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A REVIEW ON GASTRORETENTIVE DRUG DELIVERY SYSTEM

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ABSTRACT

The purpose of writing this review was to investigate, compile and present the recent as well as past literatures in more concise way with special focus on approaches which are currently utilized in the prolongation of gastric residence time. One novel approach in this area is Gastro Retentive Drug Delivery System (GRDDSs). GRDDSs can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site. These includes floating system, swelling and expanding system, bio/ mucoadhesive system, high density system and other delayed gastric emptying devices. The present review addresses briefly about the, factors controlling gastric retention, advantages, Disadvantages and applications of gastro retentive drug delivery systems, commonly used drug in formulation of GRDDS, Gastro retentive products available in the market, types of GRDDS.

Keywords: GRDDS, Gastroretentive, Floting System, Gastric Retention.

INTRODUCTION

The goal of any delivery system is to provide a therapeutic amount of drug to proper site in the body to achieve promptly and then maintain a desired drug concentration. Oral drug delivery system is the oldest and most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation. Oral dosage forms are intended for systemic effects resulting from drug absorption through gastro intestinal tract. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT)1, 2.

Anatomy of Stomach:

The stomach is a 'J' shaped enlargement of the GI tract directly inferior to the diaphragm in the epigastric, umbilical and left hypochondria regions of the abdomen. The stomach connects the oesophagus to the duodenum (the first part of the small intestine).

Cardia:

The cardia surrounds the superior opening of the stomach. The cardia is the portion of the stomach surrounding the cardioesophageal junction, or cardic orifice. (the opening of the esophagus into the stomach).

Fundus:

The fundus is the enlarged portion to the left and above the cardiac orifice.

Body:

The body or corpus is the central part of the stomach.

Pylorus:

The region of the stomach that connects to the duodenum is the pylorus. It has two parts, the pyloric antrum, which connects to the body of the stomach and the pyloric canal, which leads into the duodenum. When the stomach is empty, the mucosa lies in large folds, called rugae. The pylorus communicates with the duodenum of the small intestine via a sphincter called the pyloric sphincter. The concave medial border of the stomach is called the lesser curvature and it is in left side of stomach and the right side convex lateral border is called the greater curvature.

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Physiology of Stomach :-

Anatomically the stomach is divided into three regions Fundus, Body and Antrum (pylorus) The proximal part made of fundus and body acts as a reservoir for undigested materials, whereas the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions[3,4]. Gastric emptying occurs in both the fasting and fed states. During the fasting state an interdigestive series of electrical events take place which cycle both through stomach and intestine every 2-3 hrs, which is called as inter digestive myloelectric cycle or migrating myoelectric cycle (MMC) which is further divided in to four phases. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state which is also termed as digestive motility pattern[5].

Phase 1- (Basic phase) last from 30-60 minutes with rare contractions.

Phase 2- (Preburst phase) last for 20-40 minutes with intermittent action potential and contractions.

Phase 3- (Burst phase) last for 10-20 minutes which includes intense and regular contractions for short period.

Phase 4-last for 0-5 minutes and occurs between phase 2 and 1 of 2 consecutive cycles.[5]

Factors affecting gastric retention time of the dosage form.[6-10]

a) Density

The density of the dosage form should be less than that of the gastric contents (1.004g/ml)

b) Size

Dosage form having diameter of more than 7.5mm have more gastric residence time than that of 9.9mm diameter dosage form.

c) Shape of the dosage form

The tetrahedron resided in the stomach for longer period than other devices of similar size. Single or multiple unit formulation multiple unit formulation show a more predictable release profile and insignificant impairing of the performance due to failure of the units allow co-administration of units with different release profile or containing incompatible substances and permit larger margin of safety against dosage form failure compared with single unit dosage form.

d) Fed or unfed state

Under fasting conditions, the GI motility is characterized by periods of strong motar activity that occurs every 1.5-2 hrs. The MMC sweeps undigested material from the stomach and if the timing of the formulation coincides with that of MMC, the GRT of the unit can be very short, however in fast state MMC is delayed and GRT is longer.

e) Nature of meal

Feeding of indigestible polymers or fatty acids can change the motility pattern of the stomach to a fed state,thus decreasing gastric emptying rate and prolonging drug release.

f) Caloric content

GRT can be increased by 4-10 with a meal that is high in protein and fat.

g) Frequency of feed

The GRT can be increasing over 400 min when successive meals given are compared with the single meal due to low frequency of MMC.

h) Gender

Mean ambulatory GRT in male (3.4hrs) is less compared with the age and race matched female counterparts (4.6hrs) regardless of height, weight and body surface.

i) Age

People with age more than 70 have a significant longer GRT. Concomitant drug administration-anticholinergic like atropine and propetheline, opiates like codeine can prolong GRT

Advantages of gastro-retentive drug delivery system.[11-13]

a) Gastro retentive dosage forms minimize the fluctuation of drug concentrations and effect

b) Reduction of fluctuation in drug concentration makes it possible to obtain improved selective receptor activation.

c) The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT by this gastro retentive drug delivery approach in comparison to the administration of non-gastro retentive drug delivery.

d) For drugs with relatively short half-life, sustained release may result in a flip- flop pharmacokinetics and also enable reduced frequency of dosing with improved patient compliance.

e) They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET).

f) Gastro retentive drug delivery can produce prolong and sustain release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.

g) The controlled, slow delivery of drug form Gastro retentive dosage form provides sufficient local action at the diseased site, thus mini mizing or eliminating systemic exposure of drugs. This site specific drug delivery reduces undesirable effects of side effects.

h) Gastro retentive drug delivery can minimize the counter activity of the body leading to higher Drug efficiency.

Disadvantages of Gastro-Retentive Drug Delivery Systems

a) Unsuitable for drugs with limited acid solubility. E.g. Phenytoin.
b) Unsuitable for drugs those are unstable in acidic environment. E.g. Erythromycin.
c) Drugs that irritates or causes gastric lesions on slow release. E.g. Aspirin &NSAID's.
d) Drugs that absorb selectively in colon E.g. Corticosteroid[14].

Applications:

a) Enhanced bioavailability
b) Sustained drug delivery
c) Site specific drug delivery system
d) Absorption enhancement
e) Minimized adverse activity at the colon
f) Reduced fluctuation of drug concentration**.**

POTENTIAL DRUG CANDIDATES FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS

a) Drugs those are locally active in the stomach e.g. misroprostol, antacids etc.
b) Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. L-DOPA, paraaminobenzoic acid, furosemide, riboflavin etc.
c) Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.
d) Drugs that disturb normal colonic microbes e.g.
e) Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide, verapamil HCl.

DRUGS THOSE ARE UNSUITABLE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS

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[7]

TYPES OF GASTRO RETETENTIVE DOSAGES FORM

a) High density system

This approach involves formulation of dosage forms with density that must exceed density of normal stomach content (1.004g/ml). These formulations are prepared by coating drug on a heavy core or mixed with heavy inert material such as iron powder, zinc oxide, titanium dioxide, barium sulphate. The resultant pellets can be coated with diffusion controlled Membrane.[15]

b) Floating or low density system

By virtue of their low densities, floating drug delivery system (FDDS) remain afloat above the gastric contents for prolonged periods of time and provide continuous release of the drug. These systems in particular have been extensively studied because they do not adversely affect the motility of the GIT. Their dominance over the other types of GRRDS is also evident from the large number of floating dosage forms being commercialized and marketed world-wide.[16]

a. Effervescent System

Effervescent systems include use of gas generating agents, carbonates (e.g. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature. These effervescent systems further classified into two types.[17]

i. Gas generating systems

These buoyant delivery systems utilize effervescent reactions between Carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2, which gets entrapped in the jellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over gastric content.[18]

1. Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS)

These are formulated by intimately mixing the CO2 generating agents and the drug within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach.[19]

2. Bilayer Floating Tablets:

These are also compressed tablet shown in fig.5 there are two layers i.e. (1) Immediate release layer (2) Sustained release layer.

3. Multiple Unit Type Floating Pills:

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO_2 within the systems.[20]

4. Ion exchange resin:

Ion-exchange resins, a multiple-unit type of oral floating dosage system has been prepared to prolong gastric emptying time of dosage form. The system is

composed of beads of drug-resin complex, which are loaded with bicarbonate ions and coated with a hydrophobic polymer. The system is so designed that when the beads reach the stomach, chloride ions are exchanged with bicarbonate and drug ions. The generated CO2 is entrapped in the polymeric coated resins and causes the beads to float.[21]

ii. Volatile liquid/vacuum systems

These have an inflatable chamber which contain a liquid e.g. ether, cyclopentane, that gasify at body temperature to cause the inflation of the chamber in the stomach. These systems are osmotically controlled floating system containing a hollow deformable unit. The device may also consist of abioerodible plug made up of Poly vinyl alcohol,Polyethylene etc. that gradually dissolves causing theinflatable chamber to release gas and collapse after apredetermined time to permit the spontaneous ejectionof the inflatable systems from the stomach.[22]

1. Intragastric Floating Gastrointestinal Drug Delivery System:

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporous compartment.[23]

2. Inflatable Gastrointestinal Delivery Systems:

In these systems an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix then encapsulated in a gelatin capsule.[24]

b. **Non-effervescent Systems**

Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment. These are a type of floating gastro retentive drug delivery system in which gel forming hydrocolloids, polysaccharides and matrix forming polymers like polycarbonate, polystyrene, polymethacrylate etc. are used. These are further classified as follows.[25, 26]

I. **Colloid gel based system:**

Hydrodynamically balanced system (HBS), which contains drugs with gel forming hydrocolloids, was first designed by Sheath and Tossounian in 1975. These systems incorporate a high level (20-75%w/w) of one or more gel forming, highly swellable, cellulose type hydrocolloids, polysaccharides and matrix forming polymers. This gel barrier controls the rate of fluid penetration into the device and consequent release of the drug.[27]

II. Microporous compartment system:

This approachis based on the principle of the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls.Theperipheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolved drug.[28]

III. **Floating microspheres:**

Hallow microspheres are considers as most promising buoyant system as they are more advantageous because of central hallow space inside the microsphere.[29]

IV. **Alginate floating beads:**

Talukdar and Fassihi recently developed a multiple-unit floating system based on cross-linked beads. They were made by using Ca^{2+} and low methoxylated pectin (anionic polysaccharide) or Ca^{2+} low methoxylated pectin and sodium alginate.[30]

a) Mucoadhesive systems:

Mucoadhesive drug delivery systems contain a mucoadhesive polymer that adheres to the gastricmucosal surface and prolong its gastric retention in the git. The capability to adhere to the mucus gel layermakesmucoadhesive polymers very useful exicipientsin the GRRDS. These polymers can be natural such assodium alginate, gelatin, guar gum etc semisynthetic polymers such as HPMC, carbopol, sodium carboxymethyl cellulose the adhesion of polymers with mucous membrane may be mediated by hydration bonding, or receptor mediated. In hydration mediated adhesion, the hydrophilic polymer become sticky and mucoadhesive upon hydration[31].

b) Swelling system:

These are the dosage forms, which after swallowing swells to such an extent that their exit from the pylorusis prevented, as a result the dosage form is retained in the stomach for a prolonged period of time. These systems are called as plug –type system as they have the tendency to remain lodged at the pyloric sphincter. Controlled and sustained release may be achieved by selection of proper molecular weight polymer, and swelling of the polymers retard the release[32].

c) Superporous hydrogels:

These are swellable systems that differ from conventional types. Absorption of water by conventional hydrogel is very slow process and several hours may be required to reach the equilibrium states during which the

premature evacuation of the dosage form may occur. Superporous hydrogel have a pore size >100µm which swell to equilibrium size with in aminutes, due to rapid intake of water by capillary wetting through inter connected open pores[33, 34].

d) Magnetic system:

This system is based on the simple idea that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Using a extracorporeal magnet, gastric residence time of the dosage form can be enhanced for a prolonged period of time[35].

Figure 1. Structure of Stomach

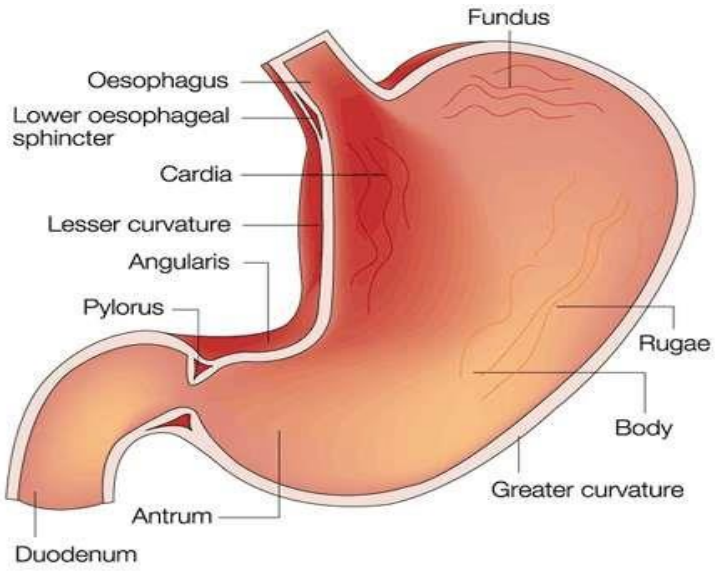

Figure 2. Phase Of Gastric Cycle

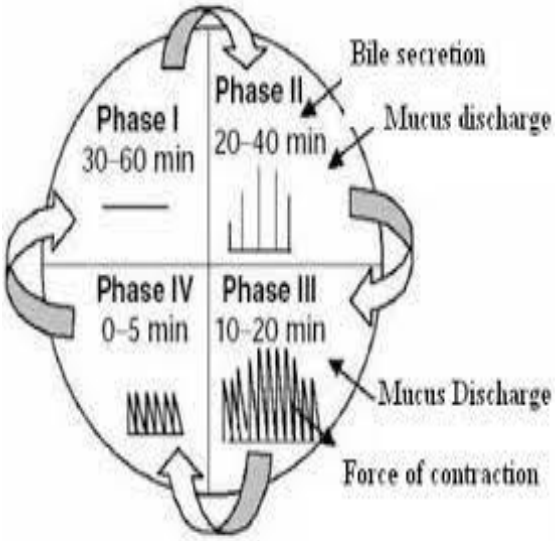

Figure 3. Effervescent (gas generating) systems

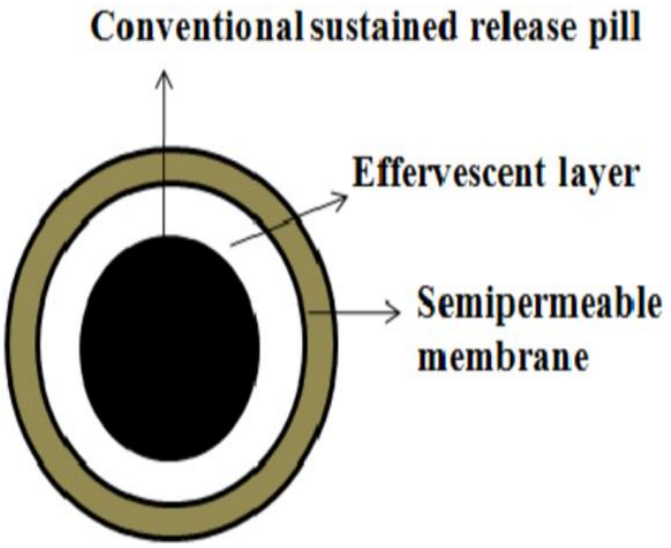

Figure 4. Single layer floating tablets

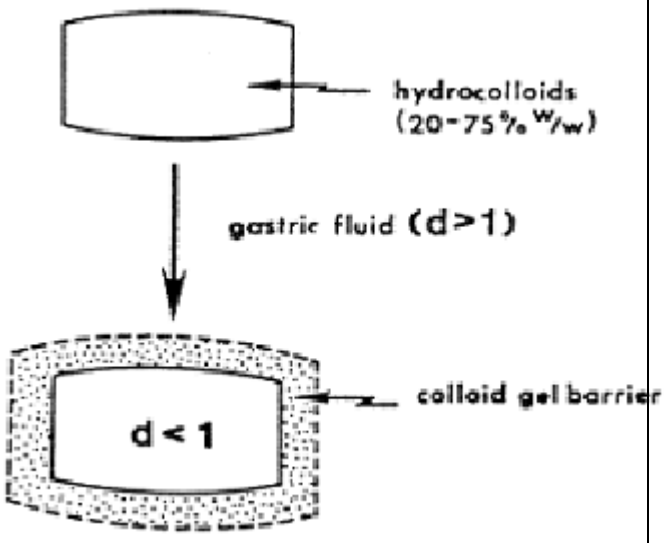

Figure 5. bilayer floating tablets

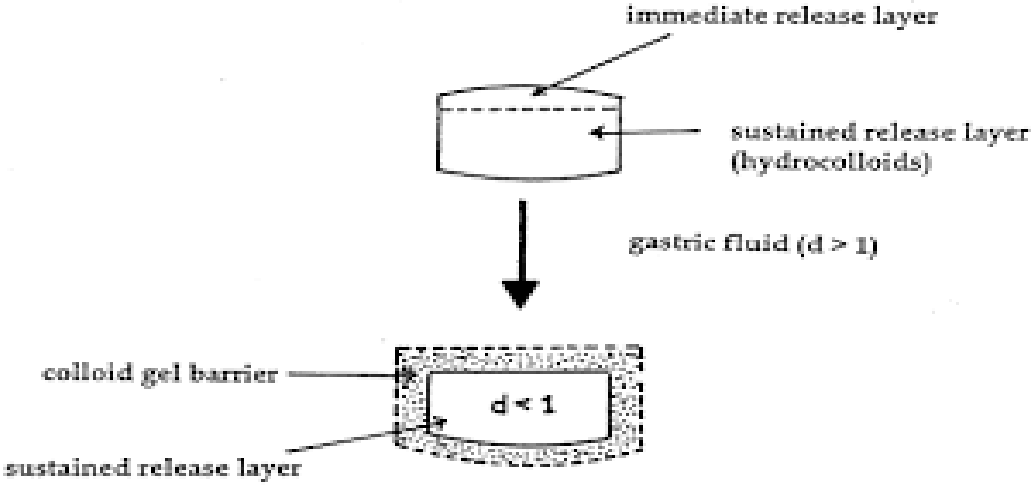

Figure 6. Multiple Unit Type Floating Pills

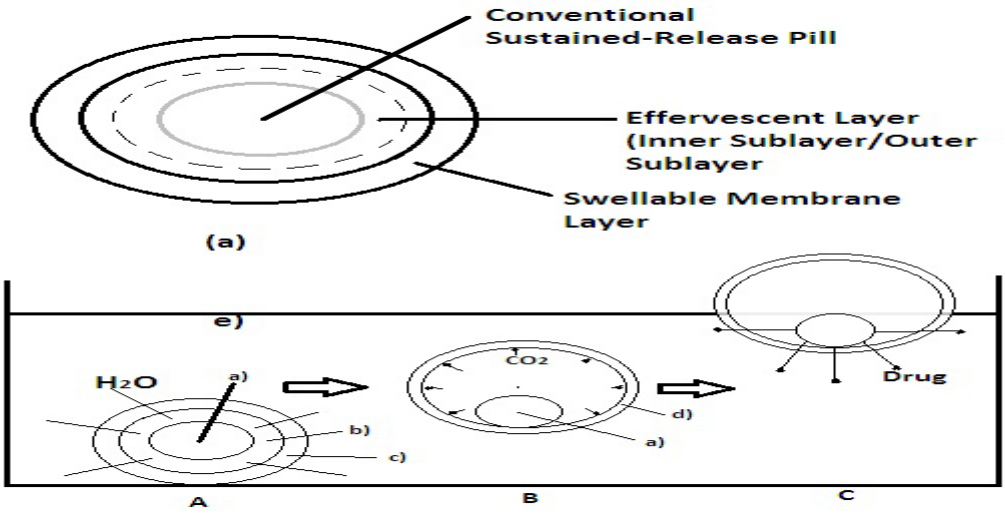

Figure 7. Intragastric floating drug delivery device

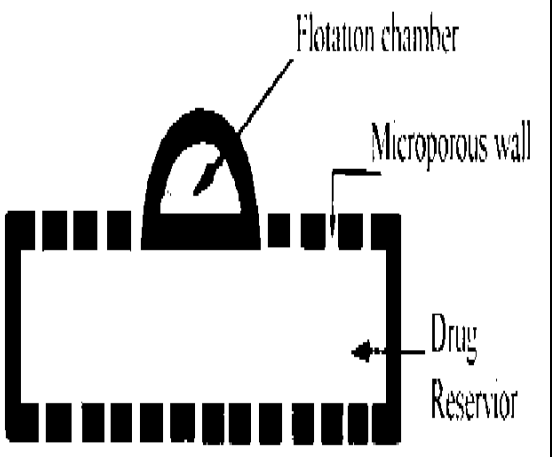

Figure 8. Inflatable Gastrointestinal Delivery Systems

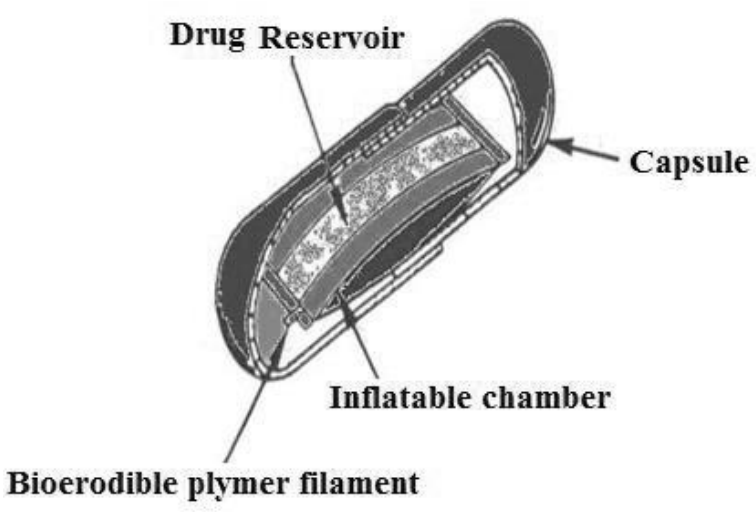

Table: 1 Commonly used drug in formulation of gastro retentive dosages forms.36

Dosages forms	Drug
Floating tablets	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerzine, Chlorpheniramine maleate, Ciprofloxacin, Diltiazem, Fluorouracil, Isosorbidedinitrate, Isosorbidmononitrate, pAminobenzoic acid(PABA), Prednisolone, Nimodipine, Sotalol, Theophylline, Verapamil ChlordiazepoxideHCl, Diazepam,
Floating Capsules	Furosemide, L-DOPA and Benserazide, Nicardipine, Misoprostol, Propranolol, Pepstatin
Floating Microspheres	Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfenadine, Tranilast
Floating Granules	Diclofenac sodium, Indomethacin, Prednisolone
Powders	Several basic drugs
Films	Cinnerzine
Mini tablets	Furosemide
Mucoadhesive nanoparticle	Fluconazole
Tablets	Ranitidine, ofloxacin, propranolol HCL, Norfloxacin, Pregapalin

Table: 2 Gastroretentive products available in the market.37

Brand Name	Active Ingredients
Liquid gaviscon	Alginic acid and sodium bicarbonate
Cipro XR	Ciprofloxacin HCL and betaine
Prazopress XL	Prazosin hydrochloride
Tramadol LP	Tramadol
Baclofen GRS	Baclofen
Gabapentin GR	gabapentin
Cifran OD	ciprofloxacin
Cytotec	Misoprostal
Madopar	L-DOPA and Benserazide
Valrelease	Diazepam
Topalkan	Aluminum -magnesium antacid
AlmagateFlatCoat	Aluminum -magnesium antacid
Liquid Gavison	Aluminium hydroxide
Conviron	Ferrous sulphate

CONCLUSION:

Based on the literature surveyed, it may be concluded that gastro retentive drug delivery offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper gastrointestinal tract (GIT) and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability. Gastro retentive drug delivery technologies have been extensively explored in recent years. Gastroretentive drug delivery systems are the most preferable systems in order to deliver the drugs which have a narrow absorption window near the gastric region. Now a day's numbers of drug delivery devices are being developed which aim at releasing the drug at gastric region.

CONFLICT OF INTEREST: The authors have no conflicts of interest regarding this study.

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