed with

drugs and administered. When capsule shell comes in contact with water get dissolves and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period.[26]

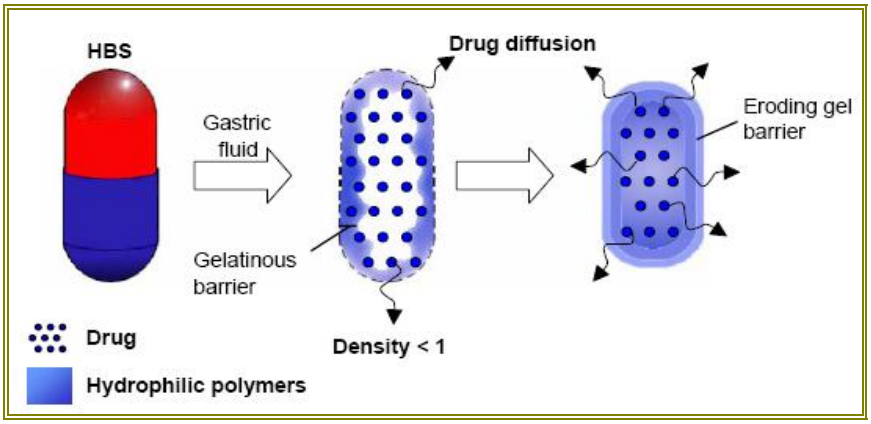

Figure 4. Hydrodynamically balanced system (HBS).

4. Bioadhesive or Mucoadhesive drug delivery systems

These systems are used as a delivery device within the human to improve drug absorption in a site-specific manner. Bio adhesive polymers are used and may adhere to the epithelial surface in the stomach.[30] Thus, they enhance the prolongation of gastric retention.

On the basis of adhesion a dosage form can stick to the mucosal surface by different mechanism as follows: [31-32]

1) On the basis of wetting theory , ability of bioadhesive polymers to spread and develop intimate contact with the mucous layers.

2) The physical entanglement of mucin strands the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate proposed by diffusion theory.

3) The bioadhesion is due to secondary forces such as Vander Waal forces and hydrogen bonding suggested by absorption theory.

4) Attractive electrostatic forces between the glycoprotein mucin net work and the bio adhesive material proposed by the electron theory,

5. Expandable, unfold able and swell able systems

In stomach the dosage form will withstand gastric transit if it is large than pyloric sphincter. The dosage form must be small enough to be swallowed, does not cause gastric obstruction. Thus, their configurations are required to develop an expandable system to prolong gastric retention time.[33-34]

1) for oral intake a small configuration,

2) an expanded gastroretentive form.

a. Swellable systems

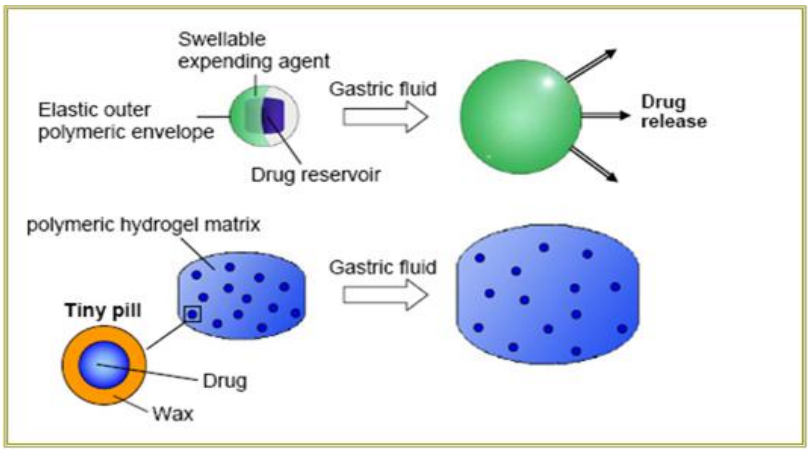

Figure 5. Swellable system.

b. Unfolding system

Unfolding takes place due to mechanical shape memory i.e. the gastroretentive dosage form (GRDF) is fabricated in a large size and is folded into a pharmaceutical carrier e.g. a gelatin capsule, for convenient intake.

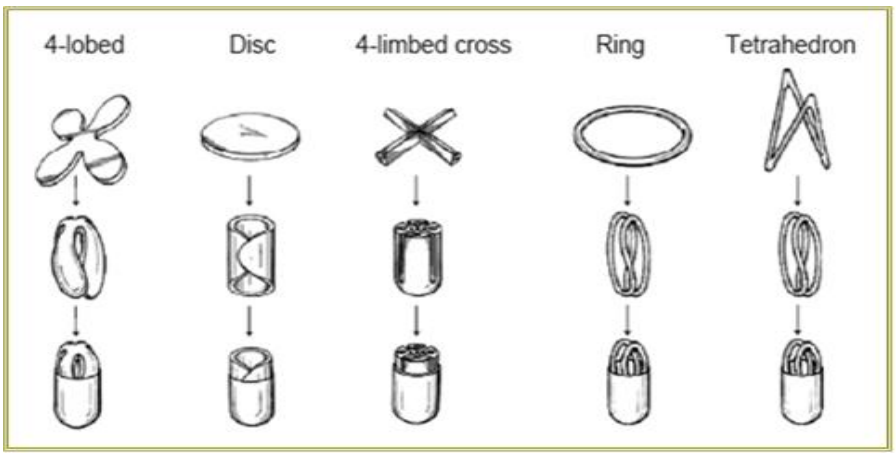

Figure 7: Different geometric shapes of unfolding systems.

6. Super porous hydrogel systems

These swellable systemsvaries enough from the traditional types to have separate classification. For improvement of gastric retention time super porous hydrogels of average pore size >100 micro meter, swelling to the equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores. [35] Large size swelling are intended to have enough mechanical strength to withstand pressure.

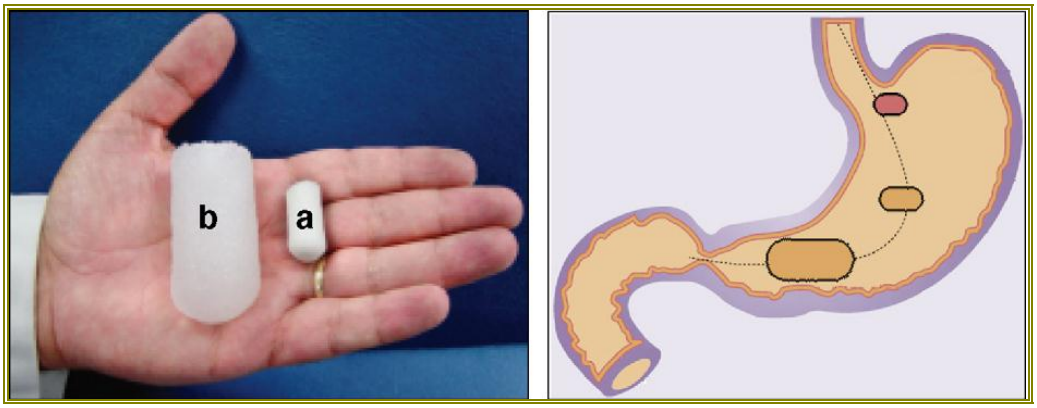

Figure 6: Superporous hydrogels.

7. Magnetic Systems

This method is to improve the gastric retention time which is based on the principle that the dosage form contains a small internal magnet which is placed on the abdomen over the position of the stomach. However,the external magnet must be positioned with a degree of precision.[32]

MECHANISM OF GASTRORETENTIVE DOSAGE FORMS[18]

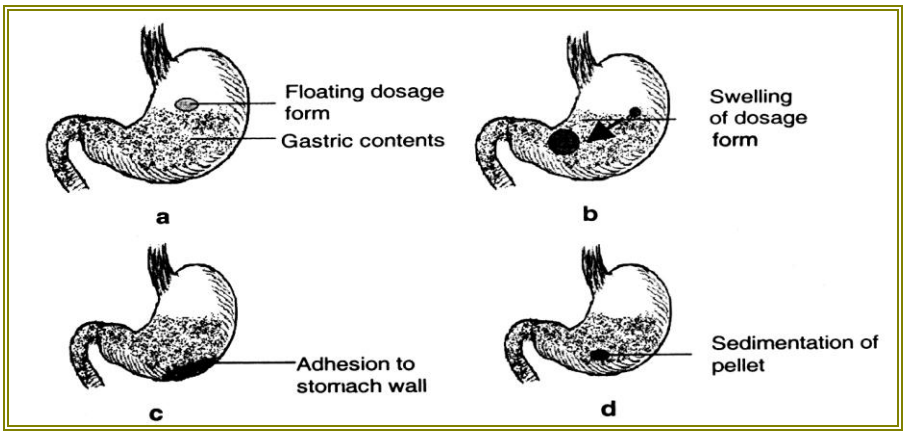

Figure 8. Various forms of gastroretentive systems; (a) Floating gastro-retentive drug delivery systems; (b) Swelling gastro-retentive drug delivery systems; (c) Bioadhesive gastroretentive drug delivery systems; (d) High-density gastro retentive drug delivery systems.

To gain the dosage form in the stomach as a way of improving the retention time numerous attempts have been made. Some of these attempts consist of introducing floating dosage forms mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices.. Most commonly used dosage forms are the floating system. Floating drug delivery systems have a bulk density less than gastric fluids thus, remain

buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. As the system is floating on the gastric, the drug is released slowly at the desired rate. Thereafter, the residual system is emptied from the stomach. This results in an enhanced GRT and a better control of the fluctuations in plasma drug concentration. A minimal gastric content essential to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is required to keep the dosage form reliably buoyant on the surface of the meal. Measurement of the floating force kinetics, a novel apparatus for determination of resultant weight has been reported. Operation carried out with the apparatus by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floating possible if F is on the higher positive side. This device helps in optimizing FDDS with respect to stability and durability of floating forces generated to prevent the demerits of unforeseeable intragastric buoyancy capability variations.

F = F buoyancy - F

gravity = (Df - Ds) gv--- (1) Where, F= total vertical force, Df = fluid density, Ds = object density,

v = volume and g = acceleration due to gravity.

g = acceleration due to gravity.

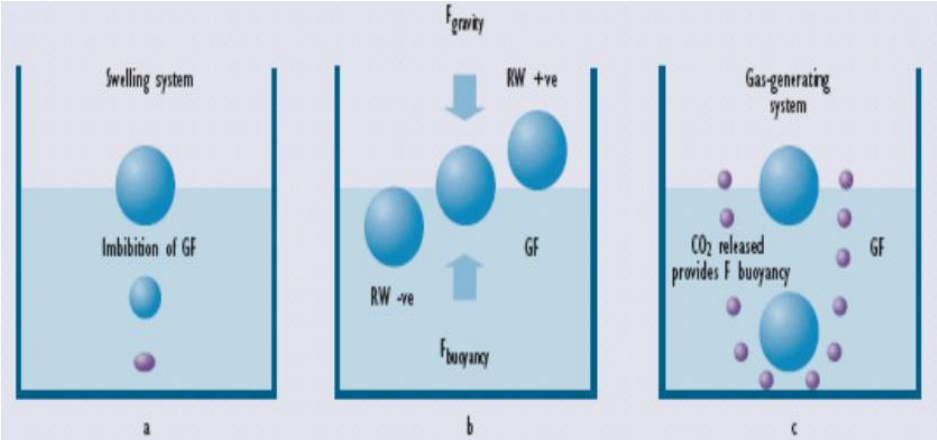

Figure 9: Mechanism of floating systems (a) Swelling system (c) Gas generating system

Types of floating drug delivery system[36]

It can be divided into two systems.

1. Effervescent systems

2. Non-effervescent systems.

1. Effervescent Systems.

A. Volatile liquid containing systems.

a) Intragastric floating gastrointestinal drug delivery system.

In this systems floating can be made in the stomach because of floatation chamber, which may be a vacuum or filled with gas, while the encapsulation of drug reservoir inside a microporus compartment carried out.

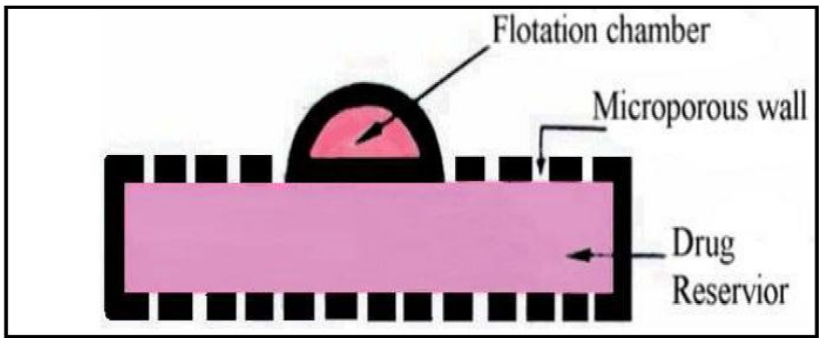

Figure 10 : Intra gastric floating gastrointestinal drug delivery device.

b) Inflatable gastrointestinal delivery systems[39]

Incorporation of inflatable chamber which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. Fabrication of these system by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. The capsule dissolves to release the drug reservoir together with the inflatable chamber after oral administration. Inflation occur automatically and retains the drug reservoir compartment in the stomach. From the reservoir the drug continuously released into the gastric fluid.

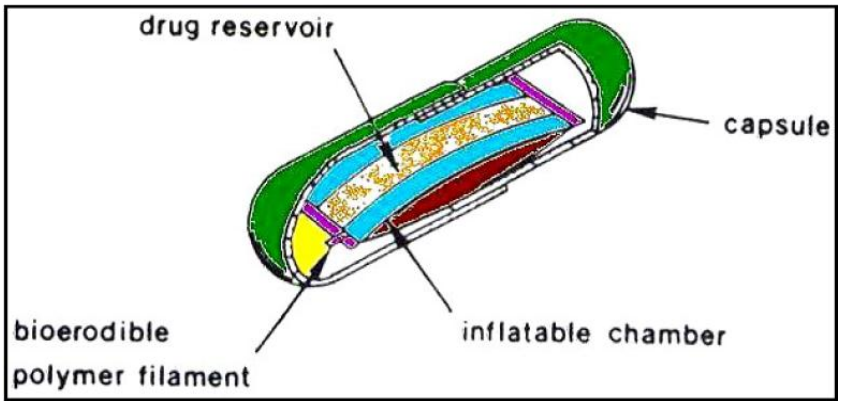

Figure 11 : Inflatable gastrointestinal delivery system

c) Intragastric osmotic ally controlled drug delivery systems

It is composed of an osmotic pressure, controlled drug delivery device and an inflatable floating support in a biodegradable capsule. The capsule in the stomach, quickly

disintegrates to release the intragastric osmotic ally controlled drug delivery device. Formation of inflatable support inside stomach and a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery equipment having two components; drug reservoir compartment and an osmotic ally active compartment. Enclosed drug reservoir compartment by a pressure responsive collapsible bag, which is impermeable to vapors and liquid. The osmotic ally active Compartment contains an osmotically active salt which is enclosed within a semi permeable membrane. Absorption of water in the GI fluid is continuously through the semi permeable membrane into osmotic ally active compartment to dissolve the osmotically active salt. Creation of an osmotic pressure which acts on the collapsible bag and in turn activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice. The floating support is prepared to contain a bio-erodible plug that erodes after a predetermined time to deflate the support.[36,38]

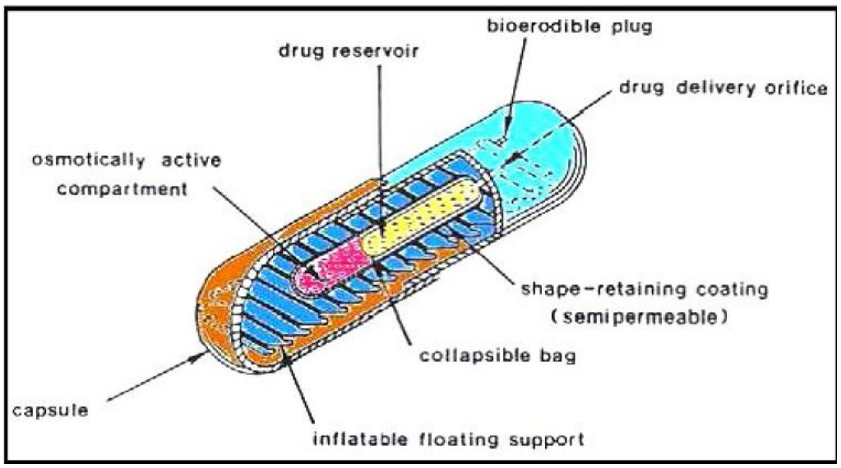

Figure 12: Intragastric osmotically controlled drug delivery system d.Effervescent (gas generating) systems

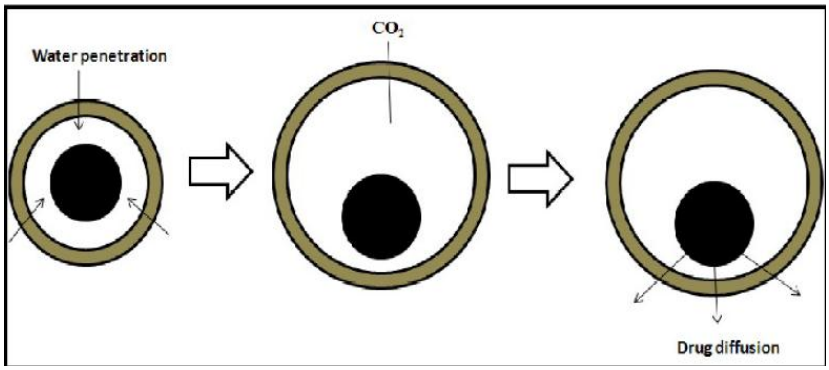

Figure 13: Drug release from effervescent (gas generating) systems.

Achievement of floatability is possible by generation of gas bubbles. These buoyant systems uses matrices made up of swellable polymers such as polysaccharides (e.g. chitosan), effervescent components (e.g. sodium bicarbonate, citric acid or tartaric acid). [29] The ratio of citric acid and sodium bicarbonate generation of gas is reported to be 0.76: 1. [18] In this system carbon dioxide is released which leads to the formulation to float in the stomach. Several techniques and materials that have been employed are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating dosage forms that generate gas when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose , and floating system based on ion exchange resin technology etc.[17]

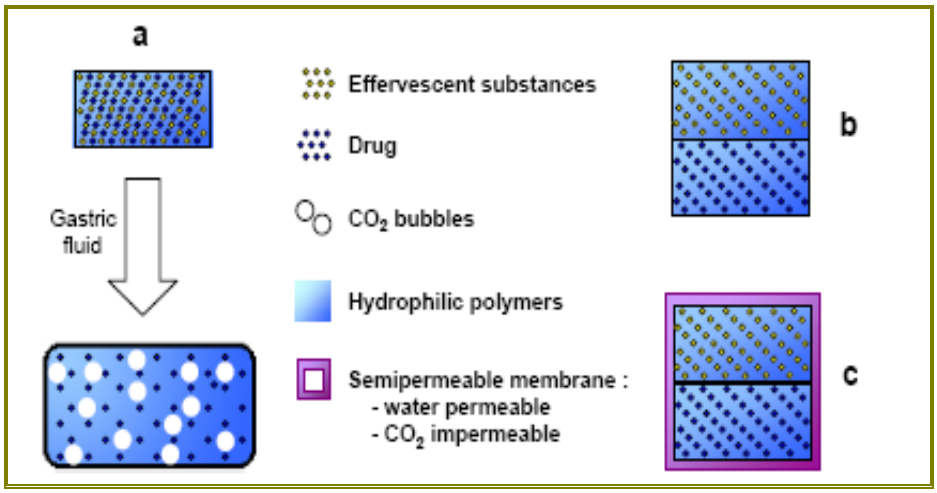

Figure 14: Gas generating system: Schematic monolayer drug delivery system (a) Bilayer gas generating system, with (c) or without (b) semipermeable membrane.

2 Non-effervescent Systems

Production of non-effervescent floating drug delivery systems from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. Mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and sustain a relative integrity of shape and a bulk density. [23] The air trapped by the swollen polymer confers buoyancy. Excipients employed include hydroxypropyl methylcellulose polyacrylates, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. [17]

A. Colloidal gel barrier systems

Sheath and Tossounian in 1975 first designed hydro-dynamically balanced system. It contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. Incorporation of a high level of one gel forming highly swell able cellulose type hydrocolloids e.g. HEC, HPMC,NaCMC, Polysaccharides and matrix forming polymers such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsules. Once they came in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier. The maintenance of a density by air trapped with the swollen polymer less than unity which leads to buoyancy to this dosage forms.[36]

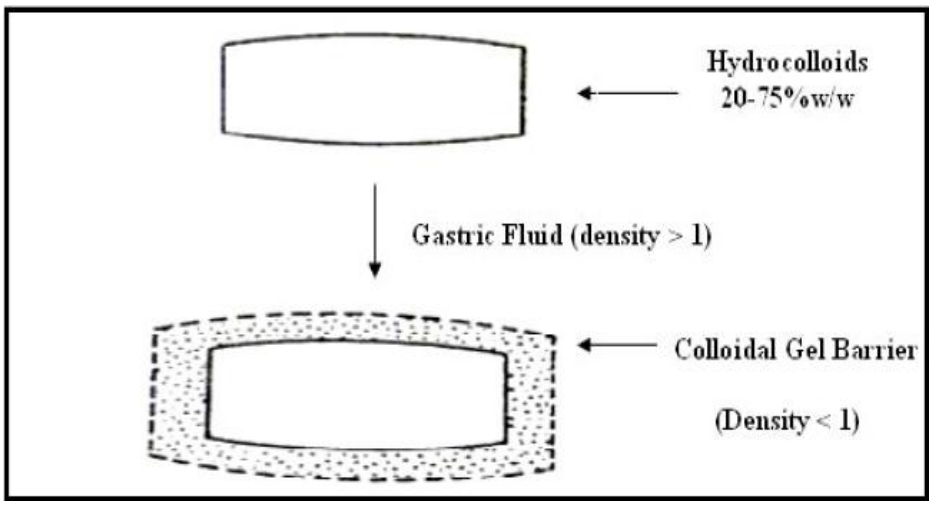

Figure 15 : colloidal gel barrier system

B. . Microballoons / Hollow microspheres

Loading of Microballoons / hollow microspheres with drugs in their other polymer shelf were produced by simple solvent evaporation technique.[27]For prolongation of the gastric retention time of the dosage form. Commonly used polymers are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar etc. drug Drug release from dosage form and it's buoyancy are dependent on quantity of polymers, the plasticizer polymer ratio and the solvent utilized for formulation. The microballoons floated continuously over the surface of an acidic dissolution media containing surfactant for >12 hours. [17] As hollow microspheres has combine benefit of multiple-unit system and good floating, hence these are considered the most promising buoyant systems.

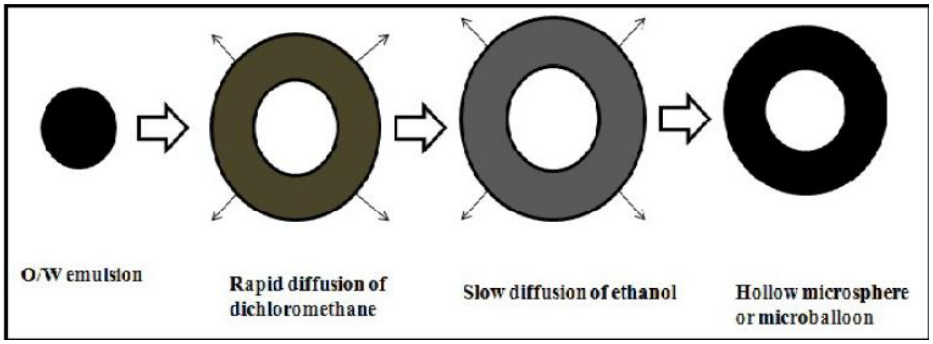

Figure 16: Formulation of floating hollow microsphere or microballoon

C. Alginate beads

Development of a multiple-unit floating system based on cross-linked beads by Talukdar and Fassihi.[22] They were prepared by using Ca2+ and low methoxylated pectin and sodium alginate. Usually, sodium alginate solution is dropped into aqueous solution of calcium chloride and causes the precipitation of calcium alginate. Separation of these beads and dried by air convection and freeze drying, causing the formulation of a porous system, which can sustain a floating force for over 12 hrs. It improve gastric retention time more than 5.5 hrs [17,28]

D.Microporous compartment system

Microporous compartment system is based on the principle of the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. [29] The walls of the apparatus were completely sealed to present any direct contact of the gastric surface with the undissolved drug. In the stomach the floatation chamber containing entrapped air leads to the delivery system to float in the gastric fluid.[13]

E. Raft Forming GF System

Raft forming systems have received much attention for drug delivery for gastrointestinal infection and disorders. The basic principle in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, where in each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids due to low density created by the formation of CO2. Usually, this system ingredients includes a gel forming agents and alkaline bicarbonates which is responsible for formation of CO2 to prepare the system less dense and float on gastric fluids.[37]

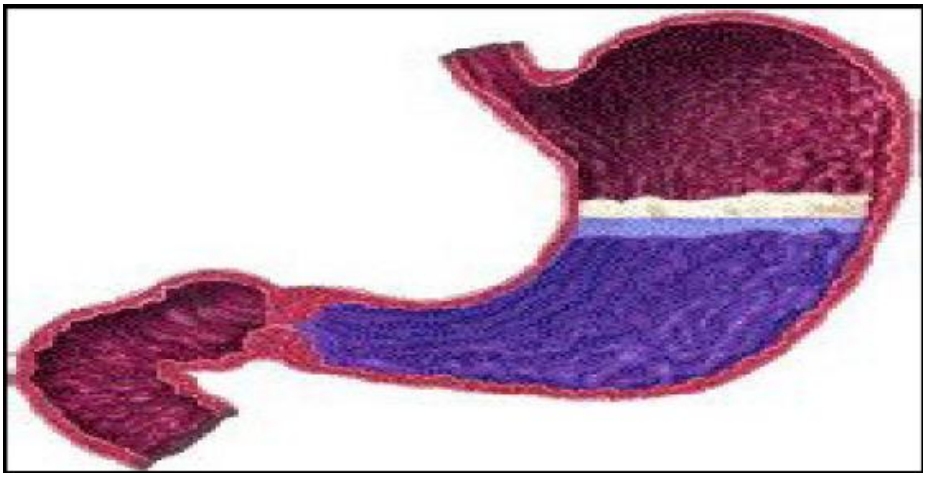

Figure 17: Barrier formed by the raft forming system

Applications of Floating Drug Delivery Systems[40]

1. Enhanced Bioavailability

The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are numerous different approaches, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.

2. Sustained drug delivery

Oral CR formulations are encountered with problems such as gastric residence time in the GIT. These problems can be overcome with the 'Hydro dynamically balanced systems' which can remain in the stomach for prolong periods and have a bulk density <1 as a result of which they can float on the gastric contents. Passing from the pyloric opening is prohibited because these systems are relatively larger in size.

3. Site specific drug delivery systems

These systems are specifically benefits for drugs that are significantly absorbed from the proximal part of the small intestine .The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and restricts the systemic exposure to the drug. This decreases side effects that are caused by the drug in the systemic circulation. However,the prolonged gastric availability from a site directed delivery system may reduce the dosing frequency. Eg: Furosemide and Riboflavin.

4. Absorption enhancement

Drugs with poor bioavailability due to site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

5. Minimized adverse activity at the colon

Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This Pharmacodynamic aspect provides the rationale for gastric retention dosage form formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

6. Reduced fluctuations of drug concentration

Fluctuations in drug effects are reduced and prevention of concentration dependent adverse effects that are associated with peak concentrations. This feature is specifically important for drugs with a narrow therapeutic index.

Future potential of floating drug delivery system[41]

- From several recent publications it is evident that floating dosage form offers various futures potential. The decrease in fluctuations in the plasma level of drug results from delayed gastric emptying.
- We can deliver the drugs efficiently that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract thereby enhancing their absorption and improving their absolute bioavailability.
- It is beneficial for the treatment of gastric and duodenal cancers as buoyant delivery system. The floating concept can be utilized for various anti-reflux formulations.
- Development of a controlled release system for the drugs, which are potential to treat the Parkinson's disease.

CONCLUSION

In the gastrointestinal tract the drug absorption is a highly variable procedure and prolong gastric retention of the dosage form which provides extension for the absorption time. Floating drug delivery system promises to be a potential approach for gastric retention. As there are numerous of difficulties to be worked out to achieve prolonged gastric retention, a large number of industries are focusing toward commercializing this approaches. An significant feature to take into account is physiology of the stomach. Important parameter considered is the time when the drug is taken during or apart from the meal. A real challenge to pharmaceutical technology is to develop an efficient gastroretentive dosage form. Retention of drug in stomach for prolong duration which is not compatible with physiology of stomach. All these Gastro retentive drug delivery systems such as high density, floating,

expandable or unfoldable or swelling, super porous, bioadhesive, magnetic systems etc. are important and present their own advantages and disadvantages. Future expectation are more with these dosage form as they have great importance. Thus, it will lead to improved efficiencies of various types of pharmacotherapy. Therefore, we can conclude that these dosage form has a vital role to play in future and it's potential to provide improved results.

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Author's statements

competing interest

The author declare no conflict of interest.

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