REVIEW ARTICLE

Technologies, optimization and analytical parameters in gastroretentive drug delivery systems

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Gastroretentive drug delivery systems (GRDDS) can overcome drawbacks associated with oral drug delivery, by defeating natural physiological principles. Various gastroretentive technologies have been developed in the past, but few of them achieved commercial success. Numerous mechanisms like floating, sinking, effervescence, swelling, bioadhesion, magnetic, etc. have been proposed over the years. At present, the polymeric swellings monolithic systems are popular. Dual working technology would be a possible way to overcome drawbacks associated with different GRDDS. Before development of a drug product, the principles of scale-up and process validation must be considered to improve the quality and market availability of GRDDS. Knowledge of all regulatory aspects will help deliver a product to the market within a reasonable time-frame and in a cost-effective manner.

Keywords: Analytical parameters, drug delivery, gastroretentive technologies, optimization studies.

ORAL route of drug delivery has been the most extensively used and preferred method since decades. Its popularity is mainly based on the convenience it offers to patients[1]. However, the oral route has distinctly failed in the delivery of oral sustained release dosage form (OSRDF). OSRDF has limitations because this system cannot stay in the absorption site in the gastrointestinal tract (GIT) till complete release of the active moiety[2]. Gastric emptying studies have revealed that the short gastric residence time (GRT) and unpredictable gastric emptying rate have altered the performance of OSRDF[3].

To improve the performance of OSRDF, researchers have developed the concept of gastroretentive drug delivery systems (GRDDS). An optimum GRDDS can be described as one which can be maintained in the stomach for an adequate time-period alongside the entire physiological barrier, liberate the active moiety into a controlled manner, and also be metabolized inside the body[4–6]. A GRDDS can be used in the delivery of drugs that are mainly absorbed within the duodenum as well as upper jejunum, and also those that encompass an absorption window within the GIT[7–9].

This system is also suitable for drugs which are nearby active in the gastric mucosa, such as antibiotic management of *Helicobacter pylori*, eradications[10,11] and the management of peptic ulcers and gastritis[12,13]. Drugs are less soluble in and degraded due to pH can be prepared in the GRDDS for prolonged gastric retention and consequently improved oral bioavailability, in addition to therapeutic efficacy by probable lessening of dose amount[14,15]. Moreover, GRDDS can play an important role in chronotherapy, which mainly refers to coordination of medical treatment with biological rhythms[16,17].

Key factors imparting gastroretentive dosage form efficiency

There are many factors impacting gastric residence period of gastroretentive dosage forms (GRDFs). These factors include function of human aspect and mechanism aspect of GRDF technology. For the human aspect the following parameters are important.

Food

Food effects as well as the multipart motility of the stomach take part in a key function during gastric retention behaviour[18–20]. The fasting state is associated with a shortening of GRT because of higher activity than in the fed state. Table 1 shows the transit time of different dosage forms across the GIT. In the fed state, the retention time is extended and shear stress on the formulation is reduced due to less movement, which improves the dosage form integrity and then its delivery according to extended retention[21,22].

The nature of the food, i.e. volume, viscosity and caloric amount is important; therefore a high-fat meal will strongly increase the GRT. Other delayed gastric emptying approaches of interest include indigestible polymers or fatty acid salts that change the motility pattern of the stomach to a fed state, in that way falling the gastric

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emptying rate in addition to allowing substantial continuation of drugs release[23,24]. The frequency of food intake will also significantly increase the GRT.

Pylorus limitation

During digestion the pylorus size is about 2–3 mm, while during the inert-digestive phase its diameter is about 12.8 ± 7.0 mm. Therefore, all particles which have a diameter smaller than 5 mm can pass through the pylorus to the duodenum. The gastric peristalsis exerts forces which are able to disintegrate dosage forms of sufficient size with hardness less than or equal to 1.89 N (ref. 25).

Gender, posture and age

Generally stomach emptying is slower in women compared to men, regardless of weight, height, body surface area and even when the hormonal changes due to the menstrual cycle[26]. Bennett *et al.*[26] reported that the function of posture in gastric emptying. They observed that an alginate raft emptied earlier than food into subjects lying on their left side because the raft exist to the pylorus in front of the meals moreover so emptied more rapidly. Elderly people generally show extended GRT independent of posture or gender. The main parameters with respect to functional factors of the GRDF technology are as follows.

Size and shape of monolithic dosage form: Greater the dosage forms, greater the GRT. Floating dosage forms are less concerned by this basic concept. Different shapes have been proposed – ring-shaped and tetrahedron-shaped devices, which were found to enhance GRT[27–29].

Monolithic versus multiple unit systems: As claimed for classical extended release, multiple units exhibit better predictable release and regarding specificity of GRDF, they avoid the possible 'all or nothing' effect. 'All or nothing' in this context means that a monolithic dosage form may eventually exit the stomach before the gastroretentional properties become functional due to a combination of lag instance and gastric emptying process.

Table 1. Transit times of various dosage forms across the gastrointestinal tract

Dosage form	Transit time (h)		
	Stomach	Small intestine	Total
Tablets	2.7 ± 1.5	3.1 ± 0.4	5.8
Pellets	1.2 ± 1.3	3.4 ± 1.0	4.6
Capsules	0.8 ± 1.2	3.2 ± 0.8	4.0
Solution	0.3 ± 0.07	4.1 ± 0.5	4.4

Drug and excipients selection for GRDDS

Development of an efficient GRDDS depends on the appropriate selection of a candidate drug molecule. GRDDS cannot deliver every drug in an effective manner and hence proper selection of the drug is important in the formulation of dosage form. Biopharmaceutical parameters play a significant role during delivery of drugs through the GIT[30]. Pharmacokinetic and pharmacodynamic properties like absorption, distribution, metabolism, excretion, half-life (absorption and elimination), therapeutic index, dosage size along with first-pass clearance are the important contributors[31].

Drug absorption either by passive or active transport is an important attribute in the selection of a drug candidate for GRDDS. In a recent study, pharmacokinetic and pharmacodynamic profiles of three drugs (atenolol, acyclovir and valacyclovir) have been assessed after administration through a GRDDS[32]. Other biopharmaceutical parameters also play a key role in the selection of appropriate active moiety for GRDDS. For example, high first-pass metabolism of propanolol in the liver, even after complete absorption, can be reduced by incorporating it into a GRDDS. P-glycoprotein is distributed through the GIT, but its level is reported to be higher in the distal region (stomach < jejunum < colon). Therefore, high first-pass metabolism of propanolol can be reduced by controlling its release in the stomach. Peak plasma concentration of propanolol is reached after 1–4 h via oral route and its $t1/2$ is 3–4 h. In consequence with first-pass metabolism, all these attributes increase its ability to be delivered via a controlled release system. Consequently, GRDDS can increase oral bioavailability of propanolol by reducing its high first-pass metabolism[33,34]. Excipients are more likely selected according requirement of the drug delivery systems. They should fulfil all the primary or basic requirements of the drug product without affecting the physical and therapeutic efficacy of the active pharmaceutical ingredient. The United States Food and Drug Administration (US FDA) provides a database of excipients that have been used in approved products[35]. This database comprises inactive ingredient guide (IIG) limits of the excipients which could be useful during initial development of the products.

Formulation design and technology in GRDDS

Various technologies have been developed for gastroretention of the drugs, but only few have been commercialized. These methods have special principles of functioning and have their individual merits and demerits. Table 2 shows the drawbacks associated with various GRDDS. Among the GRDDS, floating and bioadhesive/mucoadhesive technology-based products are mostly developed by the pharmaceutical companies. The current focus of the pharmaceutical companies is on dual working

Table 2. Drawbacks associated with various gastroretentive drug delivery systems

Technology	Drawbacks
High-density systems	Cannot manufacture with large amount of drug due to technical problems.
Floating systems	Highly depends on the fed state of stomach; higher level of fluid is required in gastric region. Floating lag time.
Expandable systems	Storage troubles due to hydrolysable, biodegradable polymers. Short-lived mechanical shape memory. Difficult to manufacture is uneconomical.
Mucoadhesive systems	Efficiency can be reduced in rapid turnover of mucus. Might bind to other mucosal linings like esophagus.
Magnetic systems	Might compromise with patient compliance.

Table 3. Gastroretentive technologies adopted by various pharmaceutical companies

Technology	Product	Company	Active pharmaceutical ingredient
Bioadhesive tablets	Xifaxan	Lupin, India	Rifaximin
Effervescent floating system	Zanocin OD	Ranbaxy, India	Ofloxacin
	Riomet OD		Metformin hydrochloride
	Cifran OD		Ciprofloxacin
Colloidal gel-forming floating system	Conviron	Ranbaxy, India	Ferrous sulphate
Foam-based floating system	Simé thicone	Sato Pharma, Japan	Inon Ace tablets
Polymer-based swelling technology: AcuForm	Gabapentin GR	Depomed, Inc., USA	Gabapentin
	ProQuin_XR		Ciprofloxacin
	Glumetza_		Metformin hydrochloride
Effervescent and swelling-based floating system	Prazopress XL	Sun Pharma, Japan	Prazosin hydrochloride
Erodible matrix-based system	Cipro XR	Bayer, USA	Ciprofloxacin hydrochloride and betaine
Gastroretention with osmotic system	Coreg CR	GlaxoSmithKline	Carvedilol
Bilayer floating capsule	Cytotec	Pharmacia Ltd, UK	Misoprostol
Floating liquid alginate	Topalkan	Pierre Fabre Medicament, France	Aluminum magnesium antacid

systems. Table 3 shows the various gastroretentive technologies adopted by the pharmaceutical companies along with the related marketed products.

The key approach used to increase the gastric residence period of pharmaceutical dosage forms includes:

- Bioadhesive delivery system which adheres to the mucosal surface[36].
- Delivery systems that quickly swell in size once they are inside the stomach to slow down the passage throughout the pylorus.
- Density-controlled delivery system which either floats or sinks in gastric liquid[37,38].

The major advantages and shortcomings of these concepts are discussed in the following sections.

Bioadhesive drug delivery system

Different types of polymers have been studied for their bioadhesive properties and several excellent review articles have been published on the fundamental aspects and potential applications of bioadhesive dosage forms[39–43]. Bioadhesive polymers are typically hydrophilic gelling, macromolecular material among abundant hydrogen-bond forming groups, such as amide, sulphate, hydroxyl and carboxyl groups (e.g. carrageenan, sodium alginate, sodium carboxymethyl cellulose and cross-linked polyacrylic acids). For example, Akiyama and Nagahara[44] developed mucoadhesive microspheres along with Carbopol ® 934P (Noveon, Inc.; polyacrylic acid, polymerized into benzene, highly crosslinked among allyl sucrose) being dispersed in a waxy matrix of polyglycerol ester of fatty acid.

Size-increasing drug delivery system

One more approach to retain a dosage form in the stomach is to increase its size greater than the diameter of the pylorus, yet in the widest condition through the housekeeper waves. Approximately, the dosage form should be >13 mm; however, even bigger units have been observed to be emptied from the stomach. In order to facilitate swallowing, it is highly desirable to design dosage forms with an initially small size, which, once they are in the stomach, significantly increase in size. Other characteristics

of an optimal size-increasing drug delivery system include: no effect happening gastric motility and emptying patterns, no other limited adverse effects (e.g. on the gastrointestinal wall), and cheap industrial make[45].

Density-controlled drug delivery system

High-density systems: The density of a drug delivery system is an important factor influencing the gastric residence time. High-density devices use their weight as a retention mechanism. When the density of the system is larger than that of the gastric juice, the device settles down to the bottom of the stomach, remaining below the pylorus[46].

Floating systems: Floating properties of drug delivery systems can be based on several principles, including inherent low density, low density due to swelling and low density due to gas generation and entrapment.

Floating drug delivery systems with inherent low density: It is highly desirable to develop drug delivery systems that float immediately following contact with gastric fluids. This can only be achieved if the low density device is provided from the beginning. Compared with systems initially settling down, the risk of premature emptying from the stomach is greatly reduced. Generally, inherent low density is provided by entrapment of air (e.g. hollow chambers)[47], or by the (additional) incorporation of low-density materials such as fatty substances or oils or foam powder[48–50]. Desai and Bolton[51] developed a moulded agar gel tablet with entrapped oil and air, which replaced evaporated water following drying.

Floating drug delivery systems with low density due to swelling: A floating single-unit dosage form with sustained drug release consisting of a capsule containing a mixture of drugs and hydrocolloids has been described by Sheth and Tossounian. Following contact with gastric fluid, the capsule shell dissolves and a mucous body with bulk density <1 is formed. Based on this principle, pharmaceutical products have been developed containing L-DOPA, combined with a decarboxylase inhibitor and diazepam. Dorozynski *et al.*[52] carried out a comparative study of the properties of different polymers that could be useful for the preparation of floating capsules. The floating properties of the dosage forms were found to depend on the type of polymer used.

Floating drug delivery systems with low density due to gas generation: A further interesting approach to provide low-density floating drug delivery systems is based on the formation of carbon dioxide within the device following contact with body fluids. For example, multi-layer matrix tablets have been proposed containing an effervescent layer loaded with carbonate and optionally citric acid[53–55]. After contact with acidic aqueous media, carbon dioxide is generated and entrapped within the gelling hydrocolloid, causing the system to float. In addition, capsules containing such an effervescent mixture have been prepared and the effects of different formulation variables on drug release and floating behaviour were studied[56]. HPMC of different viscosity grades and Carbopol 934P were used as hydrocolloids. Rouge *et al.*[57] developed floating mini-tablets based on HPMC and sodium bicarbonate as the gas-generating agent. Ichikawa *et al.*[58] developed a multiple-unit, oral floating dosage form that generates carbon dioxide.

Preformulation studies in GRDDS

Preformulation studies focus on the physico-chemical properties of compounds that can affect drug performance and development of an efficacious dosage form. A thorough understanding of these properties is necessary for formulation design. Preformulation studies are useful in the development of dosage forms. While delivering the drug with perfection, the delivery system must also be capable of providing a desirable environment through the shelf life of the product along with sufficient bioavailability without any food and drug interaction. Identification of potential physico-chemical and biological properties of the drug substance that can affect the performance of product and its manufacturability should be accomplished before the development of GRDDS. In general, pKa, solubility, particle size, permeability and drug stability in the gastric pH need to be examined[59]. However, any drug which is stable in gastric pH and is a good candidate for incorporation in GRDDS[60,61]. Another excellent example is itraconazole, an oral antifungal agent with a broad spectrum of activity. It is a weak basic drug and has dissociation constant and partition coefficient values of 3.7 and 5.66 respectively, at pH 8.1 that shows its high hydrophobic nature. Under biopharmaceutical classification system (BCS), it is categorized as a class-II drug with low water solubility and high permeability. All these attributes of itraconazole are favourable in its incorporation in a GRDDS[62]. Table 3 summarizes the list of drugs preferably incorporated in the GRDDS along with their brand name and company name. Excipients also play a major role in the performance of a drug delivery system. Therefore, selected excipients for a GRDDS must go through strong selection criteria and all the properties relevant to the drug delivery system must be evaluated. Any interaction between drug and excipients or between selected excipients should be identified through compatibility studies. Such studies are particularly important for drugs like atorvastatin which is used to treat moderate to severe hypercholesterolaemia and is a highly unstable molecule. Its hydroxy acid form can be

converted into lactone form if it is excessively exposed to heat, light and moisture. Moreover, it can be easily destabilized by components of the formulation[63,64]. Khan and Dehghan[38] developed a stable gastroretentive formulation of atorvastatin.

Analytical specification for GRDDS

Selection of appropriate analytical specifications for a drug product should be done in passable manner to precisely evaluate its performance. The International Conference on Harmonization (ICH) provides guidance regarding different analytical tests recommended for specific dosage forms. ICH also provides guidance on analytical validation[65].

During initial development phases, one scientist can refer to the different pharmacopoeias where the drug products are reported. Selection of analytical specifications depends on the type of drug delivery system. Disintegration test is excluded from the specifications of GRDDS, because the latter are controlled and sustained release drug delivery systems. After selection of analytical specification, the second step is to set-up appropriate acceptance criteria for all the specifications. Acceptance criteria can be adjusted on the basis of experience gained during the development process and by referring to different pharmacopoeias. For a new drug delivery system, analytical specifications and acceptance criteria can be modified on the basis of experience gained during development process of the drug product. However, *in vitro* mucoadhesion test methods are not very reliable for providing accurate information to correlate with *in vivo* mucoadhesion. Thus there is an urgent need to develop a more authentic *in vivo* mucoadhesion testing method. Parikh and Amin[66] described the *in vitro* and *in vivo* techniques to efficiently evaluate the floating, raft-forming and expandable systems. According to current good manufacturing practices, it is necessary to identify potential and critical in-process controls that can affect the quality of the drug product.

Optimization studies in GRDDS

In particular situations where several input variables potentially influence the performance of a GRDDS, statistical techniques can be employed to optimize the formulation to save time and cost. Before application of any statistical technique, it is of utmost importance to identify the critical formulation and process variable which can affect the performance and quality of a GRDDS. Different statistical designs such as factorial design, central composite design, box–behnken design and simplex lattice design are used for optimization of GRDDS[67–69]. El Gamal *et al.*[70] employed 3^2 full factorial design using the Design Expert software (version 7.1.6) to optimize floating matrix tablets of acyclovir. The selected independent variables were hydroxypropyl methylcellulose 4000 and Compritol 888. The percentage drug released at 1, 6 and 12 h was selected as dependent variable. Results revealed that high concentration of both the independent variables increased the quality of the tablets. Optimized batch produced good buoyancy and release patterns even after stability testing of the product at 40°C/75% relative humidity for three months. Sultana and Bhavna[71] optimized the performance of mucoadhesive microspheres of lacidipine using central composite design. Effect of independent variables such as polymer concentration, volume of glutaraldehyde, stirring speed and cross-linking time was evaluated on the dependent variables like drug entrapment efficiency and percentage mucoadhesion. The results of the optimization studies showed that dependent variables were greatly affected by the polymer concentration and volume of glutaraldehyde compared with other independent variables. Vaghani *et al.*[35] developed oral bioadhesive hydrophilic matrices of repaglinide. Simplex lattice design was employed to optimize the independent variables. Polyethylene oxide, microcrystalline cellulose and lactose were selected as independent variables and the selected dependent variables comprised of mucoadhesion and drug release at 2 and 8 h. Acceptance criteria for optimized formulation were adjusted to maximum mucoadhesion, and 20% and 80% drug release at 2 and 8 h respectively. The optimized batch showed maximum mucoadhesion at 0.211 N with drug release of 21.87% and 80.86% at 2 and 8 h respectively.

Bioequivalence/bioavailability studies in GRDDS

Final stage in the development of a GRDDS is the bioequivalence/bioavailability studies. This is a tedious, lengthy and expensive phase of the product development. It is difficult to clear this stage by GRDDS because of high variability in physiologic principles among the individuals. Generic drug product manufacturing is a challenging task and manufacturers can neglect overburden of bioequivalence studies by knowing their regulatory aspects. Important decisions should be taken before starting this phase. Initially, solubility and permeability of the active moiety should be considered and it is to be ascertained in which class of BCS the active moiety resides. According to European Medicines Agency (guidelines on the investigation of bioequivalence), if an active moiety has high solubility (BCS class-I drug) and its 85% amount of drug release from the drug product within 15 min, then it is not necessary to perform bioequivalence studies[72]. For BCS class-I and class-II drug, biowaiver can be performed, but for BCS class-II drugs it is necessary to improve the solubility. However, this concept possibly will not work in case of controlled and sustained

release delivery systems like GRDDS. Generic drug manufacturers of GRDDS may refer to the US FDA database, for making decisions about the bioequivalence/bioavailability studies of the developed GRDDS[73]. This database provides information about already performed bioequivalence studies or biowaiver reports of approved products. For most cases, it is an ideal platform for the preparation of protocols for bioequivalence studies and biwaiver applications. The US FDA also provides guidelines for bioavailability and bioequivalence studies for orally administered drug products[74].

In vitro–in vivo correlation (IVIVC) is a useful tool that can exploit potential future problems associated with the biowaiver principles. Particularly, IVIVC is helpful for modified release drug delivery systems like GRDDS. IVIVC explains the relationship between *in vitro* release and *in vivo* absorption. There are three levels of correlation described by the US FDA[75–77]. In level A, direct point-to-point (1 : 1) relationship develops between *in vitro* dissolution and *in vivo* bioavailability. Extended release drug delivery systems are considered in this phase, where dissolution is independent of the dissolution medium and mathematical models are applied to directly compare the dissolution curve with plasma drug concentration–time profile. Level B includes the correlation between *in vivo* mean residence time and *in vitro* mean dissolution time. Level C is a single point correlation between dissolution (t50% or t90%) and plasma drug concentration–time data (AUC, t_{max} or C_{max}). Level C is considered as the lowest level of correlation[78,79].

Conclusion

GRDDS are unique systems gaining considerable importance in research during the last three decades, but their market availability is low. The major advantage of GRDDS is assurance that physiological conditions like GRT will work in favour of the developed system. GRDDS are also important in chronotherapy and can effectively increase the efficacy of chronotherapeutic drug delivery systems. Drugs which are unstable in the lower GIT and have solubility problems can be delivered efficiently using GRDDS. Drug repurposing is also an open field for researchers to improve pharmacotherapy of various disease states. Before selecting an active moiety for GRDDS, each molecule should be considered for individual case study of biopharmaceutical parameters. In the future, GRDDS may gain more importance, allowing the efficiencies of various types of medical treatments to be improved. The focus will probably be on multiple unit systems, as they permit the reduction of risk of all-or-nothing effects related with single-unit dosage forms.

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