
GASTRO-RETENTIVE DRUG DELIVERY SYSTEM

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ABSTRACT

Because of its patient compliance, convenience of administration, and formulation flexibility, the oral route of medication administration is the most preferred method. However, this approach has several drawbacks, such as restricted gastric residence time (GRT) for sustained drug delivery systems and for medications that are absorbed from certain gastrointestinal tract (GIT) regions. Many strategies have been put out to extend the delivery system's gastric retention period in the upper gastrointestinal tract in order to get around these restrictions. By focussing on site-specific drug release in the upper portion of the GIT, the gastroretentive dosage form (GRDF) extends the GRT. By enabling continuous and prolonged drug release and improving the bioavailability of medications with limited therapeutic windows, GRDFs extend dose intervals and boost patient compliance. This article's goal is to gather the different gastroretentive strategies. We have compiled the key variables influencing stomach retention in order to comprehend the different physiological challenges involved in achieving it. The assessment criteria for gastroretentive medication delivery devices are finally discussed. The current study provides a brief overview of the state of many cutting-edge gastroretentive drug delivery technologies that have been developed thus far, such as high density (sinking), floating, bio- or mucoadhesive, expandable, unfoldable, ultra porous hydrogel, magnetic systems, etc. Furthermore, significant variables influencing gastroretention are examined, along with benefits and, lastly, prospects for the future.

KEYWORDS: Floating Delivery, Gastro retentive system.

INTRODUCTION

Oral sustained drug delivery system is complicated by limited gastric residence time. Rapid gastrointestinal transit can prevent complete drug release in the absorption zone and reduce the efficacy of administered dose, since the majority of drugs are absorbed in stomach or the upper part of small intestine. Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. [1] Oral formulations have

earned a significant place among the various dosage forms developed so far for human administration. In most of the cases, the conventional oral delivery systems show limited bioavailability because of fast gastric emptying time among many other reasons involved [2,3]. However, the recent technological development has resulted to many novel pharmaceutical products, mainly the controlled release drug delivery systems to overcome this problem. Gastro-retentive drug delivery system (GRDDS) is one such example where the attribute like gastric retention time coupled with the drug release for extended time has significantly improved patient compliance. Some inherent limitations of the conventional oral drug delivery systems have ignited the interest to this new delivery system. Fast gastric emptying associated with conventional oral medications leads to a bioavailability issue for many drug molecules (e.g. pranlukast hydrate, metformin HCl, baclofen, etc.), of which the main principal site of absorption is the stomach or the proximal part of the small intestine, or have the absorption issue in the distal part of the intestine [4–6]. Solubility can also be improved by prolonging the gastric retention of drugs that are less soluble in an elevated pH environment of the intestine. There are many drugs (e.g. captopril, metronidazole, ranitidine HCl, etc.) that are prone to degradation in the colonic area [7]. To attain required therapeutic activity, recurrent dosing is needed for the drugs with short half-lives as they have the tendency of getting eliminated quickly from the systemic circulation. However, an oral sustained- controlled release formulation with additional gastric retention property can avoid these limitations by releasing the drug slowly in the stomach along with maintaining an effective drug concentration in the systemic circulation for an extended period of time [8]. Apart from the systemic action, GRDDS has proved to be effective locally to treat gastric and duodenal ulcers, including esophagitis, by eradicating the deeply buried *Helicobacter pylori* from the submucosal tissue of the stomach [9–11]. The history of GRDDS formulations dates back to almost three decades [12]. The basic fabrication techniques, including their in vitro characterizations, are also well established. Even in recent times, quite a few reviews have been published on GRDDS [13–19]. These reviews are more focused on the formulation aspects or in vitro characterization studies done by various researchers or overall GRDDS. The industrial aspects covering physicochemical, biopharmaceutical and regulatory considerations of GRDDS have been reviewed by Pawar et al. [20]. Still, the number of marketed gastro-retentive formulations is not significant. So, it is very important to look through the in vivo studies done with GRDDS in order to find out the pharmacokinetic performances of the developed systems considering their significant roles in successful commercialization of any dosage form. As per our literature search, there is no review available to date focusing on in vivo performances of GRDDS, especially on recent works. In this context, the aim of this review is to summarize the in vivo studies of GRDDS in terms of pharmacokinetic parameters as well as gastro- retention times and the inherent challenges or constraints for in vivo evaluations recorded by various researchers.

POTENTIAL CANDIDATES FOR GASTRORETENTIVE DRUG DELIVERY SYSTEM

1. Drugs that are primarily absorbed in the stomach e.g. Amoxicillin.
2. Drugs that are poorly soluble in alkaline pH e.g. Furosemide, Diazepam.

3. Drugs that have narrow absorption window e.g. Levodopa, Methotrexate.
4. Drugs that degrade in the colon e.g. Ranitidine, Metformin HCL.
5. Drugs that disturb normal colonic microbes e.g. Antibiotics against *Helicobacter pylori*.
6. Drugs rapidly absorbed from the GI tract e.g. Tetracycline.
7. Drugs acting locally in the stomach. [21]

Drug delivery systems are used for maximizing therapeutic index of the drug and also for reduction in the side effects. The most preferred route is the oral route especially for the administration of therapeutic drugs because low cost of therapy and ease of administration leads to higher level of patient compliance. More than 50% of the drug delivery systems available are to be administered through oral route. Reasons behind using oral route are that it is the most promising route of the drug delivery and effective oral drug delivery may depend upon many factors such as gastric emptying process, gastrointestinal transit time of the dosage form, drug release from the dosage form and site of absorption of drug. High level of patient compliance is the major advantage of using the oral route. To modify the GI transit time is one of the main challenges in the development of oral controlled drug delivery system. Gastric emptying of pharmaceuticals is highly variable and dependent on the dosage form and the fed/fasted state of the stomach. Normal gastric residence time usually ranges between 5 minutes to 2 hours. In the fasted state the electrical activity in the stomach – the interdigestive myoelectric cycle or migrating myoelectric complex (MMC) governs the activity and the transit of dosage forms. It is characterized by four Phases.[22]

APPROACHES TO FABRICATE GASTRO RETENTIVE SYSTEMS

Different approaches have been adopted by researchers to enhance gastric residence time with the prolonged drug release. The concept of high-density formulation is one such approach. The developed dosage form was made heavy (density: 2.5 to 3.0 g/ml) to withstand in vivo peristaltic movement and remained intact in spite of the GIT disturbance. Accordingly, the GI transit time was expected to prolong for an average of

5.8 h to 25 h [23]. Barium sulfate, iron powder, titanium oxide, and zinc oxide were incorporated in the formulation to increase the density of the dosage form. Increased dose size required to achieve that high density was one of the major drawbacks of this kind of system, as reported by Chawla et al. Another novel idea was postulated to retain the dosage form within the stomach by the application of a magnetic field. The dosage form would contain magnetically active elements. One external magnet was required to position on the abdomen over the location of the stomach to retain the administered drug in place. Though innovative in design, lack of patient compliance was one of the major setbacks for in vivo design of this delivery system [24]. With the introduction of swelling and expanding system, GRDDS managed to achieve significant success both in vitro and in vivo in order to retain the dosage form in the stomach [25,26]. Bolton and Desai [27] reported one such system that was designed to increase in size bigger than the diameter of pyloric sphincter and remain lodged there. Alternatively, the system was named as 'plug type systems' due to their pyloric

sphincter blocking attribute. Once the polymer came in contact with the gastric fluid, it absorbed water and swelled [28–30]. The selection of a suitable polymer (or combination of polymers) with an appropriate molecular weight/viscosity grade and swelling properties enabled the dosage form to attain sustained-release characteristic. Further advancement of such kind of dosage form has taken place with the introduction of novel polymers with super-porous nature, causing them to swell to an equilibrium size within a minute. This characteristic rapid swelling property (swelling ratio is 1:100 or more) of the polymer with an average pore size of more than 100 μm occurs due to capillary wetting through several interrelated open pores when the dosage form comes in contact with GI fluid [31]. Another type of GRDDS has been designed utilizing buoyancy (floating) property of any dosage form experienced in GI fluid [32]. The bulk density of the dosage form attains less than the density of gastric fluid (1.004 to 1.010 g/ml) after a certain lag time. This lag time depends on the rate of swelling of the polymer used in the formulation, which again depends on the type, viscosity grade, presence of wicking agent or swelling enhancers, etc. [33–35]. The said parameters of the formulation also determine the duration of floating as well as in vitro drug release rate. The efficacy of the floating behavior also depends on the physiological conditions of the patients, like fed-state or fasting state, amount of gastric fluid, etc. After the required drug release, the used dosage form is emptied out from the stomach [36]. One additional attribute such as effervescence was incorporated within this swelling-based floating delivery system to improve the floating behavior (floating lag time as well as floating duration), as shown in [37–41].

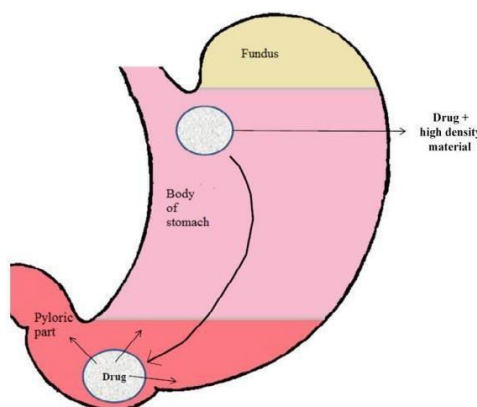


Fig. 2 – Gastro-retentive drug delivery system based on high density.

FACTORS CONTROLLING GASTRIC RETENTION OF DOSAGE FORMS

There are many parameters related to stomach's anatomy and physiology that are needed to be considered in the development of gastroretention dosage forms.

1. **Particle size:** Should be in the range of 1-2 mm to pass through the pyloric valves into the small intestine. [42]
2. **Density:** Density of dosage form should be in range of 1g/cm³ to 2.5g/cm³
3. **Size:** Size should be greater than 7.5 mm in diameter. [43]

4. **Shape of dosage forms:** Ring and tetrahedron devices with flexural modulus of 22.5- 48 KSI (keto pound/ inch² show 90-100 % gastric retention times (GRT).
5. **Single unit/multiple unit:** Multiple units are preferable because of predictable release profile, coadministration of different units, larger safety margins.
6. **Food intake:** GRT is longer in fed states.
7. **Nature, calorie content:** Indigestible polymers, fatty acid salts, increase calorie content, increase acidity increases GRT, Fat and protein meal increases GRT.
8. **Frequency of intake:** GRT increases 400 times due to low frequency of MMC
9. **Posture:** Varies between spine and upright ambulatory states.
10. **Gender:** Females have shorter GRT than males.
11. **Age:** Age > 70 shows longer GRT. [44]
12. **Nature of drug:** Drugs with impact on gastro intestinal transit time e.g. Codeine and pharmacokinetic agents e.g. metoclopramide, cisapride increases GRT. [45]

Other factors Diseased states of the individual (chronic disease, diabetes etc.)

Body mass index

Physical activity

Molecular weight and lipophilicity of the drug depending on its ionization state.[46]

ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEM

1) Enhanced Bioavailability

The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption. [47]

2) Enhanced first-pass biotransformation

In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input. [48]

3) Sustained drug delivery/reduced frequency of dosing

For drugs with relatively short biological half-life, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.

4) Targeted therapy for local ailments in the upper GIT

The prolonged and sustained administration of the drug from GRDF to the stomach may be advantageous for local therapy in the stomach and small intestine. By this mode of administration, therapeutic drug concentrations may be attained locally while systemic concentrations, following drug absorption and distribution, are minimal.

5) Reduced fluctuations of drug concentration

Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent

adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index. [49]

6) Minimization of fluctuations in drug concentration

It makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

7) Reduced counter-activity of the body

In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

8) Extended time over critical (effective) concentration

For certain drugs that have non-concentration dependent pharmacodynamics, such as betalactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration. The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.

9) Minimized adverse activity at the colon

Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for betalactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

10) Reduced counter-activity of the body

In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

CHALLENGES AHEAD WITH GRDDS

The retention time of the dosage forms in the GIT is one of the determinants of the bioavailability of oral drug delivery systems. In case of GRDDS, it is rather specific to the stomach only. Therefore, for developing a GRDDS, the main challenge is retaining the delivery system in the stomach or the upper part of the small intestine for a long time until all the drugs have been released at a predetermined rate [51]. The process of gastric emptying time is highly variable. Among many other factors, it mainly depends on the dosage form as well as fed or fasted state of the stomach. The gastric retention time is extended in the fed state, whereas shortened by the fasting state [52]. Other physiological barriers and factors like the type of food, caloric content, gender and age play significant roles in the variation of gastric emptying time [53]. Because of high caloric content, high fat meal strongly prolongs the process of gastric emptying. Indigestible polymers or fatty acid salts also modify the motility pattern of the stomach under fed state and help in reducing gastric emptying rate. Additionally, patients have variable GRT depending on gender and age, as reported by Mojave Rian et al. [54]. The pylorus limitation plays an important role in gastric retention of any GRDDS. The pylorus size is about 2 to 3 mm during the digestion

and the diameter becomes 12.8 ± 7.0 mm during the inter-digestive phase. Thus, all particles must have a diameter lower than 5 mm so that they can pass through the pylorus into the duodenum [55]. Another factor to consider here is the variation in pylorus size and its peristaltic movement of the animal (e.g. dog, rabbit model) from that of the human [56]. So, in vivo efficacy results need to be concluded carefully. Size and shape of the dosage form, individual's disease state, and body mass index are some other factors on which gastric residence time is dependent and related to the efficacy of the dosage form. However, it has been reported that sometimes multiple-unit GRDDS shows an improved and predictable drug release compared to a single unit GRDDS. Due to a combination of the lag time and the gastric emptying process, a single unit gastro-retentive dosage form (GRDF) may ultimately exit the stomach before the dosage form becomes functional. Hence, to develop an optimum GRDDS, the main challenges are to overcome the problems associated with the gastric emptying rate of the stomach together with maintaining an appropriate drug release rate for an extended period of time before it gets metabolized in the system [57].

CONCLUSION

Gastro retentive drug delivery system offers a potential advantage of enhanced bioavailability and controlled delivery of drug. Gastro retentive drug delivery system showed the potential to increase the gastric retention of drug. Growing understanding of impact of GIT physiology on drug delivery will ensure development of an increasing number of drug delivery system to optimize drug delivery of molecules exhibiting regional variability in drug absorption. The increasing sophistication of delivery technology will ensure the development of increase number of gastro retentive drug delivery to optimize the delivery of molecules that exhibit absorption window, low bioavailability and extensive first pass metabolism. Based on the literature surveyed, we 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 and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability. Gastro retentive drug delivery system gives maximum benefit to patient.

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