



AN OVERVIEW ON GASTRORETENTIVE DRUG DELIVERY SYSTEM

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Received 19 March, 2014; Revised 10 July, 2014

ABSTRACT

Oral controlled release and site specific drug delivery system has been of great interest in pharmaceutical field to achieve improved therapeutic advantage. Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. Gastro retentive drug delivery system is one of such novel approaches to prolong gastric residence time, thereby targeting site specific drug release in the stomach for local or systemic effects. This approach is useful particularly for the drugs which have narrow absorption window in the upper part of gastro intestinal tract. Various approaches of gastro retentive drug delivery system, such as floating and non-floating, have been discussed in this review. This review also gives an overview of merits, demerits and evaluation parameters of gastro retentive system.

Key words: Gastro retentive drug delivery system, non-floating system, floating system, evaluation parameters

INTRODUCTION

Despite the tremendous advancement in drug delivery, oral route is the most preferred route to the systemic circulation due to the ease of administration, low cost of drug, patient compliance and flexibility in formulation. About 90% of all drugs used to produce systemic effects are administered by oral route. Of the drugs that are administered orally, solid oral dosage forms represent the preferred class of products [1]. Tablets are the most common type of solid dosage form in contemporary use which is classified based on the drug release pattern, i.e. conventional immediate release and modified release [2]. The conventional instant release tablets have many drawbacks including non-site specific drug release. However, many drugs are absorbed from specific sites and they require release at that site only for better absorption [3].

Drug absorption in the gastrointestinal tract is a highly variable procedure and it depends upon the factors such as gastric emptying process, gastrointestinal transit time of dosage forms, drug release from the dosage form, and site of absorption of drugs [4, 5]. Drugs that are easily absorbed from the gastro intestinal 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. Also, the drugs which have a narrow absorption window (NAW) in the upper part of GIT are not suitable for oral sustained release drug delivery system due to the brief



gastric emptying time as tablets have 2.7 ± 1.5 hours (h) stomach transit and 3.1 ± 0.4 h intestinal transit time [6], thus the bioavailability of such drugs having absorption window in stomach is generally limited. Gastro retentive drug delivery is one of those approaches to prolong gastric residence time, thereby targeting site specific drug release in the stomach for local or systemic effects. These dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time of the drugs. It will release the drug in stomach in a controlled manner, so that the drug could be supplied continuously to absorption site in GIT i.e. stomach [7].

Davis, in 1968 firstly described the concept of floating drug delivery system after experiencing choking in some persons while swallowing pills. He removed this difficulty by providing the pills having density less than 1 gm/ml so that the pills will float on the water surface. Since then several approaches have been proposed for ideal floating delivery devices [8]. From the recent scientific literature it is evident that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in industrial and academic field [9].

MERITS OF GASTRORETENTIVE DRUG DELIVERY SYSTEM (GRDDS)

The GRDDS has the following advantages:

- Enhanced bioavailability: The bioavailability of the drugs having absorption in the upper part of the GIT like riboflavin, levodopa has tremendously been increased than that of the conventional dosage forms [10, 11].
- Sustained drug delivery and reduced frequency of dosing. This improves patient compliance.
- Targeted delivery of the drug at the upper part of the GIT making it suitable for the local treatment of the disease of the region eg; antacids, anti-ulcer drugs, antibacterial for *H. pylori* infection [5, 12].
- Suitable for the drugs which have pH dependent absorption from stomach eg., Furosemide [13], Captopril [14], Diazepam, Verapamil, Cefpodoxime proxetil [15].
- Suitable for the drugs which degrade in the intestine or column [16] eg., Ranitidine hydrochloride.
- Drug level fluctuation is not observed and maintains the optimal therapeutic plasma and tissue concentrations over prolonged time period. This avoids sub-therapeutics as well as toxic concentration and minimizes the risk of failure of the medical treatment and undesirable side effects.

LIMITATIONS OF GRDDS

- Not suitable for the drugs which are not stable in acidic environment.
- Not suitable for the drugs which are absorbed better in the lower part of GIT.



- Difficulty to attain the desired outcome and problem of the dose dumping.
- Gastric retention is influenced by many factors like gastric motility, pH and presence of food. Hence, the dosage form must be able to withstand the grinding and churning force of peristaltic wave of stomach.
- Poor in vitro and in vivo correlation.
- Higher cost of formulation.
- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reaction.

Other drawbacks associated with specific types of GRDDS are given the table below [17]:

Technology	Drawbacks
High density system	Very difficult to incorporate large amount of drugs. No such systems are available in the market till date
Floating system	Floating highly depends on the fed state of the stomach and higher level of fluid is required in gastric region
Expandable system	Chocking problem; storage problem due to hydrolysable and biodegradable polymers; difficult to manufacture and not economical
Mucoadhesive system	Can be detached from gastric mucosa due to rapid turnover of mucus and peristaltic wave of stomach. It may also attach to the mucus of oesophagus
Magnetic system	Problem with patient compliance

FACTORS AFFECTING THE GRDDS

Since many factors affects the gastric emptying process, which may seriously affect the release of a drug and its absorption, it is desirable to develop a drug delivery system that exhibits an extended gastric residence and a drug release profile independent of patient related variables [18].

The factors that affect the gastric emptying and hence the gastric retention of the drugs includes:

- Fasting or fed state of the stomach: During the fasting state an inter-digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. In the fed state this cycle is delayed and hence the gastric emptying rate is slowed [19]
- Density, size and shape of the dosage form [20, 21, 22].
- Intake of food with drugs: the nature of the food, calorie content and its frequency of intake have considerable effect on the retention of drugs in stomach [23, 24].
- Concomitant administration of drugs such as anticholinergic agents e.g., atropine, propantheline and opiates delay the gastric emptying while the prokinetic agents like metoclopramide and cisapride enhance the gastric emptying process [25, 26].



- Biological factors such as gender, posture, age, sleep, body mass index, physical activity and disease states e.g. diabetes and Crohn's disease [27, 20, 28].

DIFFERENT APPROACHES OF THE GRDDS

Different approaches have been pursued to increase the retention of oral dosage forms in the stomach. Some are formulated as single component whereas others are formulated as multi-component dosage forms. GRDDS can be broadly categorized into floating and non-floating system.

- A. Non-floating system: These gastro retentive drug delivery systems do not float in the stomach however they remain retained there by different mechanisms. Non-floating system is further divided into:
- a. High density (sinking) drug delivery system
 - b. Bioadhesive or mucoadhesive system
 - c. Magnetic system
 - d. Unfoldable system
- B. Floating drug delivery system (FDDS): In contrast to the high density drug delivery system, floating systems have density less than the gastric content so the system remain buoyant in the stomach for a prolonged period of time without affecting the gastric contents. Floating drug delivery systems are also known as low density system. Figure 1 shows the mechanism of floating of this system.

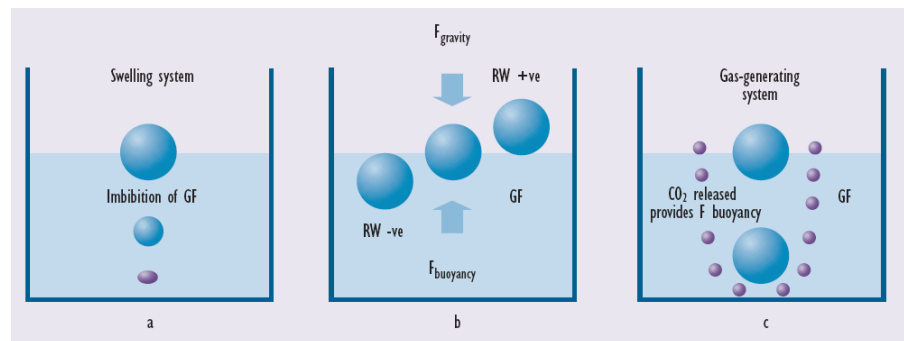


Figure 1 The mechanism of floating system [9]

Floating drug delivery system can be divided into:

- a. Effervescent system
- b. Noneffervescent system
 - i. Hydrodynamically balanced system
 - ii. Microballoons or hollow microspheres
 - iii. Alginate beads
 - iv. Microporous compartment



A. Non-floating system

a. High Density (Sinking) Drug Delivery System

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 [29]. These materials increase the density up to 1.5-2.4 gm/cm³. Depending on density, the GI transit time of pellets can be extended from an average of 5.8 to 25 hours. But effectiveness of this system in human beings was not observed [30] and no formulation has been marketed.

b. Bioadhesive or mucoadhesive system

The gastric retention time is extended by adhering the bioadhesive system to gastric mucosa membrane (Fig. 2). 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. [31]. Novel adhesive material derived from fimbriae 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. The 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.

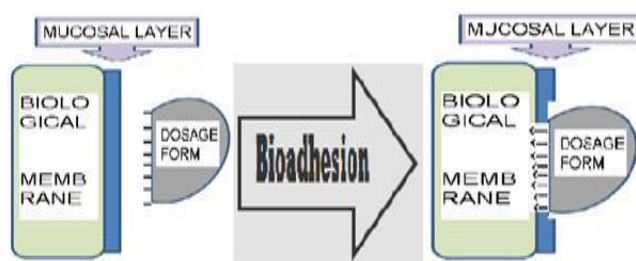


Figure 2 Bioadhesive system

c. Magnetic system

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.

d. Unfoldable system

The drug delivery system unfolds and increases in size and it remains lodged at sphincter avoiding its exit from the stomach (Fig. 3 and 4). For this the system should be small enough to

be swallowed but unfold itself when it comes in contact with gastric fluid, and after a certain period of time its size should become small so that it will be easily evacuated. The unfoldable systems are made up of different biodegradable polymers.

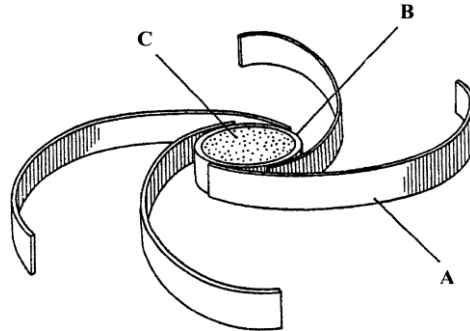
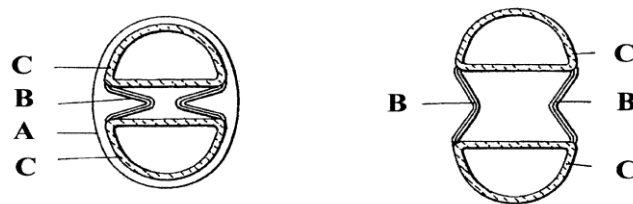


Figure 3 Partially unfolded dosage form
Prior to administration Post-administration



A - gelatin capsule

B - hydrophobic/hydrophilic strip

C - permeable material

Figure 4 Various geometric unfolding systems [11]

B. Floating Drug Delivery System

a. Effervescent System

This system consists of the swellable polymers like chitosan and effervescent substance like sodium bicarbonate, disodium glycine carbonate, cytoglycine, 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 [32]. The optimal ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1 [9]. 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 reported. Effervescent system and drug release from such system is shown in figure 5 and 6 respectively.

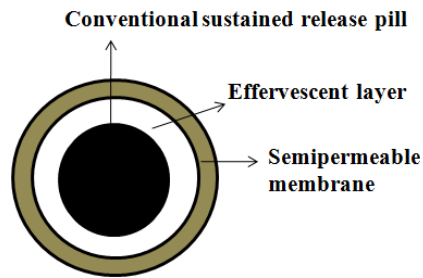


Figure 5 Effervescent System

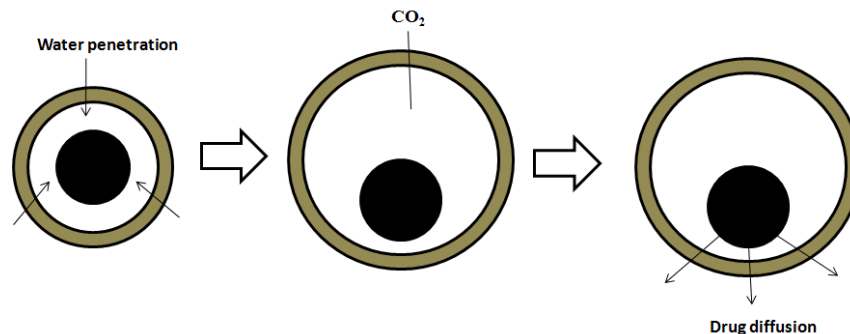


Figure 6 Drug release from effervescent system

b. Non-effervescent system

In this system, gel forming or highly swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene are used. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of less than 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass. Superporous hydrogels are an excellent example working in this approach. The dosage form swells significantly to several times of original volume upon contact with gastric fluid, the gastric contraction pushes the dosage form to the pylorus but due to larger size of the dosage form, the contractions slips over the surface of the system, due to which the dosage form pushes back into the stomach [33] (Fig. 7).



Figure 7 Gastric retention of highly swellable gastro retentive drug delivery system [34]

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



- i. Hydrodynamically balanced system: The hydrodynamically balanced system (HBS) was first designed by Sheth and Tossounian [35]. 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 polystyrene. When such system comes in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface (Fig. 8).

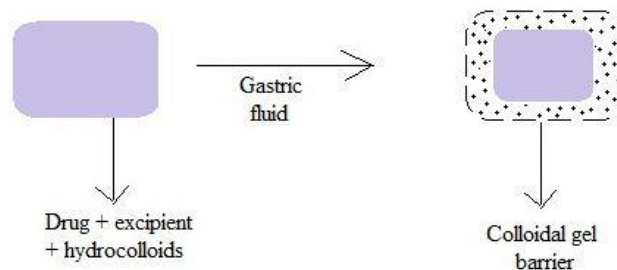


Figure 8 Hydrodynamically balanced system

- ii. Microballoons 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 figure 9. 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 continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours [36].

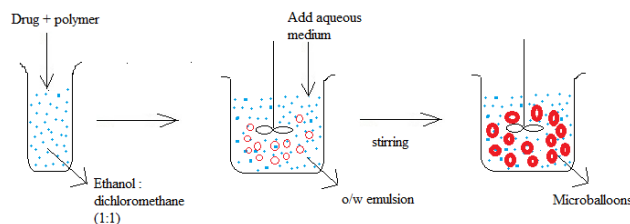


Figure 9 Preparation of microballoons

- iii. Alginate beads: Freeze dried calcium alginates have been used to develop multi unit floating dosage forms [37]. 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 aporous system which remains buoyant in the stomach.

- iv. Microporous compartment: In this system, drug reservoir is encapsulated inside a microporous compartment having pores along its top and bottom walls (Fig. 10). 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 stomach and proximal part of the small intestine for absorption.

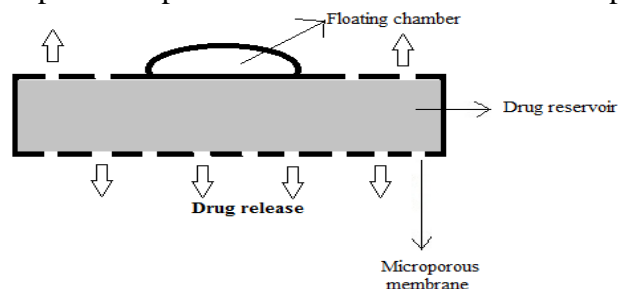


Figure 10 Microporous compartment

PROBABLE CANDIDATES FOR GRDDS

Following are the probable candidates, but not limited to, for gastro retentive drug delivery system:

- Drugs required to exert local therapeutic action in the stomach: antacids, anti-H.pylori agents, misoprostol [24]
- Drugs that have narrow absorption window in stomach or upper parts of the small intestine, e.g., furosemide [38], riboflavine-5-phosphate [39], metformin hydrochloride [40], ciprofloxacin [41], alfuzosin hydrochloride [42], ofloxacin [43], norfloxacin [44], domperidone [45] etc.
- Drugs that disturb normal colonic bacteria, e.g., amoxicillin tirhydrate [46]
- Drugs unstable in the lower part of GIT, e.g., captopril [47]
- Drugs insoluble in intestinal fluids, e.g., quinidine, diazepam [48]
- Drugs that degrade in the colon, e.g., ranitidine hydrochloride [49], metronidazole [50]

MARKETED PRODUCTS OF GRDDS

Following are some gastroretentive products which are available in market [7]:

Brand name	Active ingredients
Cifran OD®	Ciprofloxacin
Madopar®	LDopa and Benserazide
Valrelease®	Diazepam
Topalkan®	Aluminium-magnesium antacid



Almagate FlatCoat®	Aluminium-magnesium antacid
Liquid Gavision®	Aluminium hydroxide
Conviron®	Ferrous sulfate
Cytotec®	Misoprostal

EVALUATION PARAMETERS OF GRDDS [51, 52]

Evaluation parameters of GRDDS generally include:

1. Drug-excipient interaction:

It is done by using FTIR and HPLC. Appearance of a new peak and/or disappearance of original drug or excipient peaks indicate the drug excipient interaction.

2. Floating lag time

It is the time taken to emerge tablet onto the surface after it is kept in to the dissolution medium. It is measured in minutes or seconds.

3. In vitro drug release and duration of floating

It is determined by using USP II apparatus (paddle) stirring at a speed of 50 or 100 rpm at $37\pm 2^{\circ}\text{C}$ in simulated gastric fluid of pH 1.2. Aliquots of the samples are collected and analyzed for the drug content. The time for which the drug remains floating on the surface of the medium is the duration of the floating time.

4. In vivo evaluation of gastric retention

Analysis of the position of the dosage form in the GIT involves an imaging technique such as γ -scintigraphy and X-ray.

- In γ -scintigraphy, a small amount of stable isotope is compounded in the dosage forms during its preparation. The inclusion of a γ -emitting radio-nuclide in a formulation allows indirect external observation using a γ -camera or scinti scanner.
- For x-ray, barium sulfate is used as a contrast medium. It helps to locate dosage form in the GIT by which one can predict and correlate the gastric emptying time and the passage of dosage form.

In addition, gastroscopy and ultrasonography studies can be included in the in vivo evaluation of GRDDS. Gastroscopy comprises of per-oral endoscopy, used with a fiberoptic and video systems. Ultrasonography is not routinely used in the evaluation of GRDDS. In vivo plasma profile can also be obtained by performing the study in suitable animal model.

5. Water uptake study: It is done by immersing the dosage form in simulated gastric fluid at 37°C and determining the dimensional changes, such as diameter and thickness, at regular interval of time. After the stipulated time the swollen tablets are weighed and water uptake is measured in the terms of percentage weight gain, as given:

$\text{WU} = (\text{W}_t - \text{W}_0) \times 100 / \text{W}_0$; in which, W_t and W_0 are the weight of the tablet after time t and initially, respectively.



The tablets are also evaluated for hardness, friability, weight variation etc. which are applicable for conventional instant release tablets. For the multiple unit dosage forms like microsphere following tests are also essential apart from the above tests:

- Morphological and dimensional analysis: It is done with the aid of scanning electron microscopy and optical microscope.
- Percentage yield of microsphere.
- Entrapment efficiency: The drug is extracted by suitable method and analyzed to find out the amount of drug present.

CONCLUSION

Gastro retentive drug delivery technologies have been extensively explored in recent years. GRDDS has the potential to enable many drugs to provide less frequent dosing and remains undoubtedly beneficial for the drugs having NAW in the stomach and/or upper part of the intestine. However, there are many obstacles that need to be overcome to obtain the maximum benefit of the system. Despite this many researchers are working towards the best utilization of this technique, some with success and others with failure due to unpredictability of the human GIT. Thus to formulate a successful GRDDS, it is necessary to take into consideration the physiological event in the GIT, selection of correct combinations of drugs and excipients and design appropriate formulation strategies.

ACKNOWLEDGEMENTS

We would like to express our sincere thanks to Dr. Ashwinee Kumar Shrestha, Assistant Professor, Department of Pharmacy, Kathmandu University-Nepal for his valuable suggestion while preparing this article.

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