EXPERT OPINION

Industrial perspective of gastroretentive drug delivery systems: Physicochemical, biopharmaceutical, technological and regulatory consideration

Vivek K Pawar, Shaswat Kansal, Shalini Asthana & Manish K Chourasia†
†*Pharmaceutics Division, CSIR-Central Drug Research Institute, Lucknow, UP, India*

Introduction: 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 success on the market.
Areas covered: This review is focused on the key concepts required to make a high-quality drug product available in a timely and economical manner.
Expert opinion: Pharmacotherapy of various disease states can be amended by drug repurposing through GRDDS. Assessment of the effect of the fed and fasted condition on product performance should be necessary during initial development phases. 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 to deliver a product to the market within a reasonable timeframe and in a cost-effective manner.

Keywords: analytical specifications, dual working systems, gastroretentive drug delivery systems, *in vitro–in vivo* correlation, preformulation studies, scale up

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1. Introduction

Oral route of drug delivery have known from decades as the most widely used and preferred among all the routes that have been explored for the systemic drug delivery. The tremendous popularity of oral route is mainly based on the convenience it offers to patients [1]. However, oral route has distinct failure in the delivery of oral sustained release dosage forms (OSRDF). OSRDF have limited applications because these systems cannot remain in the vicinity of absorption site in gastrointestinal tract (GIT) till complete release of active moiety [2].

Fundus, body and antrum are three anatomical features of the stomach. The ingested materials reside in proximal stomach which is made up of fundus and body regions whereas distal region (antrum) is responsible for providing mixing motion and acts as a pump for gastric emptying [3]. Fasted and fed states show two distinct patterns of gastrointestinal motility. The fasted state is characterized by inter-digestive myoelectric cycle or migrating motor complex (MMC). The MMC is inter-digestive series of electrical event and cycle of 2 – 3 h through the stomach and small intestine. The MMC is composed of four consecutive phases: Phase I (basal phase; that lasts from 45 – 60 min with rare contractions), Phase II (preburst phase; lasts for 30 – 45 min with intermittent action potential and contractions), Phase III (burst phase; lasts for 5 – 15 min and includes intense

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Article highlights.

- Pharmacokinetic properties like absorption (active or passive) and first-pass clearance affects the selection of a drug candidate for gastroretentive drug delivery system (GRDDS).
- Physicochemical properties like pKa, particle size, solubility and stability in gastric fluid comes under consideration prior to development of a GRDDS.
- Dual working technology shows excellent *in vitro* and *in vivo* performance and can overcome the drawbacks associated with floating and mucoadhesive GRDDS.
- Selection of analytical specification and appropriate acceptance criteria for a drug product depends on the experience gained during the development of the product.
- Prior to development of product, principles of scale up must come under consideration to improve the quality as well as reproducibility of the product.
- *In vitro–in vivo* correlation (IVIVC) predicts the *in vivo* fate and troubles related with biowaiver application of modified release products.

This box summarizes key points contained in the article.

and regular contractions for short period) and Phase IV (lasts for 0 – 5 min and occurs between Phases III and I for two consecutive cycles) [4].

The important physiological factor which is responsible for the reduction in efficacy of OSRDF is gastric residence time (GRT). GRT considerably affects the bioavailability of pharmaceutical dosage forms [5]. Variable and short gastric emptying time results in incomplete drug release from the OSRDF which leads to diminished efficacy of the administered dose [6]. GRT is affected by both the fasting as well as fed states of the stomach. State of feeding gives direct reflection on bioavailability of the orally administered drugs. Gastric emptying studies revealed that the short GRT and unpredictable gastric emptying rate have altered the performance of OSRDF [7].

To improve the performance of OSRDF, scientists have discovered a new concept in drug delivery, that is, gastroretentive drug delivery systems (GRDDS). An optimum GRDDS can be defined as a system which retains in the stomach for a sufficient time interval against all the physiological barriers, releasing active moiety in a controlled manner, and finally metabolized in the body [8]. Over the last two decades, numerous GRDDS have been designed to prolong GRT. The major objective is to minimize the drawbacks associated with existing OSRDF and optimizing therapy coupled with substantial patient comfort [9-11].

A GRDDS can be a useful tool in delivery of drugs that are primarily absorbed in the duodenum and upper jejunum or those that have an absorption window in the GIT [12-14]. This system is appropriate for drugs which are locally active in the gastric mucosa, for example, antibiotic administration for *Helicobacter pylori* eradication [15,16] and in the treatment of peptic ulcer and gastritis [17,18]. Drugs that are less soluble in or are degraded by the alkaline pH may get benefit by being incorporated in GRDDS for prolonged gastric retention and consequent improved oral bioavailability and therapeutic efficacy by possible reduction of dose size [19,20]. Moreover, GRDDS can play an important role in chronotherapy. Chronotherapy mainly refers to coordination of medical treatment with biological rhythms [21]. Floating pulsatile system is a perfect example for application of GRDDS in chronotherapy. Pulsatile system releases drug after a certain time period but there is always an uncertainty that they may be ejected out from the body without releasing active moiety. Floating pulsatile system develops to overcome the drawbacks associated with pulsatile system and these systems have been gaining more attention in recent years due to fact that these systems can improve the pharmacotherapy of many diseases [22].

Various technologies and approaches have been developed by scientists to control the premature gastric emptying of the dosage forms. These systems can be broadly classified in the following categories: i) high density systems; ii) floating systems; iii) expandable systems; iv) superporous hydrogels; v) mucoadhesive or bioadhesive systems; vi) magnetic systems and vii) dual working systems [23-25].

High density systems have density of ~ 3 g/cm^3. Above a threshold density of 2.4 – 2.8 g/cm^3, such systems can be retained in the lower part of the stomach [26]. The expandable systems are usually expanded to prevent passage through the pyloric sphincter and after releasing active ingredient, their size decreases to enable evacuation from the gastric cavity. Expansion can be attained either by swelling or by unfolding the GRDDS in the stomach. Swelling and unfolding is mainly accomplished by osmosis and mechanical shape memory of GRDDS, respectively. Unfolding expandable systems are fabricated in a larger size followed by folding in a carrier system such as gelatin capsules. After administration, carrier system dissolves in stomach and GRDDS unfold to achieve extended mechanical shape [27].

Mucoadhesive or bioadhesive systems are developed by incorporating bio/mucoadhesive agents in GRDDS which enable the device to adhere to the stomach (or other gastrointestinal) wall and resist gastric emptying [28]. Superporous hydrogels are swellable system having average pore size > 100 µm so that they can swell to equilibrium within a minute. This is due to rapid water uptake by capillary wetting through numerous interconnected open pores. Moreover, they swell to a large size and are intended to have sufficient mechanical strength to withstand pressure by the gastric contraction [29]. The magnetic dosage forms contain a small internal magnet and an extracorporal magnet that controls the gastrointestinal transit of the dosage form [30].

Floating drug delivery systems have lower density compared with gastric fluid which enables them to float over the surface of gastric fluid [31]. The drug released from the systems is slow at the required rate which results in reduced fluctuation in the plasma concentration along with increased

GRT. Floating systems are more popular in comparison with above described systems because they do not have any adverse effect on the motility of the GIT [32]. Immediate buoyancy could be achieved if the density of the developed system is low in the beginning [33,34].

Monolithic GRDDS seem to be unreliable because they can evoke 'all or none' gastric emptying process. Therefore, they can induce local irritation in GIT due to unexpected release of drug at particular sites and high variability in bioavailability. In counterpoint, multi-particulate GRDDS such as microspheres have capability to distribute uniformly through the GIT to avoid 'all or none' gastric emptying process. Consequently, they may reduce inter-subject variability in absorption and chances of local irritation [8]. Gastric emptying of single and multi-particulate GRDDS is affected by the fed and fasted condition of the stomach. Usually, GRT of a GRDDS is low in fasted state compared with fed state of the stomach. In fed conditions, multi-particulate systems have more chances to stay in the stomach in comparison with monolithic systems because they can easily mix with food and ejected out from the stomach after a prolonged time period [1]. However, some marketed GRDDS such as Xifaxan® tablets (Lupin, Maharashtra, India) and Cipro® XR tablets (Bayer, Wayne, NJ, USA) shows somewhat reliable pharmacokinetic performance in both fasted and fed states of the stomach. That is why both the products are suggested to administer in both fed and fasted state of the stomach.

Numerous studies have been done on GRDDS since last two decades but very less number of products are available in the market. This conflict between research and industrial implementation has to be analyzed and rectified. A development scientist could make an optimized and validated product if having all the comprehensive knowledge of quality attributes regarding specific drug product. **Figure 1** shows the high quality attributes that are utilized for the development of a stable dosage form that ensures acceptable and reproducible product quality and performance throughout a product's shelf life. This review comprises important aspects of GRDDS subjected to the industrial concerns regarding preformulation studies, formulation design, optimization studies, scale up, analytical specifications and bioequivalence/bioavailability studies.

2. Drug and excipients selection

Development of an efficient GRDDS depends on the appropriate selection of a candidate drug molecule. GRDDS cannot deliver each and every drug in effective manner and hence proper selection of drug is important in the formulation of dosage form. Biopharmaceutical parameters play an important role in delivery of a drug through GIT [35]. Pharmacokinetic and pharmacodynamic properties like absorption, distribution, metabolism, excretion, half-life (absorption and elimination), therapeutic index, dose size and first-pass clearance are the key contributors. Drug repurposing either in means of new indication and or presenting it via new novel drug delivery systems like GRDDS is a present systemic plan of various research and development (R&D) organizations. This approach can improve the current therapeutic profile of various active pharmaceutical ingredients [36].

Drug absorption either by passive or active transport is an important attribute in selection of a drug candidate for GRDDS. In a more recent work, pharmacokinetic and pharmacodynamic profiles of three drugs (atenolol, acyclovir and valacyclovir) have been assessed after administration through a GRDDS. Drugs were administered to rats using different routes including gastric infusion through an implanted catheter (resembling GRDDS), intravenous, oral and colonic route. In comparison with oral route, prolonged T_{max} and reduced C_{max} were obtained when atenolol was administered through gastric infusion but both the routes showed similar bioavailability of atenolol. On the other hand, bioavailability of the atenolol significantly lowered after colonic bolus administration. Acyclovir showed similar pharmacokinetics and low bioavailability after administration via gastric infusion and oral routes. A significant change in the pharmacokinetic profile of valacyclovir was observed after gastric infusion without any variation in the bioavailability. Results demonstrated that GRDDS influence the pharmacokinetic characteristics of the drugs which are primarily absorbed by active transport in the upper GIT [37].

Other biopharmaceutical parameters also play a key role in selection of perfect active moiety for GRDDS. For example, high first-pass metabolism of propanolol in 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 distal region (stomach < jejunum < colon). Therefore, high first-pass metabolism of propanolol can be reduced by controlling its release in stomach. Peak plasma concentration of propanolol reaches after 1 – 4 h via oral route and its $t_{1/2}$ 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 [38,39].

Excipients are more likely selected as per requirement of the drug delivery systems. They should fulfill 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 [40]. This database comprises inactive ingredient guide (IIG) limits of the excipients and that can be useful during initial development of the products.

3. Preformulation studies

Preformulation studies focus on those physicochemical properties of the compounds that can affect the drug performance and development of an efficacious dosage form. A thorough understanding of these properties ultimately provides a

Figure 1. Quality attributes for the development of a stable drug product.

rational for formulation design. Preformulation studies provide very useful support in development of dosage forms. Nevertheless delivering the drug with perfection, the delivery system must be capable to provide a desirable environment through the shelf life of the product along with sufficient bioavailability without any food and drug interaction.

Identification of those potential physicochemical and biological properties of the drug substance that can affect the performance of product and its manufacturability should be accomplished before development of the GRDDS. In general, determination of pKa, solubility, particle size, permeability and drug stability in the gastric pH might need to be examined. These properties can be changed with time and hence time-dependent studies might be required.

For example, captopril, an angiotensin-converting enzyme inhibitor, is widely used for the treatment of hypertension and congestive heart failure. Captopril is highly unstable in alkaline pH and is prone to degradation in the small intestinal region of GIT [41]. However, the drug is stable in gastric pH and is a good candidate for incorporation in GRDDS [42,43]. 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 resembles its high hydrophobic nature. Under biopharmaceutical classification system (BCS), it is categorized as class II drug with low water solubility and high permeability. All these attributes of itraconazole favor its incorporation in a GRDDS [44]. **Table 1** summarizes the list of drugs preferably incorporated in the GRDDS along with their important biopharmaceutical and physicochemical characteristics.

Excipients also play a major role in performance of a drug delivery system. Therefore, selected excipients for a GRDDS must go through strong selection criteria and all the properties relevant to subjected drug delivery system must be evaluated. Any interaction between drug and excipients or between selected excipients should be identified by performing compatibility study. This study is particularly important for the drugs like atorvastatin which is used to treat moderate to severe hypercholesterolemia 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 [45,46]. Khan and Dehghan [47] developed a stable gastroretentive formulation of atorvastatin. Floating effervescent tablets were formed to deliver atorvastatin in controlled manner in gastric region. The excipients compatibility with atorvastatin and stability of the formulation were evaluated by differential

Table 1. Drug candidates for GRDDS.

Drug	Pharmacological and/or therapeutic class	Solubility	Stability in gastric and intestinal pH	Absorption and oral bioavailability	Half-life (h)	Ref.
Furosemide	Loop diuretic	Poor water solubility	-	Absorbed mostly from the stomach and upper small intestine. Oral bioavailability quite variable (20 – 60%)	1.3 ± 0.8	[90]
Tacrolimus	Immunosuppressant	Poor water solubility	-	Low oral bioavailability	-	[91]
Captopril	Angiotensin-converting enzyme inhibitor	Freely soluble in water	Stable at gastric pH but unstable in intestine	-	2	[92]
Ranitidine	Histamine H_2-receptor antagonist	Low solubility at alkaline pH	Colonic metabolism	50% absolute bioavailability	2.5 – 3	[93,94]
Repaglinide	Oral hypoglycemic agent	Poorly soluble in water	-	Low bioavailability (50%)	1	[95]
Itraconazole	Antifungal	Low water solubility	-	Variable in individuals	21	[44]
Metformin hydrochloride	Antidiabetic	Freely soluble in water	-	Absolute bioavailability (50 – 60%)	1.5 – 1.6	[96]
Trimetazidine dihydrochloride	Antianginal	Freely soluble in water	-	Rapidly absorbed	6.0 ± 1.4	[97]
Ciprofloxacin	Fluoroquinolone antibiotic	Freely soluble in water	-	Mainly absorbed in the proximal areas	4	[98]
Alfuzosin hydrochloride	Alpha-adrenergic receptor blocker	Highly water soluble	-	Absorb from upper GIT. Absolute bioavailability 49% under fed condition and 25% under fasting condition	5	[99]
Cephalexin	Cephalosporin antibiotic	-	Degrade in alkaline pH	-	1	[100]
Ofloxacin	Fluoroquinolone antibiotic	-	Highly soluble in acidic media and precipitates in alkaline media	Absorption occurs in upper GIT	8 – 9	[101,10]
Metoprolol succinate	Adrenergic blocking agent	Highly soluble throughout physiological pH	-	Absorption mainly takes place in the duodenum and jejunum	3 – 4	[72]
Norfloxacin	Fluoroquinolone antibiotic	Very slightly soluble in water	-	Mainly absorbed from stomach and upper intestine. Low bioavailability (30 – 40%)	3 – 4	[102]
Silymarin	Antioxidant	Poorly water soluble	-	Low bioavailability	6	[103]
Acyclovir	Antiviral	Slightly soluble in water	-	Absorb from the duodenum and small intestine; bioavailability 10 – 20%	1 – 2	[104]
Dipyridamole	Platelet inhibitor	High solubility in acidic solution but poor in neutral or alkaline media	-	Absorb mainly in upper part of the GIT	2 – 3	[105]
Verapamil hydrochloride	Calcium channel blocker	Soluble in water	-	Low bioavailability (10 – 20%) due to first-pass effect	4	[106]
Domperidone	Prokinetic agent	Good solubility in acidic pH but significantly reduced solubility in alkaline medium	-	Rapidly absorbed from the stomach and the upper part of GIT	7	[107]
Zolpidem tartarate	Non-benzodiazepine, sedative-hypnotic	-	-	Absorb from upper part of GIT	-	[108]

GRDDS: Gastroretentive drug delivery system.

Table 2. Drawbacks associated with various GRDDS.

Technology	Drawbacks
High density systems	Cannot manufacture with large amount of drug due to technical problems. Till date, no such system is available in the market
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 and not economical
Mucoadhesive systems	Efficiency can be reduced in rapid turnover of mucus. Might bind to other mucosal lining like esophagus
Magnetic systems	Might compromise with patient compliance

GRDDS: Gastroretentive drug delivery system.

scanning calorimetry and by X-ray diffraction studies and the results demonstrated stable nature of developed formulation.

4. Formulation design: technological consideration

As discussed previously, various technologies have been developed for gastroretention of the drugs but still only few have been commercialized. These systems have different principles of working and have their own merits and demerits. **Table 2** shows the drawbacks associated with various GRDDS. Among various GRDDS, floating and bioadhesive/mucoadhesive technology-based products are mostly developed by the pharmaceutical companies. Now the current focus of the pharmaceutical companies is associated with dual working systems. **Table 3** comprises the various gastroretentive technologies adopted by the pharmaceutical companies along with the name of related marketed products.

4.1 Floating and mucoadhesion technology-based systems

Floating and mucoadhesion technology-based systems are capable to float on the gastric fluid and can bind to gastric mucosal surfaces. FDC Ltd. (Mumbai, Maharashtra, India) launches a novel dual working system of sodium feredetate based on the principle of floatation and bioadhesion (Ferfoz + controlled-release (CR) tablets). Developed system ensures gastric retention in dual ways. This product is based on the bilayer tablet technology where one layer consists of adhesive polymers and another one is floating layer. The uniqueness of the product is the film coating of mucoadhesive layer which helps to get over the drawback related with mucoadhesive systems. Film coating of bilayer tablets prevents the undesirable mucoadhesion of tablets to buccal and esophageal mucosa. Moreover, a high concentration of iron from an immediate release dosage form can lead to GIT toxicity but the developed system releases drug in a sustained manner in gastric region that ultimately reduces the chances of toxicity and on the other hand improves the bioavailability of iron due to the fact that iron is preferably absorbed from the upper GIT [48].

Recently, several studies have been done employing dual working technology. Liu *et al.* [49] produced hollow and bioadhesive microspheres comprising ethylcellulose as the matrix, Eudragit® EPO to modulate the release rate and glyceryl monooleate as the bioadhesive polymer. Scanning electron microscopy was performed to investigate the morphological characteristics of the microspheres. Glyceryl monooleate coating did not show any effect on the release but the release of the drug was influenced by the different pH utilized. *In vitro* and *in vivo* studies demonstrated good floating and strong mucoadhesive properties of the microspheres.

Sahasathian *et al.* [50] developed mucoadhesive and floating chitosan-coated alginate beads of amoxicillin. Initially beads were prepared by utilizing alginate as the core polymer and then amoxicillin was incorporated in these cores. After that, amoxicillin-loaded alginate cores were coated using chitosan 0.5% (w/v) as the mucoadhesive polymer. Developed system showed high drug loading and excellent floating ability with strong mucoadhesion in gastric mucosal layer. In comparison with simulated intestinal fluid (phosphate buffer, pH 7.4), amoxicillin release was faster in simulated gastric fluid (pH 1.2). Zheng *et al.* [51] utilized a combined method of emulsification/evaporation and internal/ion gelation to prepare floating–bioadhesive microparticles of clarithromycin to treat *H. pylori* infection. Clarithromycin, ethylcellulose and chitosan were dispersed in dichloromethane and evaporation was done to produce ethylcellulose microspheres. These microspheres were coated with alginate by the internal gelation method to obtain alginate-ethylcellulose microparticles. Finally, the prepared alginate-ethylcellulose microparticles were dispersed into the chitosan solution to enhance the bioadhesive properties. Developed system showed excellent floating ability of 8 h in acetate buffer solution and 90% of the drug was released in 8 h. *In vivo* studies demonstrated strong mucoadhesion of the microparticles up to 8 h.

Chavanpatil *et al.* [52] developed a swellable, floating and bioadhesive GRDDS of ofloxacin using psyllium husk, hydroxypropyl methylcellulose and crospovidone. GRDDS followed Higuchi kinetics with anomalous or non-Fickian release. A similar release with similarity factor (f_2) value of 91.12 was found in comparison with marketed formulation (Zanocin OD). The swelling property was increased with increasing concentration of crospovidone. The bioadhesive property of the developed formulation was found to be significantly increased in combination compared with the hydroxypropyl methylcellulose and psyllium husk alone. Mina Ibrahim [53] developed a swelling, floating and bioadhesive GRDDS

Table 3. Gastroretentive technologies adopted by various pharmaceutical companies.

Technology	Company	Product	Active pharmaceutical ingredient
Bioadhesive tablets	Lupin, India	Xifaxan	Rifaximin
Effervescent floating system	Ranbaxy, India	Zanocin OD	Ofloxacin
		Riomet OD	Metformin hydrochloride
		Cifran OD	Ciprofloxacin
Colloidal gel forming floating system	Ranbaxy, India	Conviron	Ferrous sulfate
Foam-based floating system	Sato Pharma, Japan	Inon Ace Tablets	Siméthicone
Polymer-based swelling technology: AcuForm™	Depomed, Inc., USA	Gabapentin GR	Gabapentin
		ProQuin® XR	Ciprofloxacin
		Glumetza®	Metformin hydrochloride
Effervescent and swelling-based floating system	Sun Pharma, Japan	Prazopress XL	Prazosin hydrochloride
Minextab Floating® system	Galenix, France	Metformin hydrochloride	Metformin hydrochloride
		Cafeclor LP	Cefaclor
		Tramadol LP	Tramadol
Erodible matrix-based system	Bayer, USA	Cipro XR	Ciprofloxacin hydrochloride and betaine
Expandable film filled in capsule	Intec Pharma	Accordion Pill TM	-
Coated multi-layer floating and swelling system	Sun Pharma, India	Baclofen GRS	Baclofen
Gastroretention with osmotic system	GlaxoSmithKline	Coreg CR	Carvedilol
Floating, CR capsule	Roche, UK	Madopar	Levodopa and benserazide
		Valrelease	Diazepam
Effervescent floating liquid alginate preparation	Reckitt Benckiser Healthcare, UK	Liquid gaviscon	Alginic acid and sodium bicarbonate
Bilayer floating capsule	Pharmacia Ltd., UK	Cytotec	Misoprostol (100/200 μg)
Floating liquid alginate	Pierre Fabre Medicament, France	Topalkan	Aluminum magnesium antacid

CR: Controlled-release.

comprising ciprofloxacin hydrochloride. Hydroxypropyl methylcellulose and sodium alginate were employed to control the release and sodium bicarbonate or calcium carbonate to generate gas to induce floating. Developed system showed excellent bioadhesion and good buoyant nature along with sustained delivery of drug. X-ray photographs revealed the floating time of 5.50 ± 0.77 h in healthy volunteers. Effect of excipients on floating and mucoadhesion capabilities of the developed systems have been evaluated by various researchers. Varshosaz *et al.* [54] compared mucoadhesive capacity of carboxymethylcellulose and polyacrylic acid. Floating and bioadhesive tablets of ciprofloxacin were prepared using sodium carboxymethylcellulose, polyacrylic acid, citric acid and sodium bicarbonate. Excellent flotation of 23 – 24 h was achieved by the developed floating–bioadhesive tablets. Developed tablets showed strong mucoadhesion when the concentration of carboxymethycellulose was increased compared with polyacrylic acid. Umamaheshwari *et al.* [55,56] demonstrated the effect of cellulose acetate butyrate coating on the floating ability and gastric retention of the developed floating–bioadhesive microcapsules of acetohydroxamic acid. Coated microcapsules were found to have good buoyancy properties in comparison with uncoated resin particles but in the gastric region quantity of remaining resin particles was high.

4.2 Swelling and floating technology-based systems

These systems work on the principle of swelling and floating technology. Sun Pharma (Vadodara, Gujarat, India) developed a novel GRDDS which works on the same principle. This system has a core of drug and rate controlling excipients followed by a coating of effervescent excipients. A coating of swelling excipients is made over the effervescent layer and finally an immediate release coating is layered. **Figure 2** is depicting various coating on the core (drug and rate controlling excipients) of the novel GRDDS developed by Sun Pharma. Based on this technology, Sun Pharma is selling a once-a-day product of baclofen [57]. Other perfect examples of floating and swelling technology-based products are Glumetza® (metformin hydrochloride extended-release tablets) and ProQuin® XR (ciprofloxacin hydrochloride extended-release tablets) of Depomed, Inc. (Menlo Park, California, USA). Both these products improve the pharmacotherapy of metformin and ciprofloxacin. Studies revealed that these once-a-day preparations significantly improved the pharmacological response and reduced the associated side effects compared with conventional multi-dose products [58].

Swelling–floating technology is also an area of interest for the researchers. Chen *et al.* [59] developed a swellable and floatable system bearing losartan. The GRDDS consist of hydroxyethyl

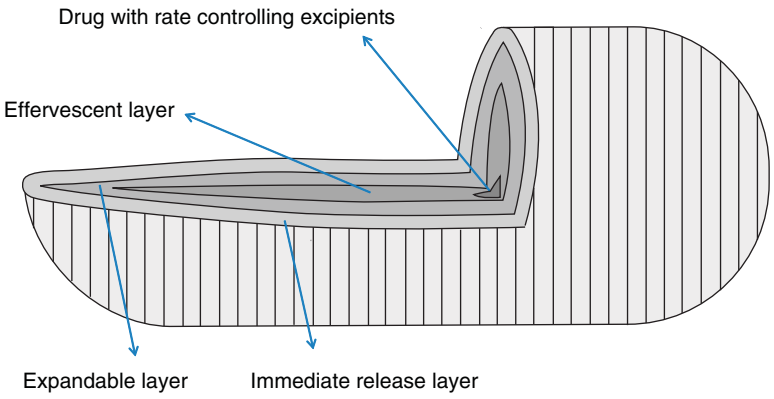

Figure 2. Sun Pharma's dual working technology.

cellulose, sodium carboxymethyl cellulose and sodium bicarbonate. Tablets were prepared with different compression pressure to evaluate swelling and floating properties. Clinical trials were also accomplished to estimate the bioavailability and extent of conversion of losartan to its active metabolite E3174 by *CYP2C9* polymorphism. The optimized formulation showed the floating time of 16 h in simulated gastric fluid with capacity of swelling of 2 cm within 3 h. Drug release was found to be dependent on the pH of the medium. High bioavailability, increased mean residence time, increased t_{max} and lower C_{max} values were observed for the developed GRDDS compared with marketed formulation Cozaar®.

Arza *et al.* [60] prepared a swellable and floating system based on the hydrophilic polymer (hydroxypropyl methylcellulose), swelling agents (crospovidone, sodium starch glycolate and crosscarmelose sodium) and effervescent substance (sodium bicarbonate). Developed formulation showed excellent floating properties. Higuchi kinetic model was adopted to evaluate the drug release mechanism and it was found non-Fickian/anomalous diffusion. Compared with marketed formulation (Cifran OD), the f_2 value was found to be 26.17. Radiographic pictures of the healthy volunteers were captured and the mean residence time of developed formulation was observed to be 320 ± 48.99 min (n = 6). Optimized formulation demonstrated good swelling, drug release and floating characters compared with the marketed formulation (Cifran OD).

5. Analytical specifications

Selection of appropriate analytical specifications for a drug product should be done in passable manner to evaluate precisely its performance. International conference on harmonization (ICH) provides guidance 'ICH Q6A specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances' [61] regarding different analytical test recommended for specific dosage form. ICH also provides guidance on analytical validation 'Q2 (R1) validation of analytical procedures: text and methodology' [62]. Moreover, during initial development phases an analytical development scientist can refer the different pharmacopoeias, if drug product is reported there. Selection of analytical specifications depends on the type of drug delivery system. For example, if someone is developing a tablet technology-based dual working GRDDS (floating–swelling and floating–bioadhesion) then its analytical specifications could be as given in **Table 4**.

Usually, disintegration test is skipped from the specifications of GRDDS because GRDDS are controlled and sustained release drug delivery systems. After selection of analytical specification second step is to setup appropriate acceptance criteria for all the specifications. Acceptance criteria can be adjusted on the basis of experience gained during the development process and by taking reference from the different pharmacopoeias. For a new drug delivery system, analytical specifications and acceptance criteria can be modifying on the basis of experience gained during development process of the drug product. However, *in vitro* mucoadhesion test methods are not much reliable for giving accurate information to correlate with *in vivo* mucoadhesion and there is an urgent need to develop a more authentic *in vivo* mucoadhesion testing method [63]. Parikh and Amin [64] 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 [65]. General in-process controls performed during various stages of manufacturing of gastroretentive floating tablets are provided in **Table 5**.

6. Optimization studies

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 utmost important to identify critical formulation and process variable which can affect the performance and quality of a GRDDS. Different statistical design such as factorial design [66-68], central

Table 4. Analytical specifications for tablet technology-based dual working GRDDS (floating–swelling and floating–bioadhesion).

S. no.	Analytical specifications	Remarks
General tests		
1	Description of dosage form	Detailed description of tablet like its shape, color, coating and marking or embossing
2	Identification test of active moiety and coloring agent, if available in composition	-
3	Average weight	-
4	Uniformity of mass or uniformity of content	Selection of test depends on type of tablet and concentration of the active moiety
5	Friability	-
6	Dissolution	-
7	Assay	-
8	Related substances (impurities)	If any
9	Residual solvent	If any
10	Microbiological limits	–
Specific tests		
11	Test for specific gravity	For floating tablets and floating-based dual working tablets
12	Buoyancy/floating ability test	For floating tablets and floating-based dual working tablets
13	Test for swelling	For swelling tablets and swelling-based dual working tablets
14	Test for mucoadhesion	For mucoadhesive tablets and mucoadhesion-based dual working tablets

GRDDS: Gastroretentive drug delivery system.

Table 5. In-process controls required during manufacturing of floating tablets.

S. no.	Stage of manufacturing	In-process controls
1	During blend preparation	Appearance of the blend
2		Loss on drying
3		Assay of active moiety
4	During compression of tablets	Description
5		Average weight
6		Uniformity of weight
7		Diameter
8		Thickness
9		Hardness
10		Friability
11		Dissolution test
12		Assay
13		Buoyancy test
14		Test for specific gravity

composite design [69-71], Box–Behnken design [72,73] and simplex lattice design [74-76] are used for optimization of GRDDS.

El Gamal *et al.* [77] 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 were selected as dependent variables. Results revealed that high concentration of both the independent variables increase the quality of the tablets. Optimized batch produced good buoyancy and release patterns even after stability testing of product at 40°C/75% relative humidity for 3 months. Sultana *et al.* [78] optimized performance of mucoadhesive microspheres of lacidipine using central composite design. Effect of independent variable 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 highly affected by the polymer concentration and volume of glutaraldehyde compared with other independent variables. Oral bioadhesive hydrophilic matrices of repaglinide have been developed by Vaghani *et al.* [79]. 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 mucoadhesion, drug release at 2 and 8 h. Acceptance criteria for optimized formulation was 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.

7. Scale up and postapproval changes

Scale up and process validation of developed manufacturing process comes under consideration after successful optimization studies. These are important aspects to find out the reproducibility and adaptability of developed manufacturing process by large-scale production machines. Manufacturing of small-scale batch in the R&D is very easy in comparison with manufacturing large-scale batch in the production house. This is the reason that large number of investigations are limited to laboratories and do not reach to the market. GRDDS like unfolding expandable dosage forms are difficult

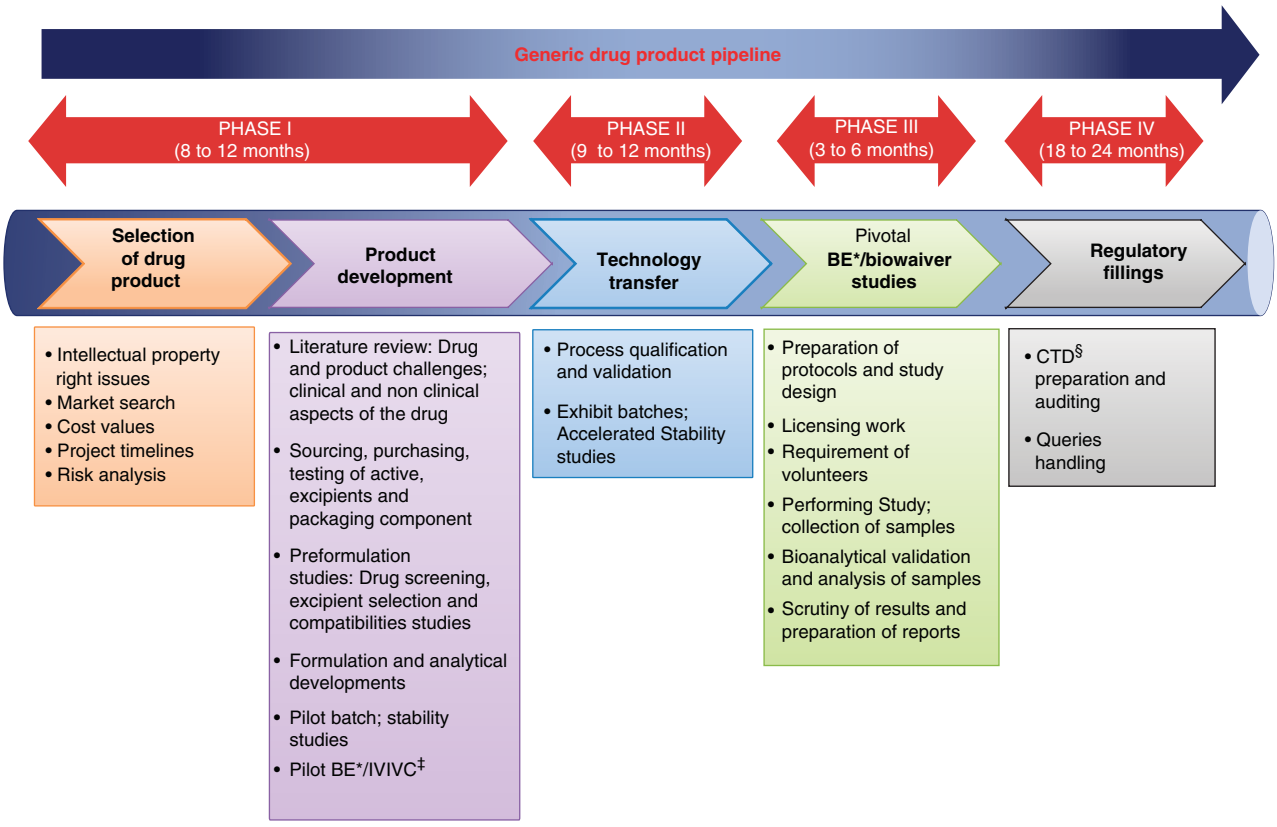

Figure 3. Generic drug product development pipeline.

*Bioavailability studies.
‡*In vitro-In vivo* correlation.
§Common technical document.

to scale up and their commercialization is not easy in contrast to swelling systems [27].

Any changes made in analytical procedures, manufacturing procedures and packaging of the drug product after its approval for marketing by US FDA is known as postapproval changes. If any change takes place in formulation component like replacement of excipient(s) or change in initial material for preparation of the active moiety, afterward it is necessary to scale up the formulation again. It is also necessary to ensure that the changes made in drug product are not affecting its quality and efficacy. The US FDA provides guidance for the scale up and postapproval changes (SUPAC) and process validation, that is, 'guidance for industry SUPAC-IR/MR: immediate release and modified release solid oral dosage forms manufacturing equipment addendum' [80] and 'guidance for industry process validation: general principles and practices' [81]. The US FDA recommends process validation of the first three production scale batches.

8. Bioequivalence/bioavailability studies

Final stage of the development of a GRDDS is the bioequivalence/bioavailability studies. This is quite tedious, long and costly phase of the product development. It is very difficult to clear this stage by GRDDS because of high variability in physiologic principles between the individuals. Generic drug product manufacturing is a challenging affair and manufacturers can neglect overburden of bioequivalence studies by knowing regulatory aspects of the studies. **Figure 3** shows the different attributes involved during development of a generic drug product. 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 is released from drug product within 15 min then it is not necessary to perform bioequivalence studies [82]. For BCS class I and II drugs, 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 manufacturer of GRDDS can refer the US FDA database, that is, 'bioequivalence recommendations for specific products' for making decision about the

bioequivalence/bioavailability studies of the developed GRDDS [83]. This database provides information about already performed bioequivalence studies or biowaiver reports of approved products. For most of the cases, it is an ideal platform for the preparation of protocols for the bioequivalence studies and for biowaiver applications. The US FDA also provides guidelines for the bioavailability and bioequivalence studies for orally administered drug products [84].

In vitro–in vivo correlation (IVIVC) is a very 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 relationship between *in vitro* release and *in vivo* absorption. As a result, someone can predict the *in vivo* fate of developed GRDDS by utilizing IVIVC data. However, traditional dissolution methods do not provide accurate *in vivo* conditions for GRDDS. In dissolution vessel, swelling system tends to bind with peddle whereas floating systems float on the dissolution medium and released drug could establish a layer on the surface of dissolution medium. To overcome such problems, several studies have been done to modify traditional dissolution apparatus and dissolution conditions which in turn mimic more *in vivo* conditions for getting further reliable IVIVC data [64]. There are three levels of correlation described by the US FDA. 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 regarding dissolution medium and mathematical models are applied to directly compare 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 single point correlation between dissolution ($t_{50\%}$ or $t_{90\%}$) and plasma drug concentration–time data (AUC, t_{max} or C_{max}). The level C is considered as the lowest level of correlation [85,86].

9. Expert opinion

GRDDS are the unique systems and are getting considerable importance in the research during last three decades but the availability of GRDDS in the market is very less. The major advantage of GRDDS is assurance that physiological conditions like GRT will work in favor of developed system. GRDDS can overcome drawbacks associated with OSRDF in an efficient manner. Apart from this, GRDDS have great importance in chronotherapy and can effectively meliorate the efficacy of chronotherapeutic drug delivery systems [87-89]. Drugs which are unstable in lower GIT and have solubility problems can be delivered efficiently using GRDDS. Drug repurposing is also an open field for researcher to improve pharmacotherapy of various disease states. Before selecting an active moiety for GRDDS, each molecule should be passed through the individual case study of biopharmaceutical parameters. Furthermore, it is necessary to predict the working capabilities of GRDDS in fed and fasted conditions of the gastric region.

Varieties of investigations have been done that lead to development of various GRDDS. However, only few can make way to market. These technologies show excellent *in vitro* results but fail to give desirable *in vivo* performance. Mucoadhesive and floating technologies are getting substantial attention and most of the drug products available in the market are based on the principle of these technologies. In consequence, dual working systems based on mucoadhesive and floating principles have more potential to increase industrial implementation of GRDDS and can improve the *in vivo* performance of the active moiety. Furthermore, combination of mucoadhesion technology with floating technology can ameliorate loopholes associated with floating technology like floating lag time. In future, some more gastroretentive technologies can be combined to improve the gastric retention and to reduce the associated drawbacks.

The quality of the developed system can be more precisely evaluated by developing appropriate analytical specifications with respect to the particular system. Floating dosage form should be characterized *in vitro* for parameters such as specific gravity, porosity, buoyancy and floating lag time. Specific gravity and porosity can indirectly affect the buoyancy of the floating systems, whereas, higher floating lag time can lead to complete dose dumping due to evacuation of floating system from the stomach prior to drug release. There is also a need to develop an optimum *in vitro* floating time testing method for a floating dosage form that can efficiently evaluate the effect of fed and fasting states of the gastric region on the floating capabilities of the developed product. On the other hand, available mucoadhesion tests are lacking to provide sufficient *in vivo* correlation. *In vivo* environmental factors like tonicity and mucus turnover rate must be considered when an *in vitro* mucoadhesion test is demonstrated. It is necessary to understand principles of scale up, process and analytical validation to develop a reproducible manufacturing process that can deliver a high quality drug product. Large-scale production requires more easiness in the formulation accompanying economic drug delivery systems. Therefore, the researchers should also keep in mind these concepts before starting their research which can ultimately lead to development of a reproducible high quality and low cost drug product.

The pricey and difficult job of bioavailability and bioequivalence studies of GRDDS can be smoothly accomplished by understanding regulatory aspects of these studies. Development of IVIVC and application of mathematical models would be helpful in prediction of problems associated with SUPAC and biowaiver application. In conclusion, market appearance of GRDDS can be improved by opting an appropriate drug and delivery system with incorporating all the relevant quality attributes.

Declaration of interest

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Affiliation

Vivek K Pawar, Shaswat Kansal, Shalini Asthana & Manish K Chourasia[†]
[†]Author for correspondence
Pharmaceutics Division, CSIR-Central Drug Research Institute,
Lucknow, UP 226001, India
Tel: +91 522 2612411 18;
Fax: +91 522 2623405;
E-mail: manish_chourasia@cdri.res.in
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