Original Article

An Recent Advantage On Gastroretentive Drug Delivery System: An Overview

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Abstract

The gastro-retentive drug delivery system (GRDDS) has attracted the attention of researchers in the area of oral medication delivery in recent years. To keep the dose forms in the stomach and release the medication slowly over an extended period of time, many GRDDS techniques can be used. GRDDS can be utilised to extend the delivery system's duration in the stomach. As a result, the medicine is released specifically at that location for either local or systemic effects. In order to optimise the bioavailability of a certain therapeutic substance, GRDDS can be utilised to get around problems with traditional oral dosage forms and release the medication at a particular absorption site. Fast stomach emptying of the dose form, which causes poor drug bioavailability, is one of the difficulties. The solubility of medications is improved by keeping them in the stomach for a longer period of time when the intestinal pH is high. GRDDS has shown to be useful in treating gastric or duodenal ulcers both locally and systemically. By increasing the residence duration of the delivery system in the stomach, local action in the upper section of the small intestine can be attained. Drugs with low solubility or permeability in the small intestine or those that are unstable in the intestine can benefit from the system. High density (sinking) systems, low density (floating) systems, muco-adhesive, expandable, unfoldable, ultra porous hydrogel systems, and magnetic systems are some of the several GRDDS techniques.

Keywords: Gastro-retentive drug delivery system, Gastric residence time, Migrating motor complex, Oral controlled release, Floating drug delivery, Gastrointestinal tract.

INTRODUCTION:

For systemic or local medication distribution, the oral route is the most suitable and recommended method. Researchers are becoming more interested in oral controlled release delivery systems in order to increase therapeutic benefits such straightforward dosage, patient compliance, and dose safety. Medicines with short half-lives that are easily absorbed by the Gastrointestinal tract are quickly removed from the bloodstream. Thus, regular administration of those medications is becoming necessary to achieve therapeutic activity. Other straightforward oral dose forms quickly empty the stomach, which causes issues with many medication compounds' bioavailabilityTo address this issue, oral sustained/controlled release formulations are created. These formulations work by slowly releasing the medicine into the gastrointestinal tract (GIT) for an extended period of time, allowing for an effective concentration of the drug in the systemic circulation. When administered orally, this medication can be kept in the stomach and released in a controlled, prolonged manner. As a result, the medication is continuously delivered to the GIT's particular site of absorption. Improvement in medication solubility and prolongation of retention of pharmaceuticals in the stomach for those with low solubility at high intestinal pH. Many medications, including captopril, metronidazole, and ranitidine HCL, are susceptible to breakdown in the colon.

To treat gastric or duodenal ulcers, the gastro-retentive drug delivery system (GRDDS) has shown to be beneficial both locally and systemically. The short gastric retention time (GRT) of GRDDS in the stomach and the unpredictably short gastric emptying time of the delivery system (gastric emptying time [GET]) are the two main issues with GRDDS. These issues may result in insufficient drug release from the dosage form in the absorption area, which lowers the effectiveness of the medication that is being administered. It is advantageous to enhance a GRT of medication formulation in order to create an oral controlled release drug delivery system tailored to a given place. Long-term gastric retention enhances bioavailability, lengthens the time that pharmaceuticals are released from the stomach, and increases the solubility of medications that are poorly soluble in the acidic environment of the intestine or breakdown in alkaline pH. By increasing the delivery system's residence duration in the stomach, one can increase local activity in the upper region of the small intestine. GRDDS can be utilised to extend the delivery system's duration in the stomach. As a result, the medicine is released specifically at that location for either local or systemic effects. Several GRDDS techniques have been created and developed during the past few decades. Low density or floating systems that continue to float on gastric fluid are

two of these ways. High density or sinking systems that can be held in the basal region of the stomach are another. Superporous hydrogel systems, magnetic systems, unfoldable, extendible, or swellable systems, which prevent the emptying of delivery systems from the stomach's pyloric sphincter, are examples of muco-adhesive systems that cause adherence to the mucosa of the stomach.

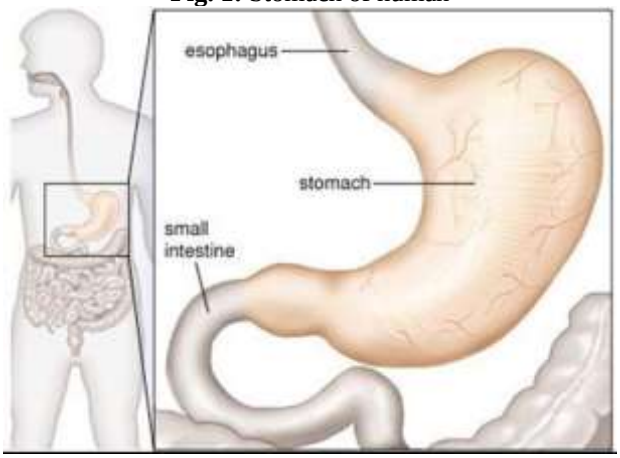
Stomach physiology:

Knowing the stomach physiology and associated gastric emptying process plays the major role in the success of GRDDS. The stomach is present in the upper left part of abdominal cavity immediately after diaphragm [12]. The human stomach consists of three anatomical parts which are fundus, body, and antrum or pylorus, as shown inFig. 1 [15]. The remaining volume of the stomach is only 25–30 ml after food has been emptied from the stomach. The antrum is a main site for the mixing process in the stomach, while the undigested material is stored at the region formed by fundus and the body. Antrum is the bottommost part of the stomach which acts as a gastric emptying pump by ejecting the stomach contents [16]. The stomach and duodenum are separated by the pylorus, which has an important role in residence time of the ingested substances in the stomach. The fasting or fed state influences the motility pattern of individual [17, 18]. The gastric motility pattern has different cycles of activity. Each cycle is continued for four phases and the time span of each cycle is 90–120 min, as shown in Table 1 [19]. The motility pattern of the stomach is usually called as migrating motor complex (MMC) [20]. The phases of MMC are given in Table 1.

Various Factors Affecting Gastric Residence Period of Delivery Systems:

The stomach anatomy and physiology parameters shouldbe considered while formulating the gastro-retentive dosage form. The size of particles must be within the range of 1–2 mm to pass through the pyloric sphincter into the small intestine [22]. The important factors thataffect the residence time of the delivery systems in the stomach are food intake and its nature, frequency ofintake [23,24], density, size and shape of dosage forms [25,26], patient gender, age, sex, body mass index, and disease status of the individual person (i.e., Diabetes and Chrohn's disease) [15,27,28] and drugs that have effects on gastrointestinal transit time such as anticholinergic drugssuch as atropine or prokinetic agents such as metoclopramide and cisapride [29].

Fig. 1: Stomach of human



Density of dosage forms:

Density of dosage form also influence the gastric emptying rate of the dosage form. Density also plays a key role in determining the location of the delivery system in the stomach. Dosage forms with low density than gastric contents can float on the surface, whereas high-density systems go down to the bottom of the stomach. Low-density system or floating systems should maintain bulk density less than 1 g/cm^3, so as to remain buoyant on the gastric contents [15].

Table 1: Different phases of migrating motor complex [14, 21, 19]

Phase	Statement	Time span(min)
Phase 1	Also called basal phase. This stage does not have any contractions	30–60
Phase 2	Also called pre burst phase. This stage has irregular contractions	20–40
Phase 3	The good food material migrates	10–20
	distally due to regular contraction at maximum frequency	
Phase 4	Transition period between phases 3and	10–5

Shape and size of the dosage form:

Shape and size of the dosage form are important factors in designing indigestible single unit dosage forms. The mean GRT of a non-floating dosage form is varyingaccording to their size. In most cases, bigger the dosage form the better will be the gastric residence period. The larger size dosage form cannot be passed rapidly throughthe pyloric sphincter into the intestine. Dosage forms which having the diameter greater than 7.5 mm shows better GRT as compared to that

of 9.9 mm [30]. Likewise,

Various Approaches to Accomplish Gastric Retentionof Dosage Forms:

High density or sinking systems or non-floating systems

In this approach, the density of formulation must be superior to the density of normal gastric content (1.004 g/cm^3) [47]. These formulations (Fig. 2) are developed by coating drug on a heavy core or mixed with inert substances such as iron powder, barium sulfate, zinc oxide, and titanium oxide [48]. Materials increase density up to 1.5–2.4 g/cm3. A density of almost 2.5 g/cm3found to be necessary for significant prolongation ofGRT [49]. This system has its disadvantage that the size of dosage form is increased to achieve the high density. As compared to other shapes, ring shaped, and tetrahedron shaped devices show better GRT [6].

Food intake and its nature

Factors such as food intake, viscosity and amount of food, caloric value, and recurrence of feeding have an intense effect on gastric retention of dosage forms. The existence and non-existence of food in the GI tract also influence the gastric retention of dosage forms. In general, the existence of food material in the GI tract increases the GRT of the dosage form and therefore drugabsorption improved by allowing its residence at the specific absorption site for the longer period of time. Theincrease in stomach acid and caloric value slows theGET [15], which can increase the gastric retention of delivery system [24].

Effect of sexual category, position, and age

Normally, females show a slower rate of gastric emptying as compared to males [3]. The effect of position does not have any notable difference in the mean GRT for individuals in standing, ambulatory or lying position. In case of aging peoples, gastric emptying is sloweddown.

Possible Drug Candidates for Grdds [31 · 46]1.

Drugs those have local activity in the stomach (e.g.,ranitidine, amoxicillin, levofloxacin, and metronidazole)2. Drugs with narrow GI absorption window (e.g., riboflavin, cilostazole, pregabalin, and metformin)3. Drugs that are unstable or degrade in intestinal or colonic environment (e.g., verapamil and captopril)4. Drugs those have little solubility at high pH of the intestine (e.g., ofloxacin and cinnarizine).

Drugs Those are Unsuitable for GRDDS [21].

Drugs with low acidic solubility (e.g., phenytoin)2. Drugs those are unstable or degrade in the acidic environment of the stomach (e.g., erythromycin)3. Drugsthose are used for targeted release in the colon (e.g., corticosteroids).

Low-density systems or floating systems:

The FDDS is an important dosage form which helps in obtaining sufficient bioavailability by prolongation ofGRT [50]. The floating system was first introduced byDavis in 1968. Fig. 2 depicted the concept of the floatingsystem. This delivery system is suitable for drugs withan absorption window in the stomach or upper small intestine [51, 52]. It is also helpful for the drugs that have action locally in the proximal portion of GIT such as antibiotics used for eradication of Helicobacter pylori in the treatment of peptic ulcer [53]. These have a bulk density less than gastric fluids and therefore remain afloat on the stomach contents without influencing the gastric emptying rate for an extended period of time and the drug is released slowly at a desired rate from the system. After the release of active drug, the deliverysystem is emptied from the stomach [54]. The key necessities for floating drug delivery systems are:

- It should release the API slowly to act as a reservoir
- It should keep specific gravity lower than gastriccontents (1.004–1.01 g/cm^3)
- It must form a cohesive gel barrier.

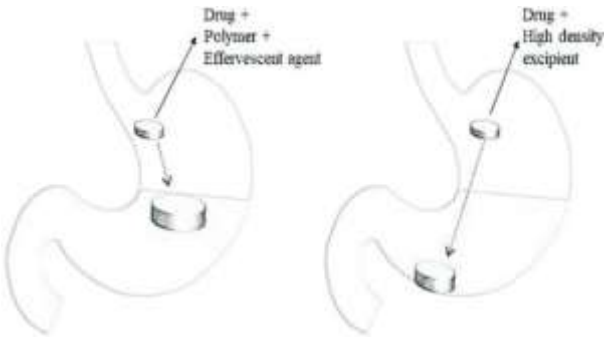


Fig. 2: Low-density and high-density systems [64]

The low density is obtained from the entrapment of air (e.g., hollow chamber) [55] or due to merging low-density materials [56] (fatty materials or oils [57] or foam powder)[58,59]. Recently, a single unit floating system was formulated by utilizing polypropylene foam powder, matrix forming polymers, drugs, and fillers [59]. Single unit dosage forms may cause problems such as sticking together or being blocked in the GIT which may cause GI irritation. Multiple unit floating

systems may be an attractive alternative as they lower the chances of dose dumping [60]. Many multiple unit floating systems such as air compartment multiple unit system [61], hollow microspheres (microballoons) formulated using the emulsion solvent diffusion method [52], microparticles based on low-density foam powder [59,62] beads prepared by emulsion gelatin method [57,63] can be distributed widely throughout the GIT, providing the opportunity of obtaining a long lasting, and more reliable release of active medicament. Depends on the mechanism of buoyancy, two clearly different techniques which areeffervescent and non-effervescent drug delivery systems have been used in the formulation of FDDS.

Effervescent or gas generating systems:

In this system, buoyancy can be resulted from generationof gas bubbles. These floating systems use the matrices developed using swellable polymers such as polysaccharides (e.g., chitosan), effervescent agents suchas sodium bicarbonate, sodium citrate, or tartaric acid. Inthese systems, the dosage form floats on the gastric fluid in stomach due to liberation of CO_2. Other approaches and materials are a mixture of sodium alginate and sodium bicarbonate [65], multiple unit floating dosage forms that produce carbon dioxide gas in the stomach after ingestion, floating mini capsule having a core of sodium bicarbonate, lactose, and polyvinyl pyrrolidone coated with hydroxy propyl methyl cellulose (HPMC), and floating system based on ion exchange resintechnology, etc. [6]. Bilayer or multilayer system has been designed [66]. Gas generating agents are incorporated in any of these layers after the drug and excipients areformulated independently.

Non-effervescent systems:

These floating systems are generally prepared by gelforming or swellable cellulose type hydrocolloids, polysaccharides, or matrix forming polymers such as polyacrylate, polycarbonate, polystyrene, and polymethacrylate [15,67]. In one approach, mixing of medicament with a gel forming hydrocolloid which in contact with gastric fluid after oral administration maintain a relative integrity of shape and a bulk density lower than that of gastric content. The air trapped by the swollen polymer grant floatability to these dosage forms [67]. The excipients utilized very commonly are HPMC, polyacry lates, po lyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide, and polyca rb on ates [6]. This system can be again classified into following sub types:

Hydrodynamically balanced systems (HBS):

These systems were first designed by Sheath and Tossounian in 1984. HBS are consisting of drug with gel forming hydrocolloids that remain buoyant on the gastriccontent. One or additional gel forming polymers are usedto prepare these single unit dosage forms. In general, used excipients are HPMC, hydroxy propyl cellulose, sodium carboxymethyl cellulose, polycarbophil, polyacrylate, polystyrene, agar carrageenans, or alginic acid. The polymer mixed with drug and generally isgiven in HBS capsule. The capsule shell breakdown in contact with water and swells which lead to the formation of gelatinous barrier, which gives floatability in dosage form in gastric content for a longer period of time. The erosion of the exterior layer permits penetration of water into the internal layers maintaining the surface hydration and floatability to the drug deliverysystem. Various approaches have been tried and examined to improve efficiencies of the floating HBS [68].

Microballoons/hollow microspheres:

Microballoons/ hollow microspheres are loaded with APIs in their outer polymer shelf were formulated using simple solvent evaporation or solvent diffusion/evaporation methods [69] to improve the residence time of the delivery system in the stomach. Some common polymers used to prepare these systems are cellulose acetate, polycarbonate, calcium alginate, eudragit S, low methoxylated pectin, agar, etc. The quality of polymers, the plasticizer polymer proportion, and solvent used for preparation have a significant effect on the floating and drug release from the delivery system. The microballoon remains buoyant without interruption on the surface ofan acidic dissolution medium more than 12 h. Hollow microspheres are ranked among the most promising floating system because they have combined the advantages of a multiple unit system and good buoyance.

Alginate beads:

Recently, multiple unit floating systems were prepared that is based on cross linked beads [63]. The system was prepared using calcium ion and low methoxylated pectin (anionic polysaccharide) or calcium ions+ low methoxylated pectin and sodium alginate. Sodium alginate solution is dropped into an aqueous solution of $CaCl_2$ which leads to the precipitation of calcium alginate. These beads are then separated and desiccated using air convection and freeze drying, results in the formulation of porous system which can remain floating for more than 12 h. These beads increase the GRT more than 5.5 h [6,50]. Recently, floating alginate beads prepared using a gas generating agent such as calcium carbonate ($CaCO_3$) and sodium bicarbonate ($NaHCo_3$) 70.

Bioadhesive or mucoadhesive drug delivery systems:

These systems were first introduced by Park andRobinson in 1984 [71]. Mucoadhesive DDS are utilized asdelivery devices within humans to increase drugabsorption at a specific site. In this approach, mucoadhesive polymers are used [72,73] which hold on to the epithelial surface in the stomach. Therefore, they canprolong the gastric retention. The delivery system (Fig. 3) can hold onto the mucosal surface by various mechanisms. These mechanisms include [74]:

1. The wetting theory – is based on the ability of mucoadhesive polymers to spread and form contact with the mucous

layers

2. The diffusion theory – is based on the interpenetration of mucin strands into the porous configuration of the polymer substrate
3. The absorption theory – states that the bioadhesion is the result of Vander Waals forces and hydrogen bonding
4. The electronic theory – is based on attractiveelectrostatic forces between the glycoprotein mucin network and the bioadhesive materials.

Materials that exhibit bioadhesive property are chitosan, HPMC, acrylic acid, cholestyramine, sodium alginate, sucralfate, dextrin, tragacanth, polyethylene glycol, polylactic acid, etc. Despite some of these polymers are effectively produce bioadhesion, it is hard to maintain this bioadhesion due to rapid turnover of mucus in the GIT [30].

Expandable, unfoldable, and swellable systems:

An expandable system (Fig. 4) can achieve a longerGRT by increasing its shape or volume. These systems were first designed for veterinary use and then explore for the human use [6]. A dosage form can be retained in the stomach still after gastric transit when it is larger in size than the diameter of the pyloric sphincter. In general, these systems composed of hydrophilicpolymers, when polymer comes in contact with gastric fluid it absorbs water and becomes swollen [12,75]. The swelling and drug release is occur due to the process of diffusion. However, care should be taken that the dosage form must be small enough to swallow and should not cause gastric blockage alone or by accumulation. Thus, their configurations should be considered whiledeveloping expandable systems to prolong GRT.

1. A small design for oral use
2. An expanded gastroretentive form
3. A small form that allows clearance subsequent todrug release from the device.

Unfoldable systems are prepared from biodegradable polymers which are folded and encapsulated inside acarrier which degrade in the stomach [12]. Unfoldable systems are available in the different geometric forms such as a tetrahedron, ring, or planner membrane (4- limbed cross or 4-label disc form) of biodegradable polymer compressed within a capsule which extends in the stomach. Swellable systems are also retained in the stomach because of their mechanical properties. The swelling is generally caused due to osmotic absorption ofwater. The expandable systems have some disbenefits such as the storage of easily hydrolyzable polymers is problematic [76], biodegradable polymers are most difficultto industrialize and not cost effective. Permanent retention of rigid, large single-unit expandable drug delivery dosage forms may cause brief obstacle, intestinal sticking, and gastric diseases [12].

Superporous hydrogel system:

In this approach, the GRT is improved by superporous hydrogel of average pore size greater than 100 μm. They swell to an equilibrium size from minute due to water uptake by capillary wetting through numerous interconnected open pores [16]. They swell to large size up to 100 or more [77]. These systems utilize the highly swellable polymers such as croscarmellose sodium and sodium alginate [68]. These formulations have high mechanical strength and elastic properties.

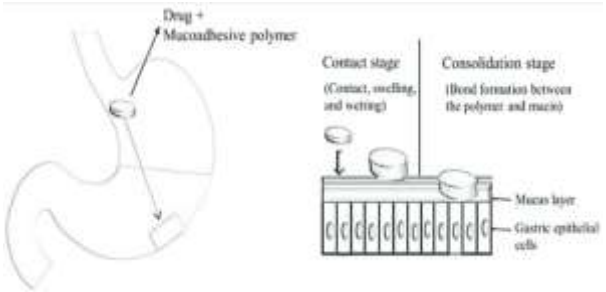


Fig. 3: Mucoadhesive drug delivery system [64]

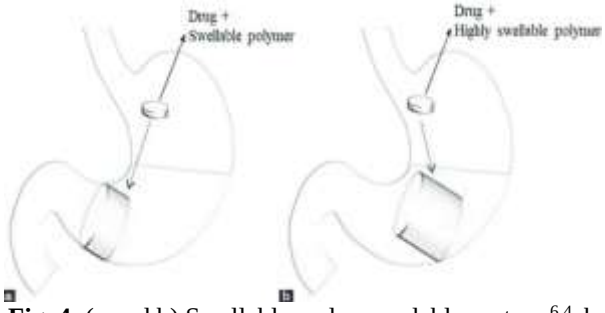


Fig. 4: (a and b) Swellable and expandable system [6 4]ab

Raft forming systems:

These systems (Fig. 5) are developed using gel forming polymers and effervescent excipients so as to obtain sustained

drug delivery. These systems are effective in achieving localized effect as they form a blockade between esophagus and stomach. Therefore, system can be utilized for the treatment of peptic ulcer andgastroesophageal reflux disease. After contact with stomach fluid these systems become swelled and forms aviscous cohesive gel which results in the formation of a continuous layer called as raft [14,78]. The antacid raft forming system is also developed recently in which sodium alginate is used as gel forming polymer, sodium bicarbonate, and acid neutralizer as gas generating agents. The raft floats on the gastric fluid due to generation of CO2 that reduce the bulk density of the system. The raft can remain floating on the gastric fluid for a few hours and release the drug in a sustained manner. Such rafts are especially useful for the delivery of antacid drugs [79]. These systems can be disrupted by MMC as they have weak mechanical strength [78,80].

Magnetic system:

In this approach, external magnet is used to improve GRT of the dosage form which consists of a small internal magnet along with the excipients and API (Fig. 6). The external magnet is placed on the abdomen over the position of the stomach that controls the position of internal dosage form [14] or improves the GRT of dosage form [81]. The external magnet must be placed with adegree of accuracy that may reduce patient compliance Some often used drugs in the development of GRDDS and some gastroretentive products available in the market are shown in Tables 2 and 3

Merits of Grdds:

- The bioavailability and therapeutic effects can be improved for those drugs which get metabolized in the alkaline environment of the intestine
- Lessen the frequency of dosing and thus improves patient compliance
- They have a benefit over their conventional systemas they can use to overcome gastric emptying time (GET). These systems are likely to remain floating on the gastric fluid without influencing the intrinsic rate of emptying as their bulk density is lower than that of the gastric fluids
- GRDDS can prolong and sustain the drug releasefrom the dosage form which facilitates local delivery in the stomach and small intestine. Thus, these systems are useful to treat diseases related to the stomach or small intestine
- The controlled, slow delivery of the active drug from the gastroretentive delivery systems provides adequate local action at the diseased site thus minimizes or eliminates the systemic disclosure of drugs. This sitespecific drug delivery minimizes undesirable effects of drugs
- GRDDS can reduce the fluctuations of drug concentrations and effects. This helps to avoid concentration dependent adverse effects that are associated with peak concentrations. This aspect is of a special importance for drugs with a narrow therapeutic index
- GRDDS can diminish the counter activity of the body, leading to higher drug effect
- Reduction in fluctuation in drug concentration ensures increased selectivity in receptor activation

The continuous release of drug for an extended period from the GRDDS allows extension of the time over the critical concentration and hence intensifies the pharmacological effects and improves chemical outcomes.

Challenges Involved in Grdds:

The GRDDS are stomach specific and required to retain in the stomach only. Therefore, the retention of the dosage form in the stomach or in the upper part of the small intestine for a long period of time until all drug from the system is released at predetermined rate is the biggest challenge in formulating GRDDS. The gastric emptying process is highly variable and depends on various factors. However, the main factor is dosage formand fasted or fed state of the stomach. The gastric emptying time is also influenced by the factors such as food, caloric content, gender, and age. The process of gastric emptying is also prolonged by high fat and high calories containing food. The GRT is varying and relatedto the patients age, gender, size and shape of dosage forms, individuals disease state, and body mass index. The GRT is also affected by the pylorus. Another fact is the animals (dog or rabbit) that have different size of the pylorus and its peristaltic movement than that of human beings. Indigestible polymers and fatty acid salts also alter the motility pattern of the stomach under fed conditions and assist in decreasing gastric emptying rate.Therefore, it is necessary to conclude the resultscarefully.

Drugs	**Dosageform**
Acetyl salicylic acid, Ciprofloxacin, Fluorouracil, Prednisolone, Theophylline [47], Acetaminophen [82], Ampicillin [48], Atenolol [51], Captopril [83], Cinnarizine [8], isosorbide dinitrate [84], Verapamil HCL [85], Acyclovir [86], Amoxicillin trihydrate [87], Losartan [88]	Floating tablets
Diazepam, Misoprostol, Propranolol, Pepstatin, L-dopa, and benserazide [47] Furosemide [89]	Floating capsule
Aspirin, Ibuprofen [47] Griseofulvin [90], Famotidine [91,92] Floating microspheres Diclofenac sodium, Prednisolone [47] Indomethacin [93]	Floating granules

Table 3: Marketed gastroretentive products [3,16,31,47,94]

Brand name	API	Delivery system	Manufactured by
Cytotec®	Misoprostol	Bilayer floating capsule	Pfizer, UK
Baclofen GRS®	Baclofen	Coated multilayer and swelling system	Sun Pharma,India
Conviron®	Ferrous sulfate	Colloidal gel forming floating system	RanbaxyIndia
ZanocinOD®	Ofloxacin	Effervescent floating system	Ranbaxy India
RiometOD®	Metformin HCL	Effervescent floating system	Ranbaxy India
CifranOD®	Ciprofloxacin	Effervescent floating system	Ranbaxy India
Topalkan®	Aluminum magnesium	Raft forming system	Pirrie fabre Medicament, France
Almagate FlatCoat®	Aluminum magnesium antacid	Raft forming system	Pirrie fabre Medicament, France
Accordion pill®	Carbidopa - Levodopa	Expandable system (unfolding)	Intec Pharma, Israel
Madopar HBS®	Levodopa and Benserzide	Floating controlled release capsule	Roche, UK
Prolopa HBS®	Levodopa and benserazide HCL	Floating controlled release capsule	Roche, UK
Valrelease®	Diazepam	Floating controlled release capsule	Roche, UK
Inon Ace tablets®	Simethicon	Foam based Floating systems	Sato Pharma, Japan
Coreg CR®	Carvedilol	Gastroretention with osmotic system	GlaxoSmith Kline, UK
Prazopress XL®	Prazocin HCL	Effervescent and swelling system	Sun Pharma, Japan
Cipro XR®	Ciprofloxacine HCL and betaine	Erodible matrix based system	Bayer, USA

CONCLUSION:

Based on the literature reviewed, it may be concluded that GRDDS can provide numerous advantages for drugswith low bioavailability as these delivery systems restrictthe absorption of the drug in the upper GIT and they can be delivered efficiently thereby improving theirabsorption and intensifying absolute bioavailability. The in vivo studies are important to create the optional dosage form for a specific drug because of complexity ofpharmacokinetics and pharmacodynamics parameters. Gastroretentive drug delivery has great significance to increase the therapeutic efficacy of drugs those having a narrow absorption window, high solubility at acidic pH (in Stomach), and low solubility or instability at alkaline pH (intestine). But understanding the anatomy and physiology of the stomach, the effect of formulation and process variables on the quality of dosage form is necessary for successful GRDDS design. Even though numerous GRDDS have been reported in the literature such as low or high density, bio or mucoadhesive, and magnetic systems, but their effectiveness or clinical significance is necessary to be studied. To understand, the influence of formulation and process variables of the dosage form performance QbD approach can be used.

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