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Review Article

Gastro-Retentive Drug Delivery Systems: A Review

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ABSTRACT

Orally administered drugs having poor Absorption window in the proximal gut can limit the bioavailability. Gastro-retention is one of the approaches to retain drug in GI tract for several hours gives prolong residence time and drug release. GRDDS is helps to improve bioavailability and polymer concentration gives sustained drug delivery. Gastro-retentive dosage forms (GRDF) has received significant interest in the past few decades as they can improve the limitation of most conventional and oral controlled release drug delivery system related to fast gastric-emptying time. Recently oral controlled release drug delivery has been of great interest in pharmaceutical field to achieve improved therapeutic advantages. In recent years, gastro-retentive drug delivery has gained abundant importance for medicine acting regionally within the proximal a part of digestive tract. Various approaches such as floating and non-floating system. GRDDS which are further classified are cited in this review. This article gives an overview on advantages & disadvantages of gastro-retentive drug delivery systems.

INTRODUCTION

Oral administration of drug is most preferable due to its patient compliance and ease of formulation. But it is not effective in cardiovascular and diabetic disease which is severe in population. Due to this reason sustained and prolonged release is necessary but gastric emptying is a major factor which affects drug release and effectiveness. For this purpose drug have to be retain in stomach for absorption. Various routes that are used these include oral, parenteral, topical, nasal, rectal, vaginal, ocular etc. But out of these routes, oral route of drug delivery is considered as the most favoured, because of following reasons:[1,2]

- Ease of administration,
- More flexibility in designing,
- More flexibility in designing,
- Low cost.

The most fashionable approach of oral management led drug delivery is gastro-retentive dose type retain in abdomen prolong amount of drug profile and control the viscus duration within the abdomen.

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GRDDS can be defined as a system which retains in the stomach for a sufficient period of time and releasing active moiety in a controlled manner, and finally metabolized in the body. Over the last 20 years, numbers of GRDDS are designed to prolong GRT. The main aim of preparing GRDDS is to minimize the problem associated with existing oral sustained release dosage form and to develop patient benefited drug delivery.[3]

Gastro-retentive Drug Delivery System

GRDDS is outlined as a system that retains within the abdomen for a ample amount of your time and emotional active moiety in an exceedingly controlled manner, and eventually metabolized within the body. After oral administration, such a delivery system would be retained in stomach for prolonged period of time. It will release the drug in a controlled & prolonged manner, the drug supplied continuously to absorption site in GIT.

Advantages of Gastro-retentive Systems

Better bioavailability profile

GRDDS provides the better bioavailability profile, achieve drug effect and gives desired drug release. Many factors influence the absorption of drug through the GI tract. [4]

Targeted Delivery of Drug
Gastric retention is achieved by the floating system. Floating system is way to achieve targeting effect particularly for the drugs having low/ poor absorption in the proximal small intestine. The slow and controlled delivery of the drug to the stomach allows sufficient levels of the drug to produce local effect. [5]

Improved Patient Compliance
GRDDS may provide an extended action of the drugs. This feature is particularly applicable for the drugs having short half-life. As the system reduce dosing frequency of the drug thereby increasing patient compliance. [6]

Avoiding Activity at the Large Bowl
Gastro-retentive dosage forms permits gastric transit thus minimizes the amount of drug reaching the colon that preventing the drug action at the large bowl, which may be of great significance in certain cases for instance, beta lactam antibiotics when presented to colon results in the development of resistance in microbes. Formulation of beta-lactam antibiotic in Gastro-retentive formulations avoids the emergence of resistance in microbes. [6]

Improves Clinical Outcomes
In some cases the pharmacodynamics of the drug is dependent upon the duration of the time for which the drug remains above critical concentration rather than the peak concentration. thus increasing the time the drug remains above critical concentration. This feature greatly impacts the pharmacological effects and enhances the clinical outcomes of the therapy. [6]

Factors controlling gastric retention of dosage forms [7-9]
There are many parameters related to stomach's anatomy and physiology that are needed to be considered in the development of gastro-retention dosage forms.

Density: A density of < 1.0 gm/ cm3 is required to exhibit floating property. Density of dosage form should be in range of 1g/cm3 to 2.5g/cm3.

Size & shape of dosage form: [18, 19, 20] Shape and size of the dosage forms are important in designing indigestible single unit solid dosage forms. in most cases, the larger the dosage form the greater will be the gastric. Size should be greater than 7.5 mm in diameter.

Single or multiple unit formulation: Multiple unit formulations show a more predictable release profile as compare to the single unit dosage forms. Multiple units are preferable because of predictable release profile, co administration of different units, larger safety margins.

Fed or unfed state: Under fasting conditions: gi motility is characterized by periods of strong motor activity or the migrating myoelectric complex (mmc) that occurs every 1.5 to 2 hours. However, within the fed state, MMC is delayed and GRT is significantly longer.GRT is longer in fed states.

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

Caloric content: GRT may be accumulated by four to ten hours with a meal that's high in proteins and fats.

Frequency of feed: The GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC.

Gender: Male- 3.4±0.6hr to Female-4.6±1.2hr.

Age: Elderly people, especially those over 70, have a significantly longer GRT.

Posture: GRT can vary between supine and upright ambulatory states of the patient. Varies between spine and upright ambulatory states.

Conventional Drug Delivery Systems Vs Gastro-retentive Drug Delivery
Drug is taken many times a day; the conventional drug delivery system retains the concentration of drug in the effective therapeutic range which is necessary for the management of a disease. A successful oral drug delivery system is dependent upon its absorption in gastrointestinal tract.[10]

Drugs those are unsuitable for GRDDs [11]
1. Drugs that have very limited acid solubility e.g. Phenytoin.
2. Medicine that suffers instability within the viscus atmosphere e.g. E-Mycin, Rabeprazole, Clarithromycin, etc.

3. Drugs intended for selective release in the colon e.g. 5-amino salicylic acid.

Table 1: Comparison between Conventional drug delivery systems and Gastro-retentive Drug delivery systems

Sr. No.	Parameters	Conventional drug delivery system	Gastro-retentive drug delivery system
1	Patient compliance	Poor	Better
2	Dose dumping	Dose dumping risk is higher	No risk
3	Drug having low absorption in small Intestine	Not appropriate	Appropriate
4	Drugs acting locally in the Stomach	Not very much useful	Much useful
5	Toxicity	Greater susceptibility towards toxicity.	Low susceptibility.
6	Drugs with poor solubility at higher pH	Not much Beneficial	Much beneficial
7	Drug that undergo degradation in colon	Not much Beneficial	Much beneficial
8	Drugs that have fast GIT Absorption	Not much Beneficial	Much beneficial

Polymers and substances utilized in gastro retentive systems

A polymer is basically described as a macromolecule and comprises of many repetitive small units. They are of two types, natural and synthetic polymers. Because of their extensive range of properties, these two types of polymers play very important role.

Approaches to the GRDDS

Non-floating system

a. High Density (Sinking) Drug Delivery System [12]

In this approach formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulfate, zinc oxide and titanium oxide so that the density of the formulation exceeds the density of the normal gastric content. On density, the GI transit time of pellets can be extended from an average of 5.8 to 25 hours. These systems that have a density of ~3 g/cm3 square measure maintained within the rugae of the abdomen and square measure capable of withstanding its peristaltic movements. Above a threshold density of 2.4–2.8 g/cm3, such systems can be retained in the lower part of the stomach. The only major drawbacks with such systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and to achieve the required density of 2.4–2.8 g/cm3. Diluents such as barium sulphate (density = 4.9), zinc oxide, titanium dioxide and iron powder may be used to manufacture such high-density formulations. But effectiveness of this system in human beings was not observed and no formulation has been marketed.

Table 2: Polymers and substances utilized in Gastro-retentive systems

Sr. No.	Structural component	Examples
1	Polymers (Hydrocolloids)	Acacia, Hydroxy Propyl Cellulose (HPC),Chitosan, Agar, Gellan gum(Gelrite®) Casein, Bentonite, Sodium Carboxy Methyl Cellulose (CMC) Veegum, Hydroxy Propyl Methyl Cellulose (HPMC) (K4M, K100M and K15M), , Pectin, Methyl Cellulose (MC).
2	Inert fatty constituents	Fatty acids Long chain fatty alcohols, Bees wax, Gelucires® 39/01 and 43/01 Fatty acids,
3	Effervescent materials	Tartaric acid, Sodium bicarbonate, Di-SGC (Di-Sodium Glycine Carbonate), Citric acid, Tartaric acid, CG (Citroglycine).
4	Release rate enhancers	Lactose, Mannitol
5	Retardants of Release rate	Talc Di-calcium phosphate, Magnesium stearate.
6	Buoyancy enhancing agents	Ethyl cellulose
7	Materials with Low density	Polypropylene foam powder (Accurel MP 1000®)

b. Bioadhesive or mucoadhesive system [13]

Bioadhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a site specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial cell surface or mucin in the stomach. The gastric retention time is extended by adhering the bioadhesive system to gastric mucosa membrane. The adherence of the delivery system to the gastric wall increases residence time thereby improving bioavailability. The chemicals used for the mucoadhesion purpose include polycarbophil, carbopol, lectin, chitosan, carboxy methyl cellulose, gliadin etc. Novel adhesive material derived from fimbrae of

bacteria or its synthetic analogues have also been tried for the attachment to the gut. However, gastric mucoadhesive force does not tend to be strong enough to resist the propulsion force of stomach wall. Continuous production of mucus and dilution of the gastric content is another limitation for such type of system. Many investigators have tried out a synergistic approach between floating and bioadhesion system.

The binding of polymers to the mucin– epithelial surface can be subdivided into three broad categories: hydration-mediated adhesion, bonding mediated adhesion, and receptor-mediated adhesion.

c. Hydration – mediated adhesion

Certain hydrophilic polymers have the tendency to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties.

d. Bonding –mediated adhesion

The adhesion of polymers to a mucus or somatic cell surface involves varied bonding mechanisms as well as physical, mechanical and chemical bonding. Physical or mechanical bonds can result from deposition and inclusion of the adhesive material in the crevices of the mucusa. Chemical bonds may be either covalent (primary) or ionic (secondary) in nature. Secondary chemical bonds consist of dispersive interactions (i.e. Vander Waals interactions) and stronger specific interactions such as hydrogen bonds.

e. Receptor – mediated adhesion

Certain polymers have the ability to bind to specific receptor sites on the cell surface. The receptor mediated events serves as a potential approach inbio/muco- adhesion, hence enhancing the gastric retention of dosage forms. Poly(acrylic acid) (Carbapol, polycarbophill), Chitosan, Gantrez (Polymethyl vinylether/maleic anhydride copolymers), chollestyramine, tragacanth, sodium alginate, sucralfate, polyethylene glycol, dextran and polylactic acid are commonly used material for bioadhesion.

Limitation

Bioadhesion is difficult to maintain due to rapid turnover of mucin in GIT.

f. Magnetic system [14]

In this system, the dosage form contains a small magnet and another magnet is placed on the abdomen over the position of the stomach. The external magnet should be placed with a degree of precision which may decrease the patient compliance.

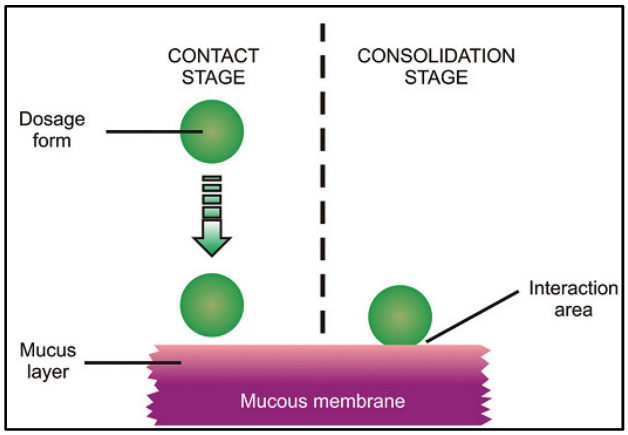

Figure 1: Bioadhesive system.

g. Expandable, unfoldable and swellable systems [15, 16, 17]

A dose type within the abdomen can face up to stomachal transit if it larger than pyloric valve. The drug delivery system unfolds and increases in size and it remains lodged at sphincter prevents its exit from the stomach. However, the dose kind should be sufficiently small to be engulfed, and should not cause stomachal obstruction either one by one or by accumulation. Thus, their configurations are required to develop an expandable system to prolong GRT:

1) A small configuration for oral intake,
2) An expanded gastro-retentive form, and
3) A final small form enabling evacuation

Following drug release from the device. Thus, gastro-retention is improved by the combination of substantial dimension with highrigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach.

Unfoldable systems are made of biodegradable polymers. They are available in different geometric forms like tetrahedron, ring or planner membrane bioerodible polymer compressed within a capsule which extends in the stomach. The swelling is usually results from osmotic absorption of water. Expandable systems have some drawbacks like problematical storage of much easily hydrolysable, biodegradable polymers relatively short-lived mechanical shape memory for the unfolding system most difficult to industrialize and not cost effective.

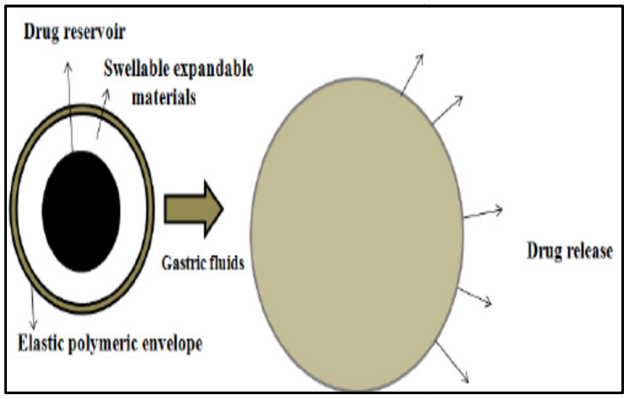

Figure 2: Unfoldable and swellable systems

Floating Drug Delivery System

a. Effervescent System

Floatation of a drug delivery system in the stomach can be achieved by incorporating a floating chamber filled with vacuum, air, or an inert gas. This system consists of the swellable polymers like chitosan and effervescent substance like sodium bicarbonate, disodium glycine carbonate, cytroglycine, citric acid and tartaric acid. When the system comes in contact with gastric fluid, it releases carbon dioxide causing the formulation to float in the stomach as a result of an effervescent reaction between organic acids and carbonate- bicarbonate salts.

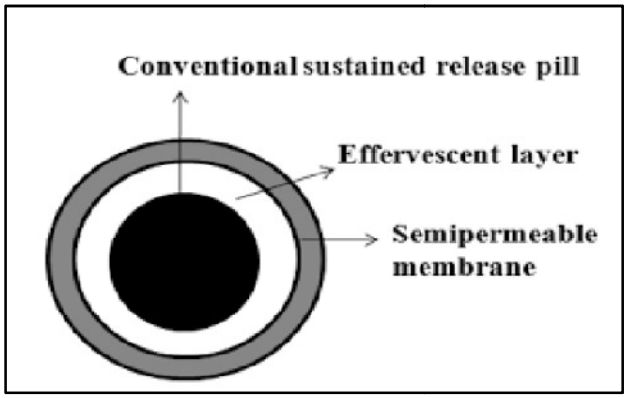

Figure 3: Effervescent system

The best magnitude relation of acid and sodium hydrogen carbonate for gas generation is rumored to be zero. This system is further divided as single unit matrix tablets or multiple unit pills. Single unit matrix tablet may be single or multilayer type. Floating system with ion exchange resins has also been used Effervescent system and drug unharness from such system is shown in Fig. 3 and 4 respectively. These devices contain a hollow deformable unit that converts from a collapsed to an expanded position and returns to the collapsed position after a predetermined amount of time to permit the spontaneous ejection of the system from the stomach.

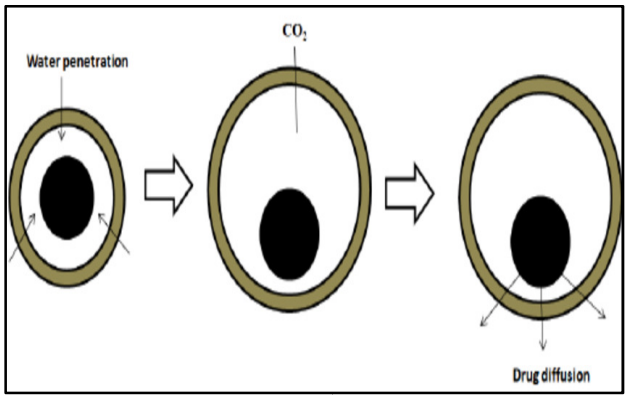

Figure 4: Drug release from Effervescent system

b. Non-effervescent system

Noneffervescent systems contains a high level (20–75% w/w) of 1 or additional gel-forming, extremely swellable, plastic hydrocolloids (e.g., hydroxyethyl polysaccharide, hydroxypropyl polysaccharide, hydroxypropyl methylcellulose (HPMC), and metal carboxy methylcellulose), polysaccharides, or matrix forming polymers (e.g., polycarbophil, polyacrylates, and polystyrene) into tablets or capsules. After oral administration this dose type swells in touch with viscous fluids and attains a bulk density of but one. Polysaccharides and polymers form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. The air entrapped inside the swollen matrix imparts buoyancy to the indefinite quantity type and permits sustained unharness of drug through the thick mass.

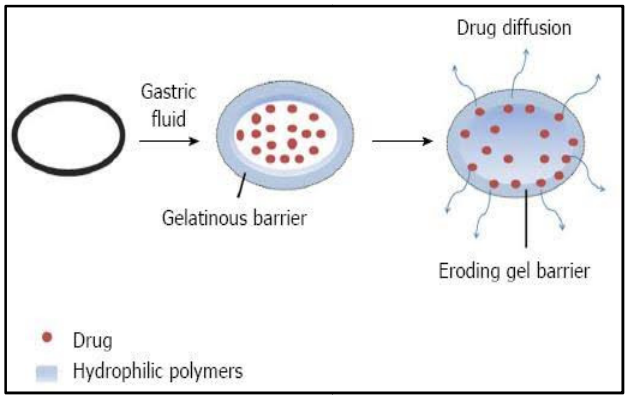

Figure 5: Gastric retention of highly swellable

Non-effervescent system can be further divided in to: hydrodynamically balanced system, microbaloons, alginate beads and microporous compartment.

c. Hydrodynamically balanced system

The hydrodynamically balanced system (HBS) was first designed by Sheth and Tossounian. HBS contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This system contains one or more gel forming cellulose type hydrocolloid e.g., hydroxypropyl methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, agar, carrageen or alginic acid. It also contains matrix forming polymers such as polycarbophil, polyacrylate and the capsules speedily dissolve within the stomachal fluid, and association and swelling of the surface compound turn out a floating mass. Capsules rapidly dissolve in the gastric fluid, and hydration and swelling of the surface polymer produce a floating mass. Drug release is controlled by the formation of hydrated boundary at the surface. Continuous erosion of the surface allows water penetration to the inner layer, maintaining surface hydration and buoyancy. The main drawback is the passivity of operation. It depends on the air sealed in the dry mass center following hydration of gelatinous surface layer and hence the characteristics and amount of polymer. Effective drug delivery depends on the balance of drug loading and effect of polymer on its release profile.

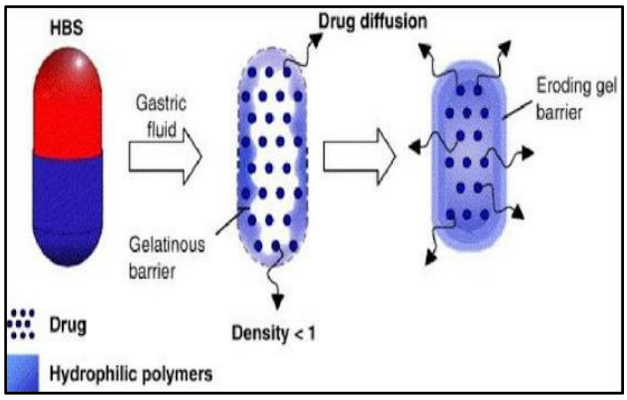

Figure 6: Hydrodynamically balanced system

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d. Microbaloons or hollow microspheres

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells, are prepared by emulsion-solvent diffusion method. The steps involved in this method are summarized in Fig.7. The ethanol: dichloromethane solution (1:1) and an acrylic polymer are poured into an agitated aqueous solution of polyvinyl alcohol at 40°C. The gas phase generated in the dispersed polymer droplet by the evaporation of dichloromethane form an internal cavity in the microsphere of the polymer with the drug. The microballoons float unceasingly over the surface of acidic dissolution media containing wetting agent for quite twelve hours.

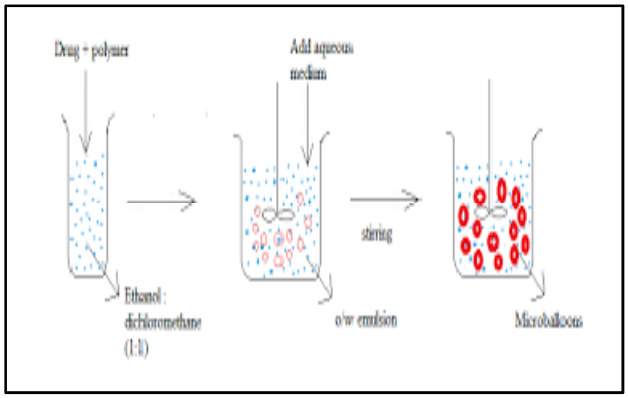

Figure 7: Preparation of microballoons

e. Alginate beads

Freeze dried calcium alginates have been used to develop multiunit floating dosage forms. By dropping sodium alginate solution into aqueous solution of calcium chloride spherical beads of about 2.5 mm diameter can be prepared. These beads are separated and air dried. This results in the formation of a porous system which remains buoyant in the stomach.

f. Microporous compartment

In this system, drug reservoir is encapsulated inside a microporous compartment having pores along its top and bottom walls (Fig. 8). The floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug in abdomen and proximal a part of the little gut for absorption.

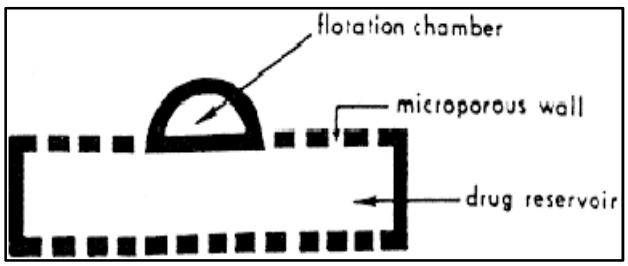

Figure 8: Microporous compartment

Rational for the use of GRDDS [17]

- Improved bioavailability
- Improved half life
- Improved stability
- Increased solubility
- Sustained/ prolonged release
- Reduce drug waste
- Increased therapeutics efficiency
- Patient compliance
- Recused frequent dosing
- Increase gastric retention time

Limitations

1. The adequate amount of the fluid must be present in the stomach, for the administration of the floating dosage forms requires normally 200-250ml fluid in the stomach, [62] to retain the buoyancy outcome effect of the formulation.
2. The drugs e.g., protein in nature having solubility/stability incompatibilities in the gastric fluids and drugs e.g., biomolecules causing gastric irritation are not good to be formulated in this type of drug delivery systems.
3. Drugs degraded by first pass effect and have good absorption in the whole gastric tract are not right choice for the floating drug delivery system due to their ability to reduce the gastric emptying that in turn reduce the bioavailability systematically.

CONCLUSION

This article provides information regarding the gastro-retentive drug delivery systems. The above information shows that gastro-retentive drug delivery systems have great potentials, for formulating both hydrophobic and hydrophilic active substance into promising deliverable drugs. Many approaches with use of different polymers and other constituents can produce different range of gastro-retentive systems. Especially the floating drug delivery system is the most widely used in gastro-retentive dosage forms.

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