APPROACHES FOR GASTROTENTIVE DRUG DELIVERY SYSTEMS

*Vinod K.R.¹, Santhosh Vasa¹, Anbuazaghan S², David Banji¹, Padmasri A¹, Sandhya S¹

¹Nalanda College of Pharmacy, Nalgonda, A.P. India
²Chilkur Balaji College of Pharmacy, Hyderabad, A.P., India.

ABSTRACT: Much attention have been focused in pharmaceutical research in the area of gastroretentive oral drug delivery systems. Henceforth a wide spectrum of dosage forms have been developed for drugs which are unstable in alkaline pH, soluble in acidic pH, having a narrow absorption window, site of action specific to stomach. This article provides the entire classification of gastroretentive systems, formulation considerations for developing gastroretentive systems, factors affecting gastroretentive systems, merits and demerits, applications in pharmacy and a comparative diagrammatic representation limelight this article. Those gastroretentive systems which depend on liberation of carbondioxide show poor patient compliance because of flatulence and belching.

INTRODUCTION

The oral ingestion is the predominant and most preferable route for drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drug. Time controlled oral drug delivery systems offer several advantages over immediate-release dosage forms, including the minimization of fluctuations in drug concentrations in the plasma and at the site of action over prolonged periods of time, resulting in optimized therapeutic concentrations and reduced side effects; a reduction of the total dose administered (while providing similar therapeutic effects) and a reduction of the administration frequency leading to improved patient compliance (Alexander, 2006). The real issue in the development of oral controlled release dosage form is to extend the duration of action of drug from the small intestine. For the successful performance of oral CRDDS the drug should have good absorption throughout the GIT, preferably by passive diffusion (Moes, 1993).
Gastroretentive dosage forms are drug delivery systems which remain in the stomach for an extended period of time and allow both spatial and time control of drug liberation. Basically gastroretentive systems swells following ingestion and is retained in the stomach for a number of hours, while it continuously releases the incorporated drug at a controlled rate to preferred absorption sites in the upper intestinal tract. Their application can be advantageous in the case of drugs absorbed mainly from the upper part of GIT or are unstable in the alkaline medium of distal intestinal regions. They can also be used beneficially in the local therapy of the stomach.

**Drugs that would benefit from GRDDS**

CNS drugs (for Parkinson disease, epilepsy, Alzheimer and migraine), Anti-viral products (for HIV, herpes and hepatitis) and certain antibiotics, Anti-hypertension drugs, Anti-diabetic agents for Type 2 diabetes, Drugs for local treatment of GI infections and gastric enzyme replacement (N.K. Jain).

**ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEM**

Gastroretentive drug delivery systems have numerous advantages listed below

The principle of HBS can be used for any particular medicament or class of medicament. The HBS formulations are not restricted to medicaments, which are principally absorbed from the stomach. Since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine e.g. Chlorpheniramine maleate. The HBS are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids. The efficacy of the medicaments administered utilizing the sustained release principle of HBS has been found to be independent of the site of absorption of the particular medicaments. Administration of a prolonged release floating dosage form tablet or capsule will result in dissolution of the drug in gastric fluid. After emptying of the stomach contents, the dissolved drug available for absorption in the small intestine. It is therefore expected that a drug will be fully absorbed from the floating dosage form if it remains in solution form even at alkaline pH of the intestine. When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhoea, poor absorption is expected under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response. Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Many drugs categorized as once-a-day delivery have been demonstrated to have sub optimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine. (Gutierrez et al., 2003). (Figure-1)
DISADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEM

There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions and slow release of such drugs in the stomach is unwanted. Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems. Furthermore, other drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system (Hou et al., 2003). Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted exactly or accurately. Gastric emptying of floating forms in supine subjects may occur at random and become highly dependent on the diameter. Therefore, patients should not be dosed with floating forms just before going to bed. High variability in gastric emptying time due to variations in emptying process. Unpredictable bioavailability.
Formulation considerations for GRDDS

It must be effective retention in the stomach to suit for the clinical demand

1) It must have sufficient drug loading capacity
2) It must be control the drug release profile
3) It must have full degradation and evacuation of the system once the drug release is over
4) It should not have effect on gastric motility including emptying pattern
5) It should not have other local adverse effects (Davis, 2005).

Requirements for gastric retention

From the discussion of the physiological factors in the stomach it must be noted that to achieve gastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms. To function as a gastric retention device, it must be resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease.

Factors affecting the gastroretentive system

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include use of floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Most of these approaches are influenced by a number of factors that affect their bioavailability and efficacy of the gastroretentive system (Sanjay et al., 2003).

Density – Gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density.

Size – Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.

Shape of dosage form – Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.

Single or multiple unit formulation – Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.
Fed or unfed state – Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer. (Caldwell et al., 1998; Murthy et al., 2000).

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 can be increased by 4 to 10 hours with a meal that is high in proteins and fats (Marvola et al., 1989) (Mojaverian et al., 1988).

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 – Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.

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.

Concomitant drug administration – Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride can affect floating time.

Biological factors – Diabetes and Crohn’s disease, etc.

**Figure. 2: Invivo picturisation of various gastro retentive formulations**
Approaches to gastric retention

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas generating systems) (Deshpande et al., 1997). Swelling and expanding systems (Urquhart and Theeuwes, 1984; Mamajek, 1980). Mucoadhesive systems (Lenaerts, 1990; Lehr, 1994). High density systems (Caldwell et al., 1988). Modified shape systems (Groning and Heum, 1989; Bechgaard and Ladefoged, 1978). Gastric emptying delaying devices and co-administration of gastric delaying drugs. Among these, the floating dosage forms have been used most commonly.

Floating DDS (FDDS), with low density providing sufficient buoyancy to float over the gastric contents, Bioadhesive systems, enabling the localized retention of the system in the stomach, Swelling and expanding systems, preventing transit from the gastric sphincter, High density system, remaining in the stomach for longer period of time by sedimenting to the folds of stomach, Superporous hydrogels, and Modified-shaped system

A number of other methods like use of passage-delaying agents, magnetically controlled systems and combination methods like floating-bioadhesive systems.

Floating drug delivery systems

The concept of FDDS was described in the literature as early as 1962. FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents the drug is released slowly at the desired rate from the system. This results in an increased GRT and a better control of fluctuations in plasma drug concentration. The device must have sufficient structure to form a cohesive gel barrier, it must maintain an overall specific gravity lower than that of gastric contents (1.004-1.010) and it should dissolve slowly enough to serve as a drug reservoir.

Types of floating drug delivery systems

Based on the mechanism of buoyancy and two distinctly different technologies have been utilized in the development of FDDS. 1) Non- Effervescent FDDS 2) Effervescent FDDS

1) Non-Effervescent FDDS

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as Chitosan and carbopol.
The various types of this system are as:

A. Single Layer Floating Tablets

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity. They are formulated by intimate mixing of drug with low-density enteric materials such as CAP, HPMC.

B. Bi-layer Floating Tablets

A bi-layer tablet contain two layer one immediate release layer which releases initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach (Oth et al., 1992).

C. Alginate Beads

Multi-unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours (Katayama et al., 1999).

D. Hollow Microspheres

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 40°C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer with drug. The microballoons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours in vitro (Kawashima, 1992).

2) Effervescent System

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO₂) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporates at body temperature. These effervescent systems further classified into two types. 1. Gas generating systems, 2. Volatile Liquid/Vacuum Containing Systems.
1. Gas Generating Systems

A. Tablets

Floating bilayer tablets with controlled release for furosemide were developed by Ozdemir et al., 2000. The low solubility of the drug could be enhanced by using the kneading method, preparing a solid dispersion with β cyclodextrin mixed in a 1:1 ratio (Singh and Brahma, 2000). One layer contained the polymers HPMC K4M, HPMC K100M and CMC (for the control of the drug delivery) and the drug. The second layer contained the effervescent mixture of sodium bicarbonate and citric acid. The in vitro floating studies revealed that the lesser the compression force the shorter is the time of onset of floating, i.e., when the tablets were compressed at 15 MPa, these could begin to float at 20 minutes whereas at a force of 32 MPa the time was prolonged to 45 minutes. Radiographic studies on 6 healthy male volunteers revealed that floating tablets were retained in stomach for 6 hours and further blood analysis studies showed that bioavailability of these tablets was 1.8 times that of the conventional tablets. On measuring the volume of urine the peak diuretic effect seen in the conventional tablets was decreased and prolonged in the case of floating dosage form.

B. Floating capsules

Floating capsules are prepared by filling with a mixture of sodium alginate and sodium bicarbonate. The systems were shown to float during in vitro tests as a result of the generation of CO₂ that was trapped in the hydrating gel network on exposure to an acidic environment.

C. Multiple unit type floating pills

The system consists 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 temp, 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 CO₂ within the system.

D. Floating system with Ion-Exchange resins

A floating system using ion exchange resin that was loaded with bicarbonate by mixing the beads with 1M sodium bicarbonate solution (Shweta Arora et al., 2005). The loaded beads were then surrounded by a semipermeable membrane to avoid sudden loss of CO₂. Upon coming in contact with gastric contents an exchange of chloride and bicarbonate ions took place that resulted in CO₂ generation thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads. The in vivo behavior of the coated and uncoated beads was monitored using a single channel analyzing study in 12 healthy human volunteers by gamma radio scintigraphy. Studies showed that the gastric residence time was prolonged considerably (24 hours) compared with uncoated beads (1 to 3 hours).
2. Volatile Liquid / Vacuum Containing Systems

A. Intra-gastric 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 micro-porous compartment.

Table 1: Differentiation between floating and muco adhesive delivery systems

<table>
<thead>
<tr>
<th>Floating drug delivery system</th>
<th>Mucoadhesive drug delivery system</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.</td>
<td>1. The term bioadhesion is defined as adhesion to biological surface i.e. mucus and/or mucosal surface. In instances when the polymeric system interacts with mucus layer only, it is referred as mucoadhesion.</td>
</tr>
<tr>
<td>2. Floating of the dosage form can be achieved by two means i.e. either incorporating a gas generating system or volatile liquid/vacuum system.</td>
<td>2. Mucoadhesion can be achieved by different mucin-polymer interactions such as Wetting and swelling of the polymer to permit intimate contact with the biological tissue/ interpenetration of bioadhesive polymer chains and entanglement of polymer and mucin chains/ formation of weak chemical bonds/ sufficient polymer mobility to allow spreading/ water transport followed by mucosal dehydration.</td>
</tr>
</tbody>
</table>

Examples: Valrelease®, Madopar® HBS, Topalkan®

B. 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, encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid.
C. Intragastric osmotically controlled drug delivery system

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semipermeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semipermeable membrane into osmotically active compartment to dissolve the osmotically active salt. The osmotic pressure thus created acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate drug release through the delivery orifice.

The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.

Bioadhesive drug delivery system

The term bioadhesion is defined as adhesion to biological surface i.e. mucus and/or mucosal surface. In instances when the polymeric system interacts with mucus layer only, it is referred as mucoadhesion. In order to develop an ideal oral bioadhesive system, it is important to have a through understanding of mucosa, bioadhesive polymers and mucin-polymer interactions in the physiological environment.

Intestinal mucosa is composed of high molecular weight glycoproteins hydrated and covering the mucosa with a continuous adherent blanket. Mucin glycoproteins are rich with fucose and sialic acid groups at the terminal ends which provide a net negative charge in the acidic environment. The thickness of the mucin gel layer varies in different regions of the GIT with thickness ranging between 50-500 μm in stomach to 15-150μm in the colon. Cohesion of the mucin gel is dependent upon the glycoprotein concentration. The mucus layer is created biologically to play a number of important functions of protecting the underlying tissues from various diffusing/corrosive elements such as enzymes, acid and other toxic molecules. Also being a visco-elastic gel, it helps in the passage of food over the epithelium, thereby minimizing potential erosive damages. The mucus layer, in addition to providing protection, provides a barrier to drug absorption.

Various investigators have proposed different mucin-polymer interactions, such as
- Wetting and swelling of the polymer to permit intimate contact with the biological tissue
- Interpenetration of bioadhesive polymer chains and entanglement of polymer and mucin chains.
- Formation of weak chemical bonds
- Sufficient polymer mobility to allow spreading
- Water transport followed by mucosal dehydration (Lehr, 1992; Mortazavi, 1993).
As the mucus layer comes into contact with bioadhesive coated system, various non-specific (Vander Waals, hydrogen bonding and/or hydrophobic interactions) or specific interactions occur between the complimentary structures. However, these interactions last only until the turnover process of mucin and, in order for a bioadhesive system to be successful; it should release its drug contents during this limited adhesion time.

Raft-forming systems

Here, a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO₂ bubbles on contact with gastric fluid. Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastro esophageal reflux treatment as with liquid gaviscon.

Low density systems

Gas-generating systems inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. Low-density systems (<1 g/cm³) with immediate buoyancy have therefore been developed. They are made of low-density materials, entrapping oil or air. Most are multiple unit systems, and are also called ‘microballoons’ because of the low-density core (Sato and Kawashima, 2004). Generally, techniques used to prepare hollow microspheres involve simple solvent evaporation or solvent diffusion methods. Polycarbonate, Eudragit S, cellulose acetate, calcium alginate, agar and low methoxylated pectin are commonly used as polymers. Buoyancy and drug release are dependent on quantity of polymer, the plasticizer–polymer ratio and the solvent used.

Expandable systems

A dosage form in the stomach will withstand gastric transit if it is bigger than the pyloric sphincter (Caldwell et al., 1988). However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, three configurations are required, a small configuration for oral intake, an expanded gastroretentive form and a final small form enabling evacuation following drug release. Unfoldable systems are made of biodegradable polymer; the concept is to make a carrier, such as a capsule, incorporating a compressed system, which extends in the stomach. Caldwell et al., 1988 proposed different geometric forms (tetrahedron, ring or planar membrane (4-lobed, disc or 4-limbed cross form) of biodegradable polymer compressed within a capsule.

Swellable System

Swellable systems are also retained because of their mechanical properties. The swelling usually results from osmotic absorption of water. The dosage form is small enough to be swallowed, and swells in gastric liquids, the bulk enable gastric retention and maintains the stomach in a ‘fed’ state, suppressing housekeeper waves.
Superporous hydrogels

Although these are swellable systems, they differ sufficiently from the conventional types to warrant separate classification (Chen and Park, 2000) with pore size ranging between 10 nm and 10 μm. Absorption of water by conventional hydrogel is a very slow process and several hours may be needed to reach an equilibrium state, during which premature evacuation of the dosage form may occur. Superporous hydrogel, average pore size > 100 μm, swell to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores. Moreover they swell to a large size (swelling ratio 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contractions. This is achieved by a co-formulation of a hydrophilic particulate material, Ac-Di-Sol (crosscarmellose sodium).

Magnetic system

These systems appear as small gastroretentive capsules containing a magnetic material, whose elimination from the stomach is prevented by the interaction with a sufficiently strong magnet applied to the body surface in the region of the stomach. Despite numerous reports about successful tests, the real applicability of such systems is doubtful because the desired results can be achieved only provided that the magnet position is selected with very high precision. Probably, the development of new conveniently applied magnetic field sources will improve this concept.

Self-unfolding systems

The self-unfolding systems are capable of mechanically increasing in size relative to the initial dimensions. This increase prevents the system from passing via the pylorus and provides for its prolonged stay in the stomach. A drug can be either contained in a polymeric composition of the gastroretentive system or included as a separate component. Several methods were suggested to provide for the self-unfolding effect.

(1) The use of hydrogels swelling in contact with the gastric juice.
(2) Osmotic systems, comprising an osmotic medium in a semipermeable membrane.
(3) Systems based on low-boiling liquids converting into a gas at the body temperature.

High density systems

Gastric contents have a density close to water (1.004 g/cm³). When the patient is upright small high-density pellets sink to the bottom of the stomach where they become entrapped in the folds of the antrum and withstand the peristaltic waves of the stomach wall. A density close to 2.5 g/cm³ seems necessary for significant prolongation of gastric residence time and barium sulphate, zinc oxide, iron powder, titanium dioxide are used as excipients.
CONCLUSION

Gastroretentive drug delivery systems have emerged as a current approaches of enhancing bioavailability and controlled delivery of drugs that exhibit an absorption window. Gastroretentive drug delivery approaches comprised mainly of floating, bioadhesive, swelling, magnetic, and high density systems. These systems not only provide controlled release of the drug but also present the drug in an absorbable form at the regions of optimal absorption. All these drug delivery systems have their own advantages and drawbacks. To design a successful GRDDS, it is necessary to take into consideration the physicochemical properties of the drug, physiological events in the GIT, formulation strategies, and correct combination of drug and excipients.

REFERENCES


Available online at www.ijabpt.com