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GASTRORETENTIVE DRUG DELIVERY SYSTEM

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ABSTRACT
Gastroretentive drug delivery system (GRDDS) help in treatment of gastritis and peptic ulcer disease. Gastroretentive dosage forms that can be retained in a stomach for prolonged and expected period of time. Recently many new and old drug molecules,either mono or combination product are formulated as gastroretentive drugs delivery system. Thus, this dosage form significantly extend the period of time over which the drug may be released in comparison to controlled release drug delivery system, and maintain therapeutic concentration for prolonged period of time.

KEYWORDS: Gastroretentive, Flotation, Mucoadhesion, Drug delivery system.

INTRODUCTION

Controlled and modified release formulation are widely used in modern era to improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Those drugs that are easily absorbed from gastroretentive tract (GIT) and having short half life are quickly eliminated from the systemic circulation. So that frequent dosing of these drugs is mainly required to achieve suitable therapeutic activity. To avoid this limitation, the development of the oral sustained - controlled release formulation is an attempt to release the drug slowly into the Gastrointestinal tract (GIT) and maintain the effective drug concentration in the systemic circulation for a long time. After oral drug delivery would be retained in the stomach and release the drug in controlled manner, so that the drug could be supplied continuously to the absorption sites in the Gastrointestinal tract (GIT). These drug delivery system suffer from the two adversities : the short gastric retention time and unpredictable short gastric emptying time, which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose. Prolonged gastric retention improves bioavailability, increase in the duration of drug release, reduce drug waste and improve the solubility of the drugs that are less soluble in pH environment, local action in the upper part of the small intestine e.g. treatment of peptic ulcer.

Gastroretentive Drug Delivery System is an approach to prolonged the gastric residence time, thereby targeting site-specific drugs release in upper Gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time of drug.

The strategies for delaying drug transit through the GIT fall into following categories[3.4]

1. Pharmacological approach
2. Physiological approach
3. Pharmaceutical approach

The first two approaches are not used commonly because of toxicity problems. The various pharmaceutical approaches are used for gastroretention can be as follows.

1. Low density system/ Floating dosage forms
2. High density systems
3. Modified shape systems
4. Mucoadhesive systems
5. Expandable, unfoldable and swallable systems
6. Magnetic systems

Advantages of GRDDS[2]

1. It is used for the treatment of peptic ulcer disease.
2. Commonly used for drugs with narrow absorption window in the small intestine.
3. Minimize dosing frequency.
4. Improved bioavailability of the drugs.
5. Used for drugs which are normally unstable in intestinal fluids.
6. Used to provide sustain the delivery of drug.
7. Used for maintaining maximum therapeutics drug concentration within the therapeutic window.

Disadvantages of GRDDS[4,5]

1. Floating drug delivery systems has limitation, that they require high level of fluids in stomach for floating and working more efficiently. So more water intake is needed with such dosage form.
2. In sleeping, floating dosage form may swept away (if not of larger size) by contractile waves. So such dosages form should not take just before going to bed.
3. Drugs that are unstable in high acidic environment, very low solubility in acidic environment and causes irritation to gastric mucosa cannot be incorporated into GRDDS.
4. Swellable dosage form must be capable to achieve larger size than pylorus aperture before they exist from stomach.
5. The success rate of bio or mucoadhesive is less because of high turnover rate of mucus layer.

Anatomy and physiology of stomach[1,8]

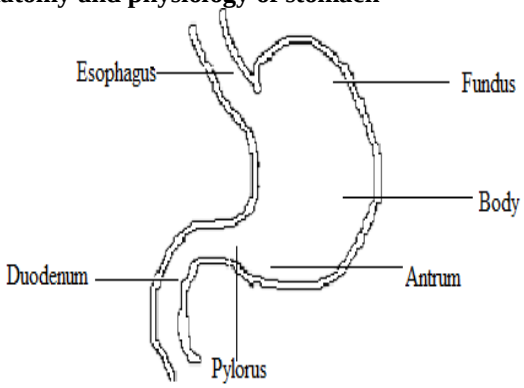

Fig1. Stomach

Anatomy

The food we eat, stomach store it for temporary period of time, grind it, and then releases slowly to them into the duodenum. The stomach is an important sites for enzymes production which are required for digestion of food material. Stomach has small surface area, very little absorption of drug candidate takes place from stomach. It provides a barrier to the delivery of drugs to the small intestine.

The stomach is located below the diaphragm. There are various factors such as volume of food ingested, posture and skeletal build affect the exact position of stomach. Anatomically stomach can be divided into four region such as

1) Fundus
2) Body
3) Antrum
4) Pylorus

1) Fundus and body: The main function of fundus and body is storage of food for temporary period of time. The fundus adjust to the increase volume during eating by relaxing the fundal muscle fibers. The fundus exert a steady pressure on the gastric content and press them toward the distal stomach. To pass through the pyloric valve into the small intestine.

2) Antrum: Antrum is involved in mixing or grinding of food material. The particle should be in the range of 1-2 mm. The antrum does this grinding.

3) Pylorus: The pylorus is the opening from the stomach into the duodenum. The main functions of the pylorus are to prevent intestinal contents from reentering the stomach when the small intestine contracts and to limit the passage of large food particles or undigested material into the intestine.

Physiology

There are several factors such as pH, nature and volume of gastric secretion and gastric mucosa play an important role in drug release and absorption.

pH

pH of the stomach affects the performance of orally administered drug. The pH of stomach in fasted condition is about 1.5 to 2, and in fed condition usually it is about 2 to 6. A large volume of water administered with an oral dosage forms changes the pH of the stomach to the pH of water initially. This changes occur due to stomach does not have sufficient time to produce as much quantity of acid before emptying of liquid from the stomach. Therefore it doesn't improve dissolution of basic drugs. In this condition basic drugs will have a better chance to dissolve in fed condition rather than in a fed condition.

Gastric mucosa

The gastric mucosa is the mucous membrane layer of the stomach, which contains the glands and the gastric pits. In humans, it is about 1 mm thick, and its surface is smooth, soft, and velvety. It consists of simple columnar epithelium, lamina propria, and the muscularis mucosae. This cell are associated with different functions. The perietal cell secrete acid whereas the peptic cell secret precursor for pepsin. The surface mucosal cell secrete mucus and bicarbonate. They also protect the stomach from digestion by pepsin and adverse effects of hydrochloric acid. Mucus layer has lubricating effect, it allow chyme to move freely through the digestive system.

Gastric motility[14]

There are three layer of stomach which produces the coordinated movement of the gastric content such as, outer longitudinal muscle layer, inner circular muscle layer, and an oblique layer. The motility pattern of the stomach at the time of administration of dosages from is different in digestive or fasted and interdigestive or fed conditions.

There are four phases of stomach movement in the fasted state. It is divided into four phase.

1) Basal phase

2) Prebrust phase
3) Brust phase
4) Short transitional phase

In phase one (basal phase): There is no contraction or secretion. It it last upto 40 to 60 min.

In phase two (prebrust phase): There are irregular contraction and bile secretion. During this phase pressure rises to 5 to 40 mm of Hg during contraction. It is last upto 20 to 40 min.

In phase three (burst phase): Mucus discharge take place. In this phase, the frequency and amplitude of contraction is at the peak. Although this is very short phase last upto 4 to 6 min. During this phase, the baseline pressure increases substantially.

The fourth phase: is a short transitional period which is last upto 0 to 5 min. and originated between phases 3 and 1.

This phases activity moves along with the esophagus, stomach, antrum, duodenum, jejunum, ileum, and caecum. Almost it takes about 2 hour for this phase to move through stomach to ileocecal junction. This phase acts as a cleaning phase, and also know as "housekeeper wave".

Gastric emptying

Particle size and feeding state strongly affect the rate of gastric emptying. Some other factors such as type of meal and caloric content, volume, viscosity, and co administered drugs have great impact on gastric emptying rate. Hunt and Stubbs have shown that nutritive density of meal help to determine the rate of gastric emptying. Generally an increase in acidity, osmolality, and calorific values shows down gastric emptying rate. Stress increases gastric emptying rate whereas depression slows it down.

Factors affecting gastric retention are[7,8,9]

1. Density
2. Shape and size
3. Food intake and its nature
4. Gender and age

Density

The density of the dosage form also affect gastric emptying rate. Dosages form having a density lower than the gastric contents can float to the surface, while high density systems sink to the bottom of the stomach. A density of < 1.0 gm/cm^3 is needed to show floating property of dosage form.

Shape and size

The mean gastric residence time of non-floating dosage form are variable and greatly dependent on the size, which may be larger to medium and medium to small unit. In number of cases, larger the size of dosages form greater will be the gastric retention time (GRT) due to larger size of the dosage form will not allow them to quickly pass through the pyloric antrum into the intestine. the diameter of dosages form more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm. Ring shaped and tetrahedron shaped devices have a better and more gastric residence time as compared with other shape like 9.9 mm. Ring shape and tetrahedron-shaped show more gastric retention time as compared with other shape or devices.

Food intake and nature of food

Food intake, viscosity and volume of food, caloric value and frequency of feeding have great impact on the gastric retention of dosage forms. Presence of food in GIT improves the gastric retention time, thus improve the drug absorption by allowing its stay at the absorption site for longer period of time. With the Increase in acidity and caloric values also increases gastric retention times and thus down the gastric emptying rate.

Gender and Age

Generally, Male have faster gastric emptying rate than female. In case of geriatric person, gastric emptying is slowed down. The posture of person doesn't have any significant difference in the mean gastric retention time for individual in upright, ambulatory, and supine position.

Requirements for Gastroretentive formulation[2]

1. Drugs that act locally in the stomach (Antacids and drugs for H. Pylori viz., Misoprostol)
2. Drugs those are primarily absorbed in the stomach (Amoxicillin)
3. Drugs that is poorly soluble at intestinal fluid (Furosemide, Diazepam, Verapamil)
4. Drugs which show a narrow window (Cyclosporine, Methotrexate, Levodopa)
5. Drugs that are absorbed rapidly in the GI tract (Metronidazole, tetracycline)
6. Drugs that usually degrade in the colon (Ranitidine, Metformin HCl)
7. Drugs that disorganize normal colonic microbes (Antibiotics against Helicobacter pylori)

Approaches through which gastric retention are possible

High density system

High density system also known as non floating drug delivery system. High density system that are retained in the bottom of the stomach, with the density that must exceed of normal stomach content (~1.004 gm/cm^3). These formulations are formulated by coating drug on a heavy core or assorted with inert materials such as iron powder, barium sulphate zinc oxide and titanium oxide etc. The materials increase density by up to 1.5- 2.4 gm/cm^3) A density almost to 2.5 gm/cm^3 seems necessary for significant prolongation of gastric residence time of the dosages form. But the success rate

of this system in human being was not perceive and none of the system is marketed.

Floating drug delivery system[13]

Floating drug delivery system is one of the dominant aspect to attain gastric retention as well as sufficient drug bioavailability. This system is convenient for drugs which have absorption window in the stomach or in the upper small intestine. This system have a less bulk density as compared to gastric fluid so that persist buoyant in the stomach without affecting gastric emptying rate for period of time and the release the drug at a desired rate from the system. With this system an increase gastric retention time and better controlled over the fluctuation in plasma drug concentration. The major requirement for floating drug delivery system are as follows.

- It should release drug contents slowly over a expected period of time.
- It must preserve specific gravity lower than gastric contents.
- It must form a cohesive gel barrier between the different layer of dosage form.

Effervescent system

Gas generation and entrapment of air not only increases the size of the drug delivery system but also decreases the density and possibly as well, and provides floating properties, thus, presenting a combination of two principles to prolonged the gastric residence time is useful.

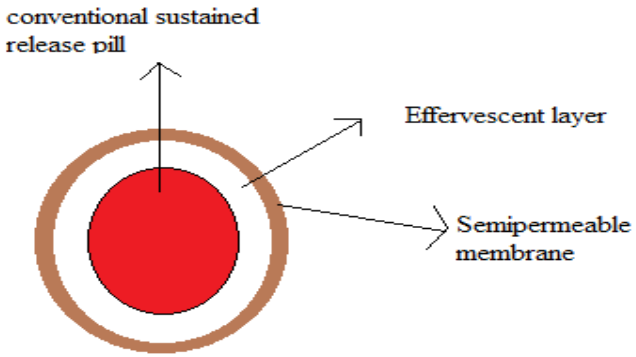

Fig 2 : Effervescent (Gas generating) systems

Following are the types of gas generating GRDDS.

a. Conventional matrix tablets
b. Layered matrix tablets
c. Core coated matrix tablets

Non - effervescent system

Non effervescent floating drugs delivery system are normally formulated by from gel forming or highly soluble cellulose type hydrocolloid, polysaccharides.

Commonly used recipients in non effervescent GRDDS are

1. Hydroxypropyl methylcellulose (HPMC)
2. Polyacrylate
3. Polyvinyl acetate
4. Carbopol
5. Agar
6. Sodium alginate
7. Calcium chloride
8. Polyethylene oxide
9. Polycarbonate

This system can be further divided into the sub type.

Hydrodynamically balance system

Sheth and Tossounian first formulated these 'hydrodynamically balanced systems'. These systems contains drug with gel-forming hydrocolloids meant to remain buoyant in the stomach for prolonged period of time. These are single-unit dosage form, mainly contain one or more gel-forming hydrophilic polymers.

Commonly used excipients to develop these system are as follows.

1. Hydroxypropyl methylcellulose (HPMC)
2. Hydroxethyl cellulose (HEC)
3. Hydroxypropyl cellulose (HPC)
4. Sodium carboxymethyl cellulose (NaCMC)
5. Polycarbophil
6. Polyacrylate
7. Polystyrene
8. Agar
9. Carrageenan
10. Alginic acid

Microballoons/ Hollow microsphere

Microballoons / hollow microspheres loaded with drugs in their other polymer shelf was formulated by simple solvent evaporation or solvent diffusion / evaporation methods.

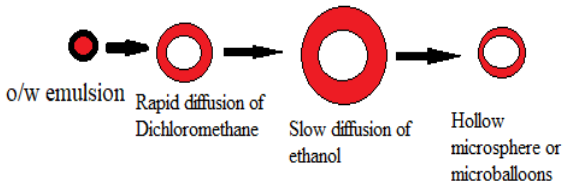

Fig 3 : Formulations of floating Hollow Microsphere or Microballoons

Commonly used polymers to develop such a systems are as follows.

1. Polycarbonate
2. Cellulose acetate
3. Calcium Alginate
4. Eudragit S
5. Agar
6. low methoxylated pectin

Alginate bead[6]

Talukdar and Fassihi recently formulated a multiple-unit floating drug delivery system based on the cross-linked beads. They were used two components for formulation of system such as Ca2+ and low methoxylated pectin (anionic polysaccharide) or Ca2+ low methoxylated pectin and sodium alginate. In this approach, the precipitation of calcium alginate is there when sodium alginate solution will be dropped in the aqueous solution of calcium chloride. Then these beads are separated and dried by mean of air convection and freeze drying also, leading to the formulation of a porous system, which can maintain a floating force for maximum 12 hrs. These beads can improve gastric retention time (GRT) more than 5.5 hrs.

Microporous compartment system

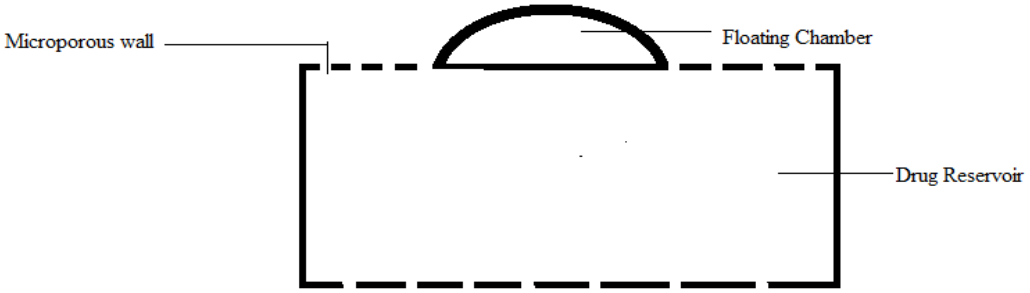

Fig.4 Microporous Compartment System

This approaches is mainly based on the principle of the encapsulation of a drug reservoir inside a Microporous compartment.

Bioadhesive or mucoadhesive drug delivery systems[12,16,17]

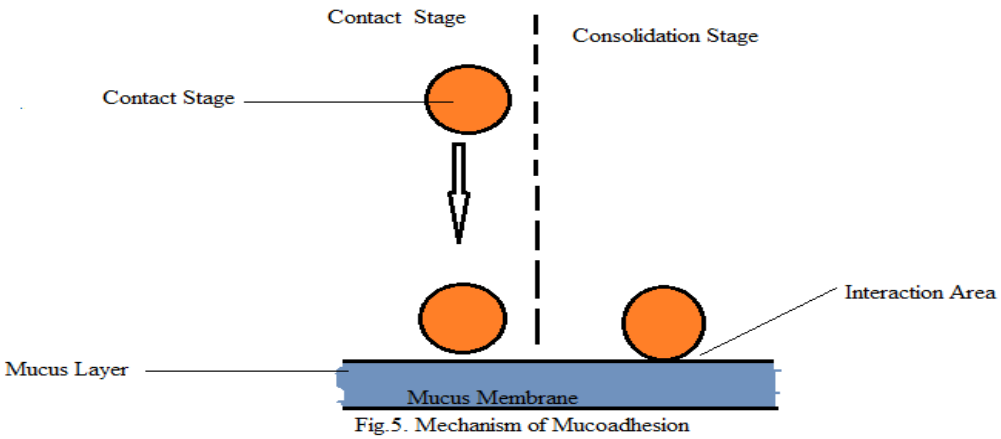

Fig.5. Mechanism of Mucoadhesion

In this system, bioadhesive or mucoadhesive polymer are used and they can adhere to the gastric mucosa in the stomach. Mucoadhesive drug delivery system are basically developed to enhanced drugs absorption in stomach for a site specific manner in the stomach. Hence, they improve the gastric retention of the dosages form in the stomach. Thereby enhance the complete absorption of drugs in the stomach.

The difference mechanism of adhesion as follows

1) The wetting theory: which is based on the ability of bioadhesive polymers used in the formulation to spread and develop intimate contact with the mucous layers of the stomach for a period of time.

2) The diffusion theory: Which proposes physical involvement of mucin strands the tensile polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate.

3) The absorption theory: Indicate that bioadhesion is due to secondary forces such as Vander Waal forces and hydrogen bonding between the polymer used in the formulation.

4) The electron theory: Which demonstrate that attractive electrostatic forces between the glycoprotein mucin network and the bio adhesive material (bioadhesive polymer).

The commonly used materials for bioadhesion are as follows

1. Polyacrylic acid
2. Chitosan
3. Cholestyramine
4. Sodium alginate
5. Hydroxypropyl-methylcellulose(HPMC),
6. Sucralfate
7. Tragacanth
8. Dextrin
9. Polyethylene glycol (PEG)
10. Polylactic acid It is very difficult to maintain it effectivity because of the rapid turnover rate of mucus in the gastrointestinal tract (GIT) and short gastric emptying rate.

Expandable, unfold able and swellable system[10,15]

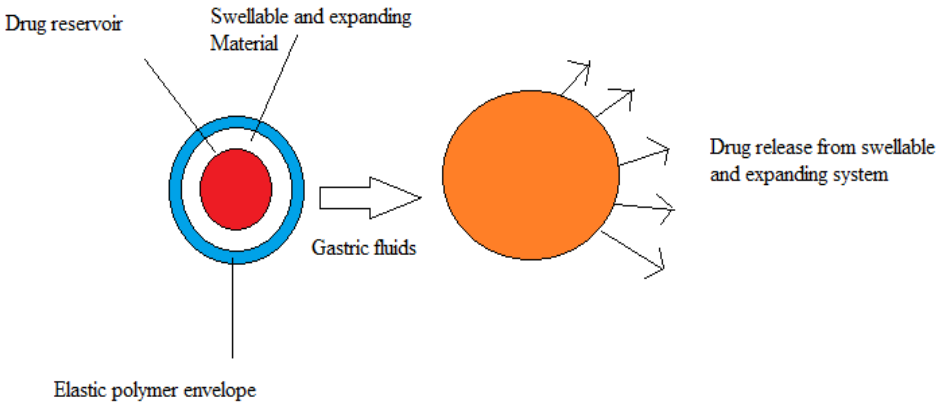

Fig.6. Swellable and Expanding system

The dosages form will remains in the stomach for prolonged period of time when the size of such dosages form will be more and bigger than that of pyloric spincher. However, it is recommended that the dosages in solid form must be small enough to be swallowed, and must not cause gastric irritation either singly or by accumulation. Thus, their arrangement are necessary to develop an expandable system to prolong gastric retention time(GRT) to remains dosages form in the stomach.

Magnetic system

This is a another approach to enhance the gastric retention time (GRT) is based on the simple principle of dosage form contains a small amount of internal magnet, and a magnet is placed over the stomach. Although magnetic system seems to work, the external magnet must be positioned with a degree of condition that might accommodate patient compliance.

Commonly used drug in formulation of GRDDS[18,19]

Sr.no.	Dosages form	Drugs
1.	Floating tablets	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerzine, Chlorpheniramine maleate, Ciprofloxacin, Diltiazem, Fluorouracil, Isosorbide dinitrate, Isosorbid mononitrate, p-Aminobenzoic acid(PABA), Prednisolone, Nimodipine, Sotalol, Theophylline, Verapamil
2.	Floating capsule	Chlordiazepoxide HCl, Diazepam, Furosemide, L-DOPA and Benserazide, Nicardipine, Misoprostol, Propranolol, Pepstatin
3.	Floating microcapsule	Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfenadine, Tranilast
4.	Floating granules	Diclofenac sodium, Indomethacin, Prednisolone
5.	Powders	Several basic drugs

Gastroretentive products available in the market[18,19]

Sr.no.	Brand Name	Active Ingredient
1.	Cifran OD®	Ciprofloxacin
2.	Madopar ®	L-DOPA and Benserazide
3.	Valrelease ®	Diazepam
4.	Topalkan ®	Aluminum-magnesium antacid
5.	Almagate Flat Coat ®	Aluminum-magnesium antacid
6.	Liquid Gavison ®	Aluminium hydroxide,
7.	Conviron	Ferrous sulfate
8.	Cytotec®	Misoprostal

CONCLUSION

Based on the literature survey it may be concluded that gastroretentive drug delivery system is promising approach for drug with poor bioavailability prior to their absorption is restricted particularly in upper gastrointestinal tract (GIT) and therefore they can be delivered effectively by maximizing their absorption and enhancing absolute bioavailability. Another promising area for research for gastroretentive drug delivery system is gastritis and peptic ulcer. Although, in the treatment of gastritis and peptic ulcer for the eradication of Helicobacter pylori we use antibiotics, for the effective treatment it require higher concentration of antibiotics to be maintained in stomach for prolonged period of time. To develop an effective gastroretentive drug delivery system it is need to system remain in the stomach for prolonged period of time. Which it not compatible with system due to high turnover rate of gasrtic mucosa. Now, a lot of work has been done in gastroretentive delivery systems. In the future, it is expected that they will become promising drug delivery system,ultimately leading to improved efficiencies of various types of pharmacotherapies.

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