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GASTRO RETENTIVE DRUG DELIVERY SYSTEM: A SYSTEMATIC REVIEW

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ABSTRACT

This article provides a general parameter of gastric discharge in humans and also on its use to form doses with prolonged gastric residence times. It has a high pH. Value with low solubility. Single and multiple doses have been recognized and if the required results of in vivo tests are reported. The most convenient way to administer the drug is the oral route. In this study we read about its advantages and disadvantages, its methods of preparation and procedure. Recently it has been formed that the increase in the rate of frequency of gastric residence of the drug release system includes swelling, floating, non-floating system, magnetic and bioadhesive system.

KEYWORDS: GRDDS, system of administering fluctuating drugs, administration of prolonged-release drugs, raft formation systems, GRDDS application

INTRODUCTION

The main goal of any drug delivery system is to achieve the desired drug concentration in the blood or tissue, which is non-toxic and is therapeutically effective over a prolonged period.[1] An ideal dosing regimen in the pharmacological treatment of any disease is that which immediately reaches the desired therapeutic concentration of the drug in the plasma (or at the site of action) and keeps it constant for the duration of the treatment.

The most important goals of these new drug delivery systems are:
First, it would be a single dose, which releases the active ingredient over an extended period of time. Secondly, it must provide the active pharmacological entity directly to the site of action and minimize or eliminate side effects.[2]

To overcome the limits of the system of administration of conventional drugs, a system of administration of drugs with gastrointestinal retention has been developed. Drugs that have a narrow absorption window in the gastrointestinal tract (GIT) will have a low absorption and lower, for these drugs, the systems of administration of reserve drugs offer the advantages of prolonging the time of gastric emptying.[3]

Gastroretentive Drug Delivery Systems (Grdds)

The systems of administration of gastro retentive drugs are the systems that are kept in the stomach for a longer period of time and, therefore, improve the bioavailability of the drugs. The principle is that the flotation of the drug in the stomach takes place due to the low density of the dosage form. Prolonged gastric retention time improves bioavailability, reducing waste of the drug and improving the solubility of drugs that are less soluble at high pH [4]. Energy retention helps improve the bioavailability of new products with improved therapeutic possibilities and substantial benefits for patients.

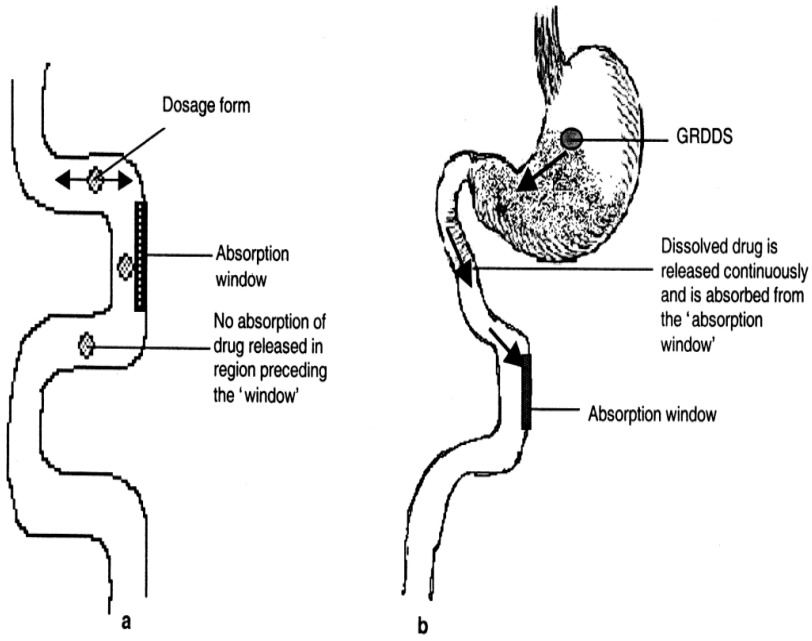

Fig. 1: (a) Conventional dosage form system[5]
(b) Gastroretentive drug delivery[5]

Anatomy of Stomach And Its Physiology

Basically the stomach divided into 3 regions:

1. Context: the bottom of the stomach is the left side of the stomach, and is separated from the body by a plane passing horizontally through the cardiac orifice. The rounded part of the upper part of the stomach allows stomach gas accumulation produced by chemical digestion.

2. Body: it is also called the body and is an anatomical region of the stomach in humans.

3. Antrum (pylorus): the region of the stomach that connects to the duodenum is the pylorus and has two parts, the antrum that is connected to the body of the stomach and the second pyloric channel, leading to the duodenum.[4]

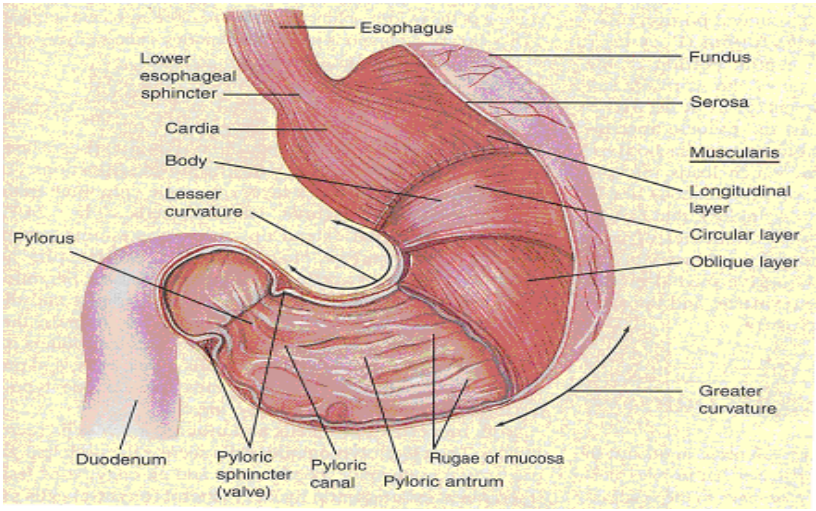

Fig. 2: Basic anatomy of Stomach[8]

The stomach is an organ for storage and mixing. Anatomically, the stomach is divided into 3 regions: lower part, body and antrum (pylorus). The basic structure of the gastrointestinal tract and the stomach are shown in (Figure 1.2). The mucous lining is covered by the entire stomach under this layer there are specialized cells that secrete gastric juice in the stomach. Every day about 2/3 liters of gastric juice are secreted by specialized cells in the mucosa. It consists of:

• Water

• Gastric enzymes (pepsin, gastric lipase, renin, gastrin and other enzymes)

• Mucus glycoprotein

• Intrinsic factor

• Hydrochloric acid, sodium, potassium, calcium, chloride, phosphate, sulphate and bicarbonate. The gastric pH is the next healthy fasting subject of 1.1 ± 0.15. , Fed, healthy subject 3.6 ± 0.4.

Gastric Empty and Motivity

Gastric emptying occurs during fasting, as well as fed states. The passage of the drug from the stomach to the small intestine is called gastric emptying. It is the limiting step in speed for drug absorption because it is the main site for absorption in the intestine. In general, rapid

gastric emptying increases the bioavailability of drugs. A faster onset is required for drugs that degrade in the gastric environment. Delayed gastric emptying favors the dissolution of drugs, which are poorly soluble drugs and drugs that are mainly absorbed by the stomach or the proximal part of the intestine.[9]

Some parameters are used to quantify gastric emptying:[2]

- The rate of gastric emptying (GER) is the rate at which the stomach contents are emptied into the intestine.
- Gastric emptying time (GET) is the time required to empty the gastric contents into the small intestine. The longer the gastric emptying time, the lower the gastric emptying rate.
- T1 / 2 gastric emptying is the time required to half the contents of the stomach to empty. The motility model is however different in the 2 states. During the fasting state, a series of inter-digestive electrical events occur, which pass through the stomach and intestines every 2 to 3 hours. This is called the migratory myoelectric cycle (MMC) or interdigestive myoelectric cycle, which is divided into the following 4 phases:[8]
- Phase I (baseline phase): lasts 30 to 60 minutes with rare contractions.
- Phase II (pre-burst phase): lasts 20 to 40 minutes with an intermittent action potential and contractions. As the phase progresses, the frequency and intensity also gradually increase.
- Phase III (burst phase): lasts from 4 to 6 minutes. Include a regular and intense contraction for a short period. Because of this wave, all the undigested material is swept from the stomach to the small intestine. These waves are also known as the wave of the housekeeper.
- Phase IV: lasts from 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

Factors that influence gastric retention[5-11]

The gastric retention time (GRT) of the dosage form is controlled by several factors that influence its effectiveness as a gastro-retentive system.

- Density: GRT is a function of the hydrostatic thrust of the dosage form depending on density. A density of <1.0 g. / cm3 is required to view the mobile property.
- Dimensions: different properties have been formulated and analyzed, floating and non-fluctuating capsules of 3 different sizes with a diameter of 4.8 mm (small units), 7.5 mm (medium units) and 9.9 mm (large units) . Dosage forms with a diameter> 7.5 mm show a better gastric residence time compared to 9.9 mm dosage forms.

- Form of dosage form: it has been reported that the tetrahedron and ring-shaped devices have a better TRG.
- Single or multiple unit formulation: multiple unit formulations show a more predictable release profile and negligible performance degradation due to unit failure, allow joint administration of units with different release profiles or containing incompatible substances and they allow a greater safety margin against the failure of the dosage form compared to the individual unit dosage forms.
- State fed or not fed: under fasted conditions, gastric motility is characterized by periods of strong motor activity or by the migratory myoelectric complex (MMC) that occurs every 1.5-2 hours. The migrating myelectric complex sweeps the undigested material from the stomach and, if the timing of the drug formulation coincides with those of the MMC, it can be expected that the GRT of the drug unit is very short. In the power state, MMC is late and GRT is considerably longer.
- Nature of food: feeding of non-digestible polymers or salts of fatty acids can modify the motility pattern of the stomach in a nourished state, thus decreasing the gastric acid and prolonging the release of the drug.
- Calorie content: GRT can be increased from four to 10 hours with a meal rich in protein and fat.
- Feeding frequency: GRT can increase in more than 400 minutes when successive meals are given compared to a single meal due to the low frequency of MMC.
- Gender: women have a shorter MRT than men.
- Age: Older people, especially those over the age of 70, have a significantly longer TSL.
- Posture: GRT can vary between the patient's supine and vertical walking states.
- Administration of concomitant drugs: anticholinergic drugs such as atropine and propantheline, opioids such as codeine and prokinetic agents such as metoclopramide and cisapride.
- Biological factors: gastric ulcer, hypothyroidism, diabetes, increased TGR. Duodenal ulcers and hyperthyroidism decrease the TGR

Gastrace Technologies

Several systems have been implemented to increase the gastric residence time of dosage forms using different concepts. These systems were classified according to the basic principles of gastric retention.[12]

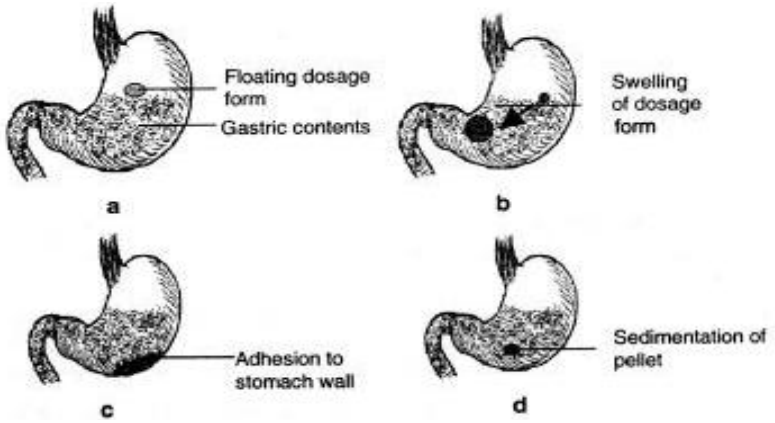

Fig. 3: Various forms of gastroretentive drug delivery systems[12]

(a) Floating system (b) Swelling system

(c) Bio adhesive system (d) High-density system

Floating drugs delivery system

Low-density floating drug systems provide sufficient buoyancy to float on gastric contents. Fluctuating drug delivery systems (FDDS) or hydrodynamically balanced systems have a lower mass density than gastric fluids and therefore remain fluctuating in the stomach without affecting the rate of gastric emptying over a prolonged period of time.[13] While the system floats on the contents of the stomach, the drug is slowly released at a desired rate from the stomach. After the drug is released from the formulation, the residual system is emptied from the stomach. Because of this increase in gastric retention time and better control of fluctuations in the plasma concentration of the drug.[13]

Swelling systems

Swelling system are those that prevent the transit of the gastric sphincter. These are the dosage forms, those that swell up when they arrive in the contents of the gastric liquid and swell to such an extent as to prevent it from exiting the pylorus. Thus the dosage form is retained in the stomach for a longer period of time. These systems can be referred to as "plug-in type systems". The controlled and prolonged release of the drug can be obtained by the selection of a suitable molecular weight polymer and the swelling of the polymer delays the release of the drug in contact with the gastric fluid; the polymer absorbs water and swelling.[14]

Bioadhesive systems

Biological adhesion: in simple terms, it can be described as the union of a synthetic or biological macro-molecule with a biological tissue. An adhesive bond can be formed with the

layer of epithelial cells, the continuous layer of mucus, or a combination of the two.[7] In these systems, the given drug is incorporated with bioadhesive / mucoadhesive agents, which allow the device to adhere to the stomach mucosa, thus resisting gastric emptying. Adherence to the gastric wall increases the time spent in a particular site, thus improving bioavailability. The basis of adhesion is that a dosage form can adhere to the mucosal surface with a different mechanism[13]

1) The wetting theory, which is based on the ability of bioadhesive polymers to spread and develop an intimate contact with the mucous layers.
2) The diffusion theory which proposes the physical interweaving of the mucin chains with the flexible chains of the polymer or an interpenetration of the wicks in the porous structure of the polymeric substrate.
3) The absorption theory suggests that bioadhesion is due to secondary forces such as Vander Waal's forces and hydrogen bonds.[14]

High density systems

The high-density system remains in the stomach for a longer period, establishing the folds of the stomach. These systems with a density of about 3 g / cm3 are retained in the antrum of the stomach and are able to support their peristaltic movements. This system has only major drawbacks with such systems, since it is technically difficult to produce such formulations with a large amount of drug (> 50%) and reach a density of about 2.8 g / cm3. It is necessary to use diluents such as barium sulphate, titanium dioxide, zinc oxide, iron powder, etc. makes these high density formulations.[14]

ANOTHER SYSTEM

Magnetic systems

This approach to improving TSO is based on the simple principle that the small internal magnet placed in the dosage form and a magnet placed in the abdomen on the position of the stomach. Although this magnetic system seems to work, the external magnet must be positioned with a degree of precision that could compromise patient compliance.[13]

Rafting training systems

Raft formation systems have received a lot of attention due to the supply of antacids and the administration of drugs for gastrointestinal infections and disorders. The mechanism involved in the formation of the raft comprises cohesive viscous gel form in contact with gastric fluid, wherein each portion of the fluid inflates to form a continuous layer called a raft. The

resulting raft floats in gastric fluids due to the low apparent density created by CO2 formation. This system generally contains a gelling agent or carbonates of alkali metals and bicarbonates responsible for CO2 formation to make the system less dense and floats in gastric fluids.[15]

Advantages and Disadvantages of Grdds

Benefit

• Improves bioavailability and therapeutic efficacy of drugs.

- Maintains constant therapeutic levels over a prolonged period and, therefore, reduces the fluctuation of therapeutic levels.
- Some types of drugs may benefit from the use of FDDS. They include:

1. Drugs that act locally in the stomach
2. Drugs that are absorbed mainly in the stomach.
3. Drugs that is poorly soluble at alkaline pH.
4. Drugs with a narrow absorption window.
5. Drugs rapidly absorbed from the gastrointestinal tract.
6. Drugs that degrade in the colon.[6]

Disadvantages

1. These systems require a high level of liquid in the stomach to administer the drug, so that the dosage form of the drug will float and function efficiently.
2. It is not suitable for those drugs that have problems of solubility or stability in gastric fluids.
3. It is not suitable for medications that are irritating to the gastric mucosa.
4. These systems also require the presence of food to delay gastric emptying.[7]

Floating Drug Delivery System (Fdds)

FDDS is one of the most important approaches for obtaining gastric retention and obtaining sufficient bioavailability of the drug. This system is suitable for drugs with an absorption window in the stomach or upper small intestine. These have a density lower than that of gastric fluids and therefore remain fluctuating in the stomach without affecting the rate of gastric emptying for a prolonged period and the drug is released slowly as desired system rate. After releasing the drug from the dosage form, the residual system is emptied from the stomach. This results in a longer retention time in the stomach and better control of the fluctuation of the plasma concentration of the drug.[13]

Mechanism of floating systems

Several attempts have been made to maintain the dosage form in the stomach as a way to increase gastric retention time (GRT). These attempts include the introduction of dosage forms (gas Generator systems and swelling or expansion systems), high density systems, mucoadhesive systems, modified forms, delayed gastric emptying devices and co-administration of drugs that delay floating gastric emptying Among these , the fluctuating dosage forms are the most commonly used.[11] Floating drug management systems (FDD, with its acronym) have an apparent lower density of the gastric fluid and thus remain in the stomach without affecting the gastric emptying speed over a prolonged period of time. During system flotation on gastric contents (shown in Fig) the drug is released slowly at the desired system speed. After releasing the drug from the formulation, the residual system is removed from the stomach. This result increased gastric retention time and improved control over fluctuations in the plasma concentration of the drug. However, in addition to the minimum gastric contents necessary to achieve an adequate buoyancy retention effect, also a minimum level of hydrostatic thrust (F) required to maintain the buoyancy of the dosage form on the surface of the food or gastric fluid. To measure the flotation force kinetics, a new device was reported to determine the resulting weight. The device operates by continuously measuring the force equivalent to F (as a function of time) necessary to maintain a submerged object. This object floats better if F is on the upper positive side. This device helps to optimize the FDDS with respect to the stability and sustainability of the flotation forces produced to avoid unpredictable variations of intragastric buoyancy.

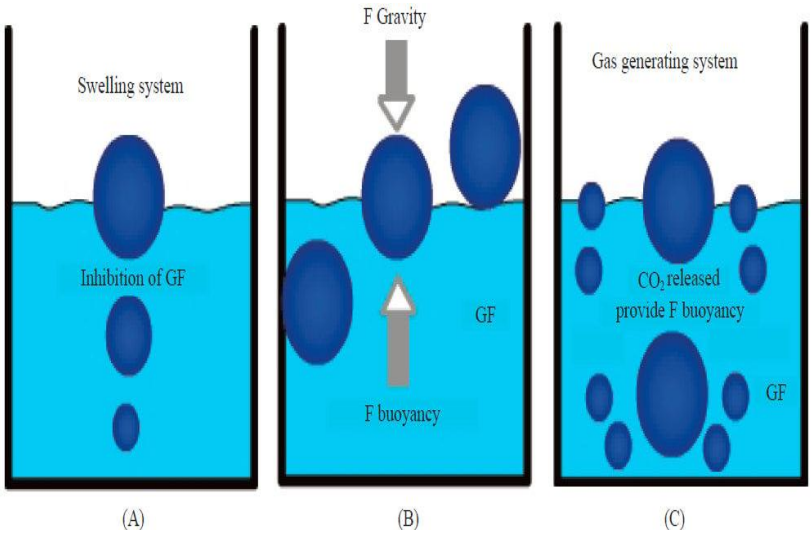

Fig. 4: Mechanism of floating systems[11]

F = Fbuoyancy - Fgravity = (Df - Ds) g v

Where, F = total vertical force,

Df = density of the fluid, Ds = density of the object,

v = volume and g = acceleration due to gravity.

Classification of The Floating Pharmacy Delivery System[4-5,16-17]

Effervescent system

1. Gas generator system.
2. Volatile system that contains liquid.

Non-effervescent system

1. Colloidal gel barrier system.
2. Alginate beds.
3. Hollow microspheres / Micro balloons.
4. Intragastric floating drug delivery device / microporous compartments system
5. Other systems
6. Application

Effervescent system

Effervescent systems include the use of gas-generating agents, carbonates (e.g., sodium bicarbonate) and other organic acids (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO2) gas 30, which reduces the density of the system and makes it float on the fluid gas An alternative is the incorporation of the portion of liquid that contains the matrix, like the gas that produces the liquid that evaporates at body temperature. A drug delivery system can be floated in the stomach by incorporating a floating camera. This floating chamber can be filled with inert gas, air or vacuum. The gas inflation chamber can be introduced by the volatilization of the organic solvent or by the effervescent reaction between organic acids and bicarbonate salts.[14]

Gas - Generating systems

These floating administration systems used effervescent reactions between carbonate / bicarbonate salts and citric / tartaric acid to release carbon dioxide (CO2), which is trapped in the acid layer gelled hydrocolloid systems, thereby reducing its specific gravity and causing it to fluctuate during time prepared with the help of swollen polymers such as methyl cellulose and chitosan and various effervescent compounds, such as sodium bicarbonate, citric acid and tartaric acid. They are formulated in such a way that when it is not in contact with acidic

gastric fluids, CO2 is released and trapped in swollen hydrocolloids and the system floats in gastric contents. In single-unit systems, in capsules or tablets, effervescent substances are incorporated into hydrophilic polymers and CO2 bubbles are trapped in the swollen matrix. In vitro, the delay time before the unit floats is <1 min and buoyancy lasts for 8 to 10 *hours.*

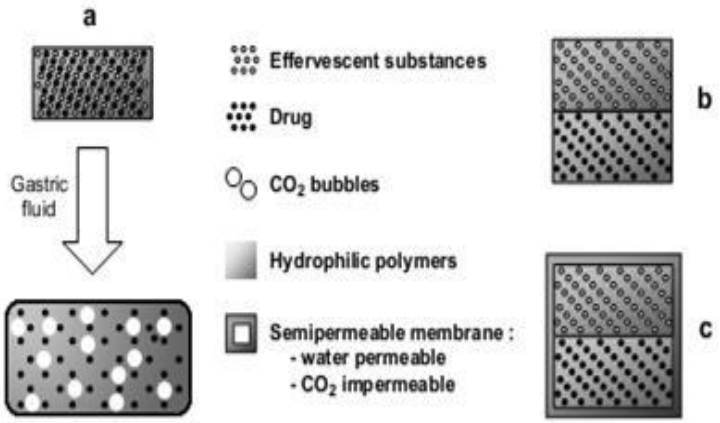

Fig. 5: Effervescent systems Schematic monolayer drug delivery system[14]
[a] bilayer with [c] or without [b] semipermeable membrane.

Volatile Liquid / Vacuum Containing Systems

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid (such as ether, cyclopentane), which is gasified at body temperature to cause room inflation in the stomach. This type of system consists of two chambers separated by an impermeable and pressure sensitive mobile air chamber.[4] The drug is incorporated into the first chamber and the second chamber contains the volatile liquid. The GRT of a drug delivery system can be supported by incorporating an inflatable chamber, which contains a liquid (such as ether, cyclopentane) which gasses at body temperature to induce room inflation in the stomach contents.[13] The device can also consist of a bio-erodible plug made of polyvinyl alcohol (PVA), polyethylene, etc., which gradually dissolves and causes the inflatable chamber to release gas and collapse after a predetermined time to allow spontaneous expulsion of inflatable systems from the stomach. The device inflates, and the drug is continuously released from the reservoir into the gastric fluid.

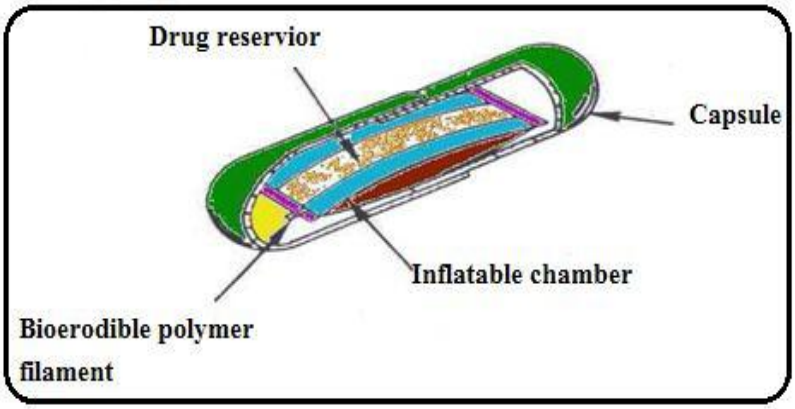

Fig. 6: Volatile liquid containing system[5]

Non-Effervescent System

Non-effervescent dosage forms floating use a type of hydrocolloid gel form polysaccharides and swellable cellulose or, and matrix forming polymers such as polycarbonate, polymethacrylate, polyacrylate and polystyrene. Postoral administration, this formulation swells in contact with the gastric fluid and has an apparent density of <1. The air trapped inside the swollen matrix gives buoyancy to the formulation. The gel-like structure thus formed swollen acts as a reservoir and allows prolonged drug release through the gelatinous[1] mass. This system can be subdivided into subtypes:

Balanced hydrodynamic systems

The dynamic balance hydraulic system (HBSTM) was designed by Sheth and Tossounian in 1975. This system contains a drug with gelling hydrocolloids intended to remain floating on the stomach contents.[11] This system incorporates a high level of one or more highly inflatable cellulose-type hydrocolloids which form, e.g. HEC, HPMC, polysaccharide and matrix-forming polymers, such as polyacrylates, polycarbophiles and polystyrene, incorporated into capsules or tablets. In contact with gastric fluid, the hydrocolloid present in the system is hydrated and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density lower than unity and confers buoyancy to these dosage forms.[19]

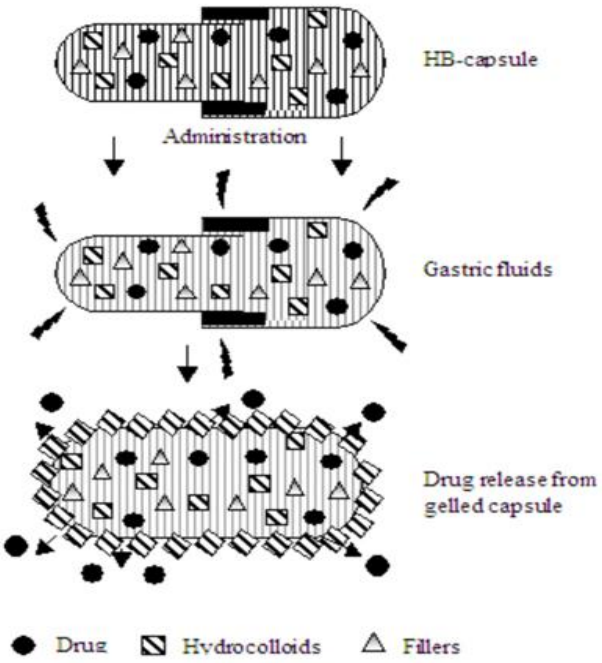

Fig. 7: Hydrodynamic balanced systems[3]

Alginate beads

Multi-unit floating dosage forms were developed from freeze-dried calcium alginate. The spherical beads (about 2.5 mm in diameter) are prepared by dropping a sodium alginate solution into an aqueous solution of calcium chlorides, causing the precipitation of calcium alginate. Then, these beads are immediately separated and frozen in liquid nitrogen and lyophilized for 24 hours at -40 ° C, which results in the formation of a porous system, which maintains a fluctuating force for over 12 hours. These floating pearls have a prolonged stay time of more than 5 hours.[10]

Hollow microspheres / Micro balloons

Hollow microspheres are considered to be one of the most promising flotation systems, as they have the unique advantages of multi-unit systems and the best flotation properties, due to the central hollow space within the microsphere. The techniques involved in its preparation include evaporation and diffusion of simple solvents. Eudragit S, polycarbonate, cellulose acetate, agar, calcium alginate and low methoxyl pectin are commonly used as polymers in the preparation of empty microspheres or microspheres. The buoyancy and release of drugs depend on the amount of polymer, plasticizer, polymerization and solvent used.[5] The hollow microspheres / micro balloons are loaded with the drug in their external polymers, the cells being prepared by a novel diffusion solvent emulsion method. The dichloromethane: ethanol solution of the drug and an enteric acrylic polymer were poured into an aqueous solution of

agitated PVA which was thermally controlled at 400 ° C. The gaseous phase is generated in the form of polymer droplets by evaporation of the dichloromethane which forms an internal cavity in the polymer microsphere with the drug. The microspheres or micro balloons floated continuously on the surface of the acid dissolution medium containing surfactant more than 12 hours in vitro.[20]

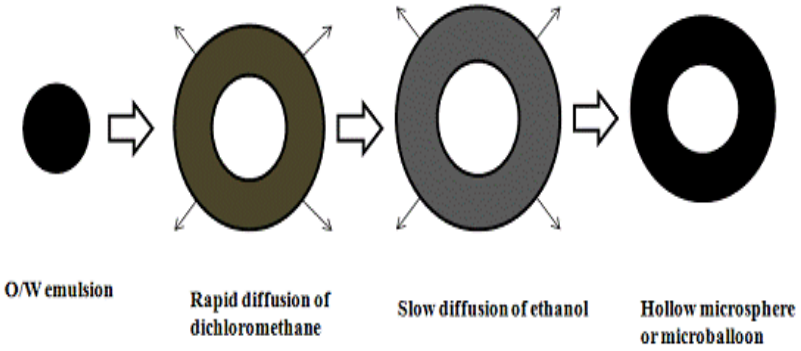

Fig. 8: Formulation of floating hollow microsphere or microballoon[13]

Micro porous Compartment System

This technology is based on the encapsulation of a drug reservoir inside a microporous compartment with pores along its bottom and top walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the gastric fluids, the floatation chamber containing entrapped air causes the delivery system to float over the gastric fluids. The fluid in the stomach enters through the aperture and dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.[21]

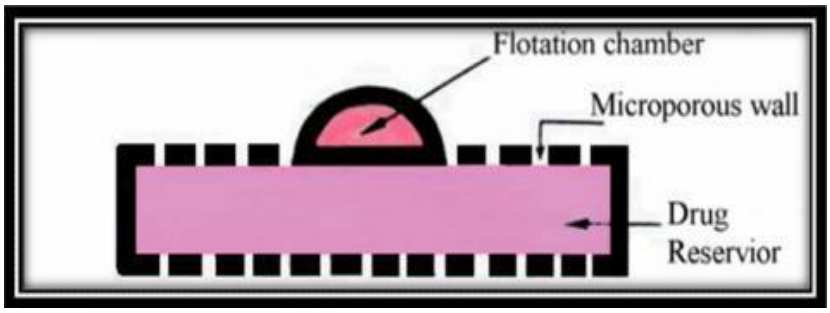

Fig. 9: Gas filled floatation chamber[22]

Application of The Float Drive Supply System

The fluctuating supply of drugs offers different applications for drugs that have poor bioavailability due to the narrow absorption window at the top of the gastrointestinal tract.

The FDDS maintains the storage form at the site of absorption and, therefore, increases the bioavailability of the drug. These are summarized below.[6]

Delivery of prolonged-release drugs

HBS systems can remain in the stomach for long periods of time and, therefore, can release the drug for a prolonged period of time. The short GRT problem encountered with an oral CR formulation can therefore be solved with these systems. These systems have an apparent density <1 as a result of which they can float in gastric liquids. These systems are relatively large and the transition from pyloric opening is prohibited.[4]

Delivery of medicines to a specific site

The fluctuating drug delivery system is particularly beneficial for drugs that are specifically absorbed from the stomach or the proximal part of the small intestine, such as riboflavin and furosemide. Control; slow stomach drug delivery provides sufficient local therapeutic levels and limits systemic exposure to the drug. Reduces the side effects caused by the drug in the bloodstream. Prolonged gastric availability of a site-directed delivery system may also reduce the frequency of administration.

Improvement of absorption

Drugs that have poor bioavailability due to the specific absorption of sites in the upper part of the gastrointestinal tract are possible candidates for being formulated as floating drug delivery systems, which maximize their absorption. This system also serves as an excellent drug delivery system for the eradication of H. pylori, which causes chronic gastritis and peptic ulcer disease. This treatment requires high drug concentrations to be maintained at the site of infectionthat is within the gastric mucosa. Because of its floating ability these dosage forms can beretained in the gastric region for a prolonged period so that the drug can be targeted.

Delivery of poorly soluble and insoluble medicinal products

Particularly effective in the administration of poorly soluble and insoluble drugs, since the solubility of any drug decreases, the time available for dissolution of the drug becomes less adequate and, therefore, transit time becomes an important factor influencing the absorption of the drug. To solve this problem, oral administration of poorly soluble drugs is often performed several times a day.

Reduce fluctuations in drug concentration.

Continuous injection of the drug after administration of the controlled-release gastro-retentive dosage form produces drug concentrations in the blood within a narrower range than immediate-release dosage forms. Therefore, fluctuations in the effects of drugs are minimized and even adverse effects dependent on the associated concentration are minimized.[11]

CONCLUSION

The present study was conducted to provide complete information on the system of administration of gastrointestinal retentive drugs. The study helps to provide which type of drug shows greater bioavailability in the gastrointestinal tract. Today there are several types of drugs available for treating gastrointestinal problems, so this study helps to design a specific model of drugs. The control of drug delivery profiles has been an important goal of pharmaceutical research and development. The system of administration of gastro-retentive drugs can provide the model of drug release in a controlled manner (predetermined speed and time). This drug delivery system maintains the therapeutic levels constant over a prolonged period and, therefore, the reduction of the fluctuation of the therapeutic levels, which improves the bioavailability and the therapeutic efficacy of the drugs.

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AUTHOR CONTRIBUTION

Pankaj Bhatt designed the review and collected the information's from various sources.

CONFLICT OF INTERESTS

The author declares that there is no conflict of interests regarding the publication of this paper.

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