Progress in Controlled Gastroretentive Delivery Systems

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Abstract

Controlled release (CR) dosage forms have been extensively used to improve therapy with several important drugs. However, the development processes are faced with several physiological difficulties such as the inability to restrain and localize the system within the desired region of the gastrointestinal tract and the highly variable nature of the gastric emptying process. This variability may lead to unpredictable bioavailability and times to achieve peak plasma levels. On the other hand, incorporation of the drug in a controlled release gastroretentive dosage forms (CR-GRDF) which can remain in the gastric region for several hours would significantly prolong the gastric residence time of drugs and improve bioavailability, reduce drug waste, and enhance the solubility of drugs that are less soluble in high pH environment. Gastroretention would also facilitate local drug delivery to the stomach and proximal small intestine. Thus, gastroretention could help to provide greater availability of new products and consequently improved therapeutic activity and substantial benefits to patients. Controlled gastric retention of solid dosage form may be achieved by the mechanisms of floatation, mucoadhesion, sedimentation, expansion or by a modified shaped system. The purpose of this paper is to review the recent literature and current technology used in the development of gastroretentive dosage forms.

Keywords: Gastroretention, Oral controlled release, Swelling, Narrow absorption window, Floating dosage form

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INTRODUCTION
Oral controlled release (CR) dosage forms (DFs) have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is bedilled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility. Furthermore, the relatively brief gastric emptying time (GET) in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose. Therefore, control of placement of a drug delivery system (DDS) in a specific region of the GI tract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem.

These considerations have led to the development of a unique oral controlled release dosage form with gastroretentive properties. After oral administration, such a DF would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. Gastroretentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestines. Gastroretention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of CR-DFs of these drugs.

The need for gastroretentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems. These efforts resulted in GRDFs that were designed, in large part, based on the following approaches.

(a) Low density form of the DF that causes buoyancy in gastric fluid
(b) High density DF that is retained in the bottom of the stomach
(c) Bioadhesion to stomach mucosa
(d) Slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients
(e) Expansion by swelling or unfolding to a large size which limits emptying of the DF through the pyloric sphincter.

The current review deals with the gastroretentive approaches that has recently become leading methodologies in the field of controlled and site specific drug delivery system.

SUITABLE DRUG CANDIDATES FOR GASTRORETENTION
In general, appropriate candidates for CR-GRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT:

• Narrow absorption window in Gltract, e.g., riboflavin and levodopa
• Primarily absorbed from stomach and upper part of Gltract, e.g., calcium supplements, chlordiazepoxide and cinnarazine
• Drugs that act locally in the stomach, e.g., antacids and misoprostol
• Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole
• Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate

FACTORS CONTROLLING GASTRIC RETENTION OF DOSAGE FORMS
The gastric retention time (GRT) of dosage forms is controlled by several factors such as density and size of the dosage form, food intake, nature of the food, posture, age, sex,
sleep and disease state of the individual (e.g., gastrointestinal diseases and diabetes) and administration of drugs such as prokinetic agents (cisapride and metoclopramide).

1. Density of dosage form
Dosage forms having a density lower than that of gastric fluid experience floating behavior and hence gastric retention. A density of <1.0 gm/cm$^3$ is required to exhibit floating property. However, the floating tendency of the dosage form usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium$^{11}$.

2. Size of dosage form
The size of the dosage form is another factor that influences gastric retention. The mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size, which may be small, medium, and large units. In fed conditions, the smaller units get emptied from the stomach during the digestive phase and the larger units during the housekeeping waves. In most cases, the larger the size of the dosage form, the greater will be the gastric retention time$^{12}$ because the larger size would not allow the dosage form to quickly pass through the pyloric antrum into the intestine. Thus the size of the dosage form appears to be an important factor affecting gastric retention.

3. Food intake and nature of food
Food intake, the nature of the food, caloric content, and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the stomach influences the GRT of the dosage form. Usually, the presence of food increases the GRT of the dosage form and increases drug absorption by allowing it to stay at the absorption site for a longer time. In a gamma scintigraphic study of a bilayer floating capsule of misoprostol$^{13}$, the mean gastric residence time was 199 ± 69 minutes; after a light breakfast, a remarkable enhancement of average GRT to 618 ± 208 minutes was observed. The above results are supported by the experiments of Whitehead et al$^{14}$ which show an increase in the relative heights of the floating units after meal consumption.

4. Effect of gender, posture and age
A study by Mojaverian et al$^{15}$ found that females showed comparatively shorter mean ambulatory GRT than males, and the gastric emptying in women was slower than in men. The authors also studied the effect of posture on GRT, and found no significant difference in the mean GRT for individuals in upright, ambulatory and supine state. On the other hand, in a comparative study in humans by Gansbeke et al$^{16}$, the floating and non-floating systems behaved differently. In the upright position, the floating systems floated to the top of the gastric contents and remained for a longer time, showing prolonged GRT. But the non-floating units settled to the lower part of the stomach and underwent faster emptying as a result of peristaltic contractions, and the floating units remained away from the pylorus. However, in supine position, the floating units are emptied faster than non-floating units of similar size$^{17}$.

TYPES OF GASTRORETENTIVE DOSAGE FORMS

A. Floating drug delivery systems
Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.

FDDS can be divided into non-effervescent and gas-generating system

(a) Non-effervescent systems
This type of system, after swallowing, swells unrestrained via imbibition of gastric fluid to an extent that it prevents their exit from the
stomach. One of the formulation methods of such dosage forms involves the mixing of the drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier\textsuperscript{18}. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

This system can be further divided into four sub-types:

(i) Colloidal gel barrier system

Sheth and Tossounian first designated this ‘hydrodynamically balanced system’\textsuperscript{19}. Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption. This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g., hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose (HPMC), polysaccharides and matrix-forming polymer such as polycarbophil, polycrylate and polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface.

(ii) Microporous compartment system

This technology is based on the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls\textsuperscript{20}. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

(iii) Alginate beads

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate\textsuperscript{21}. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40°C for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hours.

(iv) Hollow microspheres / Microballoons

Hollow microspheres loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent diffusion method\textsuperscript{22}. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40°C. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 h.

(b) Gas-generating (Effervescent) systems

These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid)\textsuperscript{23}. The system is so prepared that upon arrival in the stomach, carbon dioxide is released, causing the formulation to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate\textsuperscript{24}, multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of
sodium bicarbonate, lactose and polyvinylpyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology, etc.

B. Expandable systems

Expandable gastroretentive dosage forms (GRDFs) have been designed over the past 3 decades. They were originally created for possible veterinary use but later the design was modified for enhanced drug therapy in humans. These GRDFs are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that prolong their GRT. After drug release, their dimensions are minimized with subsequent evacuation from the stomach. Gastroretentivity is enhanced by the combination of substantial dimensions with high rigidity of the dosage form to withstand the peristalsis and mechanical contractility of the stomach. Positive results were obtained in preclinical and clinical studies evaluating the GRT of expandable GRDFs. Narrow absorption window drugs compounded in such systems have improved in vivo absorption properties.

C. Bio/Muco-adhesive systems

Bioadhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a site-specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Gastric mucoadhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucus by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastroretentive force. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan and gliadin, etc.

D. High-density systems

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Dense pellets (approximately 3g/cm$^3$) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on the diameter of the pellets. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to 1.5–2.4g/cm$^3$.

ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

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.

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.

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.
**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.

**Reduced fluctuations of drug concentration**

Continuous input of the drug following CR-GRDF 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.

**Improved selectivity in receptor activation**

Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

**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.

**Extended time over critical (effective) concentration**

For certain drugs that have non-concentration dependent pharmacodynamics, such as beta-lactam 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.

**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 beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism’s resistance.

**Site specific drug delivery**

A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency.

**WORKS ON GASTRORETENTIVE DOSAGE FORM**

Basak et al designed floatable gastro-ententive tablet of metformin hydrochloride using a gas-generating agent and gel-forming hydrophilic polymer. The formulation was optimized on the basis of floating ability and in vitro drug release. The in vitro drug release test of these tablets indicated controlled sustained release of metformin hydrochloride and 96-99% released at the end of 8 h. Jaimini et al prepared floating tablets of famotidine employing two different grades of Methocel K100 (HPMC K100) and Methocel K15 (HPMC K15) by an effervescent technique. These grades were evaluated for their gel-forming properties. The tablets with Methocel K100 were found to float for a longer duration compared with the formulation containing Methocel K15M. Decrease in the
The drug release from the tablets was confirmed. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed.
Badve et al\textsuperscript{33} developed hollow calcium pectinate beads for floating-pulsatile release of diclofenac sodium intended for chronopharmacotherapy. Floating pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release. This approach suggested the use of hollow calcium pectinate microparticles as promising floating-pulsatile drug delivery system for site- and time-specific release of drugs for chronotherapy of diseases.

Chavanpatil et al\textsuperscript{34} developed a new gastroretentive sustained release delivery system of ofloxacin with floating, swellable and bioadhesive properties. Various release retarding polymers such as psyllium husk, HPMC K100M and a swelling agent, crosspovidone, in combinations were tried and optimized to obtain release profile over 24 h. The in vitro drug release followed Higuchi kinetics and the drug release mechanism was found to be non-Fickian.

Rahman et al\textsuperscript{35} established a bilayer-floating tablet (BFT) for captopril using direct compression technology. HPMC K-grade and effervescent mixture of citric acid and sodium bicarbonate formed the floating layer. The release layer contained captopril and various polymers such as HPMC-K15M, PVP-K30 and Carbopol 934, alone or in combination with the drug. The formulation followed the Higuchi release model and showed no significant change in physical appearance, drug content, floatability or in vitro dissolution pattern after storage at 45 °C/75% RH for three months.

Xiaoqiang et al\textsuperscript{36} developed a sustained release tablet for phenoporlamine hydrochloride because of its short biological half life. Three floating matrix tablets based on a gas-forming agent were prepared. HPMC K4M and Carbopol 971P were used in formulating the hydrogel system. Incorporation of sodium bicarbonate into the matrix resulted in the tablets floating over simulated gastric fluid for more than 6 hours. The dissolution profile of all the tablets showed non-Fickian diffusion in simulated gastric fluid.

Sharma et al\textsuperscript{37} developed a multiparticulate floating pulsatile drug delivery system using porous calcium silicate and sodium alginate, for time- and site-specific drug release of meloxicam. Prepared beads were spherical with crushing strength ranging from 182 to 1073g.

Srivastava et al\textsuperscript{38} prepared microspheres with HPMC and ethyl cellulose using solvent evaporation method. The shape and surface morphology of the microspheres were characterized by optical and scanning electron microscopy. The microspheres exhibit prolonged drug release (8 h) and remained buoyant for more than 10 h. In vitro studies demonstrated diffusion-controlled drug release from the microspheres.

Chavanpatil et al\textsuperscript{39} developed a gastroretentive dosage form for ofloxacin to be taken preferably once daily. The design of the delivery system based on a sustained release (SR) formulation with swelling and floating features in order to prolong gastric retention. Different polymers such as psyllium husk, HPMC K100M, crosspovidone and its combination were used and the formulations were evaluated for buoyancy, stability, drug content and drug release studies.

Jain et al\textsuperscript{40} designed a controlled release system to increase GRT without contact with gastric mucosa. The was achieved through the preparation of floating microspheres by emulsion solvent diffusion technique consisting of calcium silicate (FLR) as a porous carrier, repaglinide and a Eudragit polymer. The effect of various formulation and process variables were studied.

Patel et al\textsuperscript{41} formulated and evaluated floating tablets of ranitidine. Two fillers, namely, Avicel PH 102 and Tablettose 80 were used. It was observed that viscosity had a major influence on drug release from hydrophilic matrices as well as floating properties.

Muthusamy et al\textsuperscript{42} designed a sustained release floating micropellets of lansoprazole by emulsion solvent diffusion technique using drug to carrier ratios of 1:1, 1:2, 1:3. HPMC, methyl cellulose and chitosan were used as carriers. The yield of micropellets was up to 82%. The drug to chitosan ratio of 1:1 showed good incorporation efficiency and high
percentage in vitro release of lansoprazole from micropellets. The range of particle size was between 327 to 431 µm.

Sato et al.43 studied pharmacoscintigraphic evaluation of riboflavin containing microballons for floating drug delivery system in healthy human volunteers and found that microballons were very useful for improving drug bioavailability, resulting in more sustained pharmacologic action.

Dave et al.44 developed gastroretentive delivery system of ranitidine HCL. Guar gum, xanthan gum and HPMC were used as gel-forming agents. Sodium carbonate was incorporated as a gas-generating agent. The effects of citric acids and stearic acid on drug release profile and floating properties were investigated. It was indicated that a low amount of citric acid and high amount of stearic acid favoured the sustained release of ranitidine HCL.

Sato et al.45 developed microballons (MB) by emulsion solvent diffusion method using enteric acrylic polymers dissolved in a mixture of dichloromethane and ethanol. The pharmacokinetics of riboflavin was investigated by urinary excretion. MB prepared by mixing with HPMC in varying ratios, resulted in improved riboflavin release properties.

Umamaheshwari et al.46 developed floating microspheres bearing acetohydroxamic acid using polycarbonates as drug carriers by emulsion (o/w) solvent evaporation techniques. The effect of polycarbonate concentration on morphology, particle size, entrapment efficiency and drug release rate was studied.

El-Gibaly et al.47 prepared floating microcapsules containing melatonin by the interaction of chitosan and a negatively charged surfactant, sodium diocetyl sulfosuccinate. The characteristics of the floating microcapsules generated compared well with the conventional non-floating microspheres. The data obtained suggest that the floating hollow microcapsules produced would be an interesting gastroretentive controlled release delivery system for drugs.

Streubel et al.48 developed and physiochemically characterized single-unit, floating controlled drug delivery system consisting of polypropylene foam powder and matrix-forming polymers. The highly porous foam powder provided low density and thus excellent in vitro floating behavior of the tablets.

Joseph et al.49 developed floating microspheres of piroxicam capable of floating on simulated gastric and intestinal fluid. The microspheres were prepared by a solvent evaporation technique. Incorporation efficiency of over 95% was achieved and in vitro release of piroxicam from polycarbonate microspheres in simulated gastric fluid at 37°C showed no significant burst effect.

Choi et al.50 prepared floating beads from a sodium alginate solution containing CaCO₃ or NaHCO₃ as the gas-forming agent. The solution was dropped into 1 % CaCl₂ solution containing 10% acetic acid for CO₂ gas and gel formation. The effect of gas forming agent on bead size and floating properties were investigated. The results of the study indicate that CaCO₃ is superior to NaHCO₃ as a gas-forming agent in alginate bead preparation.

El-Kamel et al.51 prepared floating microparticles of ketoprofen by emulsion solvent diffusion technique. Four different ratios of Eudragit S 100 (ES) with Eudragit RL (ERL) were used. The drug retained in the floating microparticles decreased with increase in ERL content. The formulation containing 1:1 ratio of the above-mentioned polymers exhibited high percentage of floating particles in all the examined media.

**Formulation of “Floating Microspheres / Micro Balloons”**

Hollow microspheres are prepared by solvent diffusion and evaporation methods to create the hollow inner core. The polymer is dissolved in an organic solvent and the drug is either dissolved or dispersed in the polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing polyvinyl alcohol to form an oil-in-water emulsion. After the formation of a stable emulsion, the organic solvent is evaporated.
either by increasing the temperature under pressure or by continuous stirring. The solvent removal leads to polymer precipitation at the o/w interface of the droplets, forming the cavity and thus making them hollow to impart the floating properties.

CONCLUSION
Controlled release gastroretentive dosage forms (CR-GRDF) enable prolonged and continuous input of the drug to the upper parts of the gastrointestinal (GI) tract and improve the bioavailability of medications that are characterized by a narrow absorption window. CR-GRDF provides a means to utilize all the pharmacokinetic (PK) and pharmacodynamic (PD) advantages of controlled release dosage forms for such drugs. Based on the literature surveyed, it may be concluded that drug absorption in the gastrointestinal tract is a highly variable process and prolonging gastric retention of the dosage form extends the time for drug absorption. Thus gastroretentive dosage forms provide an additional advantage for drugs that are absorbed primarily in the upper segments of gastrointestinal tract, i.e., stomach, duodenum and jejunum. Due to the complexity of pharmacokinetic and pharmacodynamic parameters, in vivo studies are required to establish the optimal dosage form for a specific drug. For a certain drug, interplay of its pharmacokinetic and pharmacodynamic parameters will determine the effectiveness and benefits of the CR-GRDF compared to the other dosage forms.

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