Turk J Pharm Sci 2022;19(4):476-487
DOI: 10.4274/tjps.galenos.2021.44959

REVIEW

Features and Facts of a Gastroretentive Drug Delivery System-A Review

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ABSTRACT

English oral delivery of drug was the commonly used modality because of patient compliance and ease of administration. After oral administration of any drug, its bioavailability is affected by its residence time in stomach. Recently, gastroretentive drug delivery systems (GRDDS) have gained wide acceptance for drugs with a narrow absorption window, decreased stability at high alkaline pH, and increased solubility at low pH. This approach develops a drug delivery system, which gets retained within gastric fluid, thereby releasing its active principles in the stomach. Some methods used to achieve gastric retention of drugs include the use of effervescence agents, mucoadhesive polymers, magnetic material, bouncy enhancing excipient, and techniques that form plug-like devices that resist gastric emptying. This review provides a concise account of various attributes of recently developed approaches for GRDDS.

Key words: Bioavailability, bio/mucoadhesive system, therapeutic window, gastric emptying

INTRODUCTION

Oral administration is popular despite continuous improvement in drug delivery approaches owing to patient comfort and ease of administration. Controlled release drug delivery systems are designed for oral administration. These drug delivery systems release the medication in a predetermined, predictable, and controlled way. They are not suitable for drugs with low bioavailability due to stability or absorption issues.[1] These problems can get better through modern approaches, which are designed to increase the residence of such drugs in the stomach for an extended time. Such drug delivery systems are called gastroretentive drug delivery systems (GRDDS). GRDDS are suitable for those drugs, which are absorbed from the stomach (*e.g.* albuterol),[2] labile at alkaline pH (*e.g.* ranitidine and metformin),[3] poorly soluble at alkaline pH (*e.g.* furosemide and diazepam),[4] and having a narrow window of absorption (*e.g.* riboflavin and levodopa).[5]

Some of the common advantages associated with use of GRDDS include improved patient compliance by reducing the frequency of dosing; improved therapeutic efficacy of drugs with a short half-life; site-specific delivery of medications; sustained and controlled release of drugs in the stomach; enhanced residence time of drugs at the absorption site; improved bioavailability from the gastrointestinal tract; avoiding dose dumping of medicines.[6]

To develop GRDDS, different materials like ion-exchange resins, mucoadhesives, high-density materials, raft forming substances, magnetic substances, and super porous hydrogels are used.[7,8]

This review provides a concise account of various attributes of recently developed approaches for GRDDS.

Anatomy and physiology of the stomach

Knowledge about the anatomy and physiology of the stomach is essential for the successful formulation of gastroretentive

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Received: 10.03.2021, Accepted: 18.06.2021

dosage forms. Anatomically, the stomach is divided into three areas: the proximal portion toward the esophagus is fundus, followed by the body, which serves as a storage site for engulfed food, and the antrum, last part that connects the body to the small intestine. Antrum helps in churning action and in gastric emptying.[9] In fasting state, a sequence of contractions occurs cyclically through the stomach and intestine every 120-180 min, called the migrating myoelectric cycle. It is further divided into four phases. The pattern of contraction changes in a fed state is termed as the digestive motility pattern.[10] This pattern comprises phase 1- (basal phase); phase 2- (preburst phase); phase 3- (burst phase); and phase 4.[11] Figure 1 depicts the motility pattern in the gastrointestinal tract.

Physicochemical properties of GRDDS

Physicochemical properties of GRDDS include density, size, and shape of the dosage form, which play major roles in the formulation of GRDDS. The dosage forms having a density lower than the gastric contents can float to the surface, while high-density systems sink to the bottom of the stomach. For an ideal formulation, the density should be in the range of 1.0-2.5 g/cm^3. Dosage forms having a diameter of more than 7.5 mm show better gastric residence time (GRT). Circular, spherical or tetrahedron-shaped devices show excellent gastroretentive properties.[12]

Physiological factors affecting retention of GRDDS in the stomach

The most important factors controlling the gastric retention time of dosage forms include fed or unfed state, nature of the meal, caloric content, and frequency of feeding. In the case of a fasting environment, gastric retention time is less due to the increase in GI motility. Emptying of gastric content occurs due to peristalsis. If peristalsis coincides with dosage form administration, the gastric residence is short. However, after meals, peristalsis is delayed and may help increase the gastric residence of the formulation. A high-calorie meal containing proteins, fats, and fibrous compounds increases gastric retention time. In the case of multiple meals, the gastric retention is more than a single meal due to persistent inhibition of peristalsis.

Also, some other factors, such as sex and age, affect gastric retention. Compared with males, females have a slower gastric emptying time irrespective of height, weight, and body surface. A person at the age of more than 70 exhibits longer GRT. In comparison, neonates show less GRT compared with geriatric patients.[13-15]

Gastroretentive dosage form approaches

Continuous research and advancements in various approaches to gastroretentive dosage forms over the last few years are as presented in Figure 2. These approaches to GRDDS help in delivering the medicament in a sustained and restrained way through the gastrointestinal tract.

Classification of GRDDS

GRDDS are classified into mainly two types: floating and non-floating systems. Floating systems are further classified into effervescent system and non-effervescent systems based on the mechanism of floating, while non-floating systems classified into four different classes based on the mechanism used for gastroretention. Figure 3 depicts the classification of the GRDDS.

I- High-density system

The density of dosage form plays an important factor in the formulation of the GRDDS. A high-density system uses its weight as a retention mechanism. To enhance the gastric residence of a drug in the stomach, its density must exceed the normal stomach content (1.004 g/mL).[16] Figure 4A depicts the principle of a high-density system. Clarke et al.[17] compared

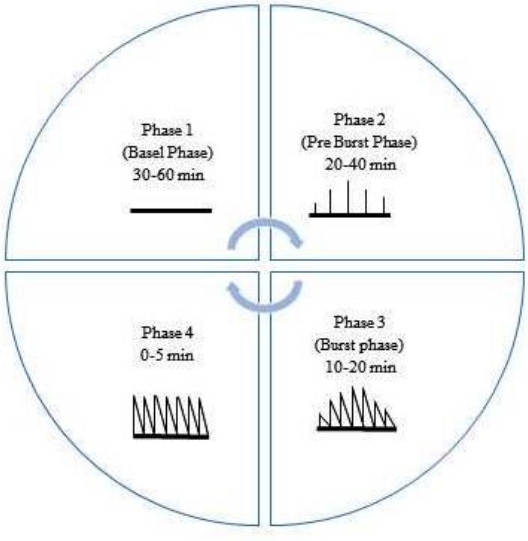

Figure 1. Motility pattern in gastrointestinal tract

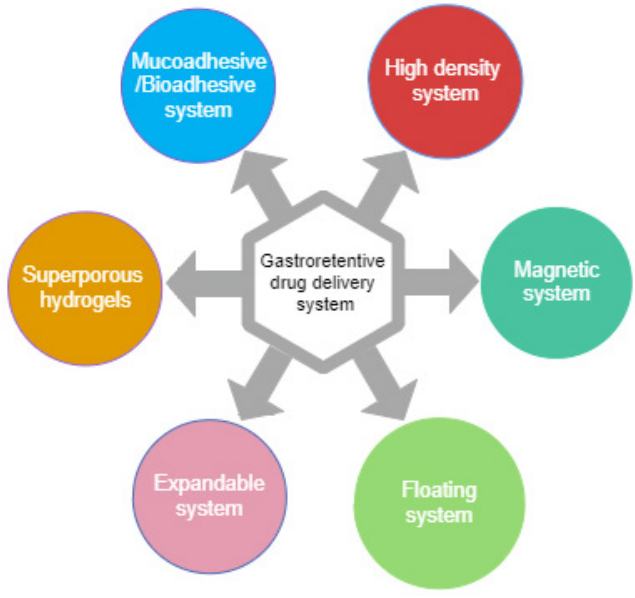

Figure 2. Approaches of gastroretentive drug delivery system

gastrointestinal transit of placebo pellet systems of varying densities using gamma scintigraphy. They reported that GRT of such a formulation can be extended from an average of 5.8 h to 25 h, depending more on density than on the diameter of the pellets.

II- Floating or low-density system

Another approach to increase gastric residence is to lower the density of dosage form than the normal gastric content. These systems remain buoyant due to lower density and provide continuous drug release. In this way, they increase GRT of the drug and improve its bioavailability.[18] Figure 4B depicts the principle of floating or low-density systems.

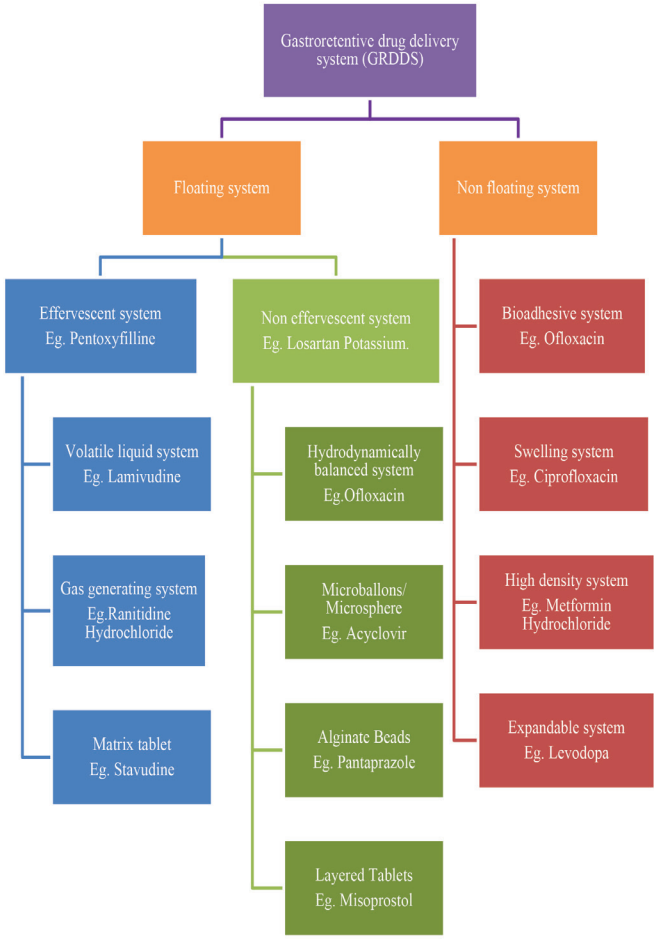

Figure 3. Classification of gastroretentive drug delivery system

(A) Effervescent system

This system uses carbonates (*e.g.* sodium bicarbonate) to generate *in situ* carbon dioxide (CO_2).[19,20] Organic acids (*e.g.* citric and tartaric acids) are added to speed up the reaction, thus reducing the density of dosage form and remaining buoyant in the stomach.[20] It is categorized into two classes:

a) Volatile liquid/vacuum type: These are further classified into three types.

i) Inflatable system

It consists of a pullout system having a space filled with volatile liquids that evaporate at body temperature. Thus, when these systems are introduced into the stomach, the chamber inflates, and the system floats. The inflatable chamber comprises a bioerodible polymer filament that is made from polymers like polyvinyl alcohol and polyethylene. When the inflatable chamber floats in the gastrointestinal fluid, the polymer gradually dissolves and releases the drug. After some time, due to polymer dissolution, the inflatable section collapses.[19,20] Figure 4C depicts a floating effervescent type of inflatable system.

ii) Intragastric floating system

It contains a chamber filled with a vacuum and includes a microporous compartment serving as a drug reservoir.[20] Figure 5 depicts a floating type of intragastric system. Patel et al.[21] developed intragastric floating tablets of verapamil HCl using hydroxypropyl methylcellulose (HPMC), carbopol, and xanthan

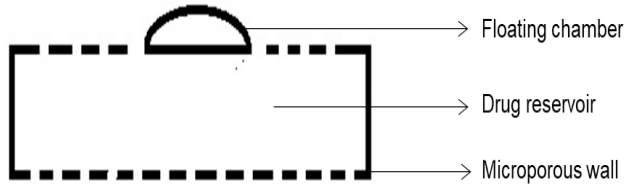

Figure 5. Intragastric floating gastrointestinal drug delivery system.

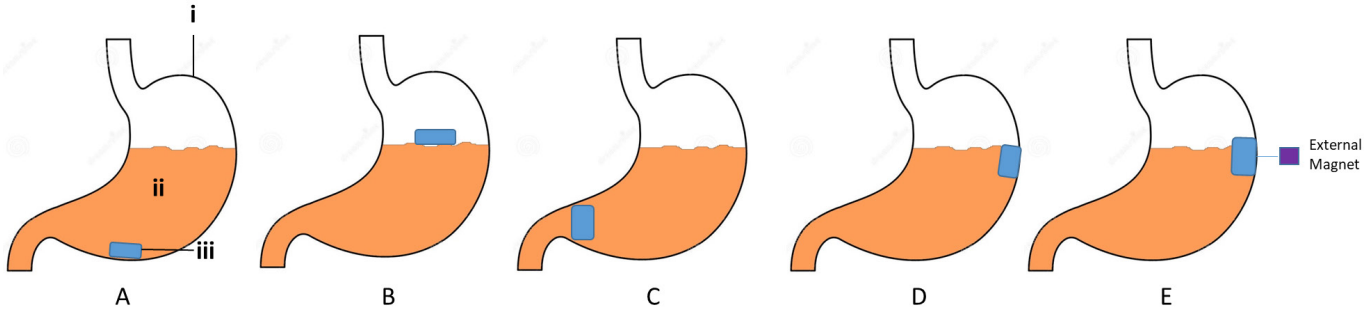

Figure 4. Different types of gastroretentive drug delivery system. A) High density system, B) floating/low density system, C) inflatable system, D) mucoadhesive system, E) magnetic system (i- stomach, ii- gastric fluid, iii- dosage form)

gum as gel-forming agents. Buoyancy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. Optimized formulation exhibited satisfactory results with a short buoyancy lag time of 36 sec, a total buoyancy time of more than 24 h, and controlled drug release for up to 24 h.

iii) Intragastric-osmotically controlled system

Osmotic control can be achieved using a biodegradable capsule comprising inflatable floating support congestion with an osmotic pressure-controlled drug delivery device.[22,23] Zhao et al.[24] used fenofibrate-loaded mesoporous silica nanoparticles to prepare an oral push-pull osmotic pump. Polyethylene oxide (100,000) and polyethylene oxide (6,000,000) were selected as suspending agents and expanding agents, respectively. Cellulose acetate was used as a semipermeable membrane along with polyethylene glycol 6,000 to increase flexibility and control the membrane permeability. The prepared system is reported to stay in the stomach for a period of 21.72 h rather than 12.48 h of the reference tablet and delivers the drug in an approximately zero-order manner for 24 h.

b) Matrix tablets: They are of two types, *i.e.* single-layer and bilayer matrix tablets. The single-layer matrix tablets are prepared using a drug and a hydrocolloid forming gel, while the bilayer matrix tablet contains one immediate-release layer and another sustained release layer. Saisivam et al.[25] developed single-layer floating matrix tablets of losartan potassium using different proportions of HPMC-K4M and karaya gum as retarding polymer and sodium bicarbonate as an effervescent agent by direct compression method. Results of an *in vivo* study of optimized formulation displayed the floatability of tablet in gastric content and prolonged the GRT to approximately 12 h. X-ray imaging study in albino rabbits indicated the residence of tablet in the stomach even after a period of 12 h.

c) Gas generating systems: Gas-generating systems are prepared using effervescent compounds along with hydrophilic polymers.

i) Floating capsules

These dosage forms involve encapsulation of drugs in hydrophilic polymers like ethyl cellulose and eudragit RS-100 with effervescent agents such as sodium bicarbonate, calcium carbonate, *etc.* Moursy et al.[26] developed a hydrodynamically balanced capsule containing a mixture of nicardipine hydrochloride and hydrocolloids. Upon contact with gastric fluid, the capsule shell dissolves with subsequent swelling, forming a gelatinous barrier, which remains buoyant in the gastric juice for an extended period.

ii) Floating pills

Multiple unit types of oral floating dosage forms have been developed using a hydrophilic polymer in the outer layer and an effervescent agent in the inner layer. When it comes in contact with the gastric fluid, the outer layer of hydrophilic polymer starts to swell and then sinks, but as the effervescent agent meets gastric content, it releases CO_2, and the system starts to float.[27,28] Meka et al.[29] prepared multiple-unit minitab of captopril based on a gas formation technique to prolong the GRT and to increase the overall bioavailability of the drug. They developed drug-containing core units using the direct compression process, which were coated with three successive layers of an inner seal coat, effervescent layer (sodium bicarbonate), and an outer gas-entrapped polymeric membrane of polymethacrylates (eudragit RL30D, RS30D, and combinations of them). They found that increasing the coating level of gas-entrapped polymeric membrane decreased the drug release.

iii) Floating systems with ion exchange resins

These floating systems are mainly developed to prolong the GRT of dosage forms using ion exchange resin. They consist of drug resin complex beads loaded with bicarbonate ions, and they are coated with hydrophilic polymers.[30] It results in the generation of CO_2 gas when it comes in contact with the gastric fluid and causes the beads to float. Atyabi et al.[31] developed a floating system based on an ion exchange resin, which consists of resin beads, loaded with bicarbonate and a negatively charged drug that was bound to the resin. Two resins, *i.e.* Amberlite IRA-400 and Dowex 2 x 10, were investigated and both exhibited *in vitro* floating times of over 24 h using a standardized procedure. The coated dosage form remained for over 3 h in the stomach with the non-coated system and demonstrated a marked increase in retention over conventional formulation.

(B) Non-effervescent systems

In non-effervescent floating systems, the drug comes in contact with gastric fluid and it swells. It maintains its shape, and its density remains less than one, hence it floats in gastric juice.[32] Matrix forming polymer, gel-forming, or swellable type hydrocolloids are used for these types of floating systems. They are further classified as follows:

i. Hydrodynamically balanced systems (HBS)

These systems mainly consist of a mixture of drugs and hydrocolloids that forms a gelatinous barrier, when it comes in contact with gastric fluid due to swelling of the combination. It remains buoyant in the stomach for an extended period as its bulk density is less than one in gastric fluid. Nayak and Malakar[33] developed gastroretentive theophylline HBS capsules using HPMC, polyethylene oxide, polyvinylpyrrolidone, ethylcellulose, liquid paraffin, and lactose to control the delivery of theophylline for a longer period in the stomach with a minimum floating time of 6 h.

ii. Microballoons

Microballoons are described by the gradual addition of drug-containing emulsion into a volatile solvent. On evaporation of the solvent, gas is generated in a dispersed polymer droplet, which results in the formation of an interior orifice in the microsphere of the drug with polymer. It is also called emulsion solvent diffusion method.[22] The floating time of microspheres depends upon the type and amount of polymer used in the formulation. Gupta et al.[34] developed pantoprazole sodium-loaded microspheres using eudragit L100 by adopting an emulsion solvent diffusion method with a non-effervescent approach. The results of *in vitro* and *in vivo* studies exhibited a suitable drug-release pattern in terms of increased bioavailability and

efficient ulcer healing effect. Figure 6 depicts the steps involved in the preparation of microballoons by solvent diffusion method.

iii. Alginate beads

These systems are prepared using a hydrocolloid gel-forming agent and sodium alginate as the interlocking agents. In the presence of gastric fluid, the hydrocolloid absorbs water and forms a barrier that results in entrapment of air in the polymer, which causes swelling of the polymer, and hence the dosage form starts to float, and results in releasing the drug for a prolonged period. Ghareeb and Radhi[35] developed trimetazidine calcium alginate floating beads using sodium alginate solution (2, 3, and 4% w/v), HPMC, and peppermint oil (15, 20, and 25% v/v) using emulsion gelation method. They found that oil entrapped floating beads gave promising results for sustaining the release of the drug over 10 h.

iv. Layered tablets

Layered tablets are more popular due to ease of their preparation, low cost, and high stability.

a. Single-layered floating tablets: These tablets were developed by mixing drug and gas generating agents within the matrix tablet. These formulations have lower bulk density than gastric fluid, and thus they remain buoyant in the stomach by increasing GRT.[36] Kim et al.[37] developed non-effervescent gastroretentive tablets of pregabalin once a day using wet granulation and compaction. They found that the amounts of HPMC and crospovidone were found be critical factors affecting *in vitro* dissolution and floating properties of the prepared tablets. Figure 7 depicts a schematic of single-layered floating tablets.

b. Double-layered floating tablets: It comprises of two formulations separated by layering, one on top of the other, having two different release profiles.[3,38] Kuldeep et al.[39] developed a bilayer floating tablet of metoprolol succinate (sustained-release layer) and rosuvastatin calcium (immediate-release layer) by direct compression method. HPMC K100, K4M, and K15M were used as gel-forming agents, while cross carmellose sodium, sodium starch glycolate, and crospovidone were used as super disintegrant. Sodium bicarbonate is used as an effervescent agent. From the *in vitro* buoyancy study, it was observed that as the concentration of gas-generating agents increases, floating lag time decreases. Also, the polymer gas generating agent ratio was found to influence the floating lag time and the total duration of floating.

III- Mucoadhesive and bioadhesive systems

A mucoadhesive and bioadhesive system uses its adhesive properties to target a drug to a specific region of the body for an extended period. Figure 4D displays a mucoadhesive system of GRDDS. For this, bioadhesive or mucoadhesive polymers

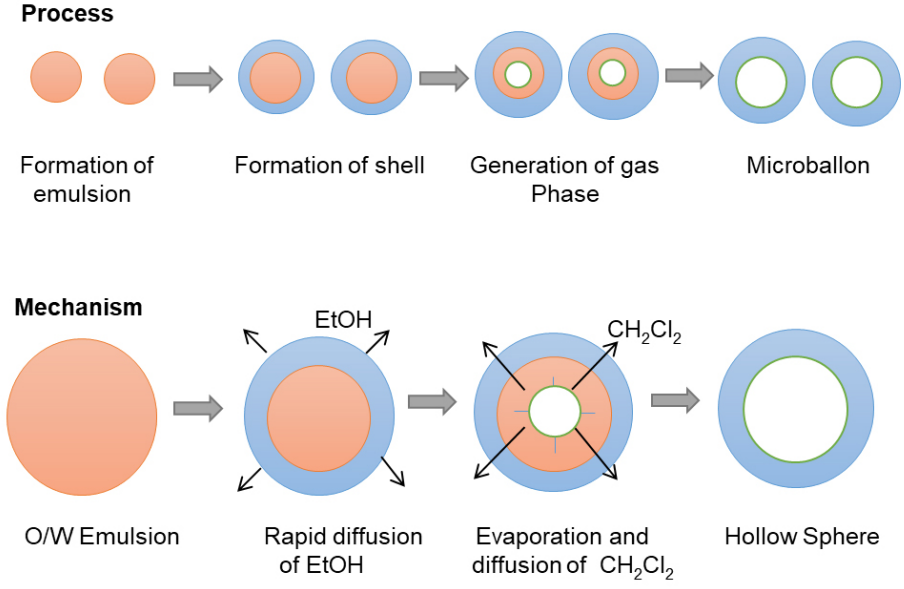

Figure 6. Preparation technique and mechanism of microballoons formation

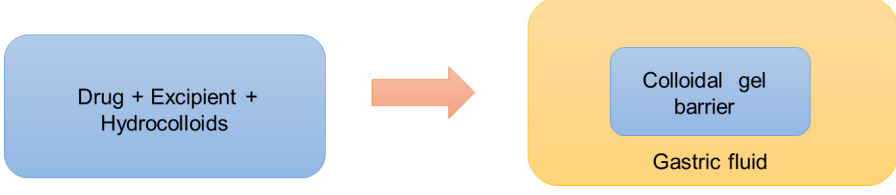

Figure 7. Mechanism of single layer tablet

are mainly used.[40] Natural polymers such as sodium alginate, gelatin, guar gum, *etc*., and semisynthetic polymers such as HPMC, lectins, carbopol, and sodium carboxymethyl cellulose are widely used for mucoadhesion. The adhesion is mediated by hydration, bonding, or receptor interactions.[41,42] Madgulkar et al.[43] developed sustained-release tablets of itraconazole using mucoadhesive polymer carbopol 934P and HPMC K4M. They confirmed sustained drug release and gastric retention for six hours in albino rats. Figure 8 depicts the principle of mucoadhesive drug delivery systems.

IV- Swelling system

These systems, when come in contact with gastric fluid, their size increases significantly than that of the pyloric sphincter and thus, after swelling, remain logged in the stomach. These are also called a "plug type system".[44] Controlled and sustained drug release is achieved using an appropriate excipient. The swelling ability of polymer mainly depends upon the degree of cross-linking of hydrophilic polymer network. The high degree of cross-linking maintains the integrity of the system, while a low degree of cross-linking causes extensive swelling resulting in rapid dissolution of the polymer.[45]

V- Superporous hydrogels

Superporous hydrogels are a three-dimensional network of hydrophilic polymers that have numerous super-size pores inside them. The swelling of superporous hydrogels occurs by the mechanism of capillary wetting through interconnected open pores. To develop superporous hydrogels, certain ingredients like initiators and cross-linkers are used to initiate the cross-linking.[46] Other ingredients were foam stabilizers, foaming aids, and foaming agents. Desu et al.[47] developed a superporous hydrogel system using *N′*, *N′*-methylene bisacrylamide as the cross-linking operator and polyvinyl alcohol as a composite specialist, ammonium persulfate and *N*, *N*-tetramethylenediamine as an initiator pair and Span 80 as a surfactant. They are used as a froth stabilizer to make a permeable structure using the gas-forming method.

VI- Magnetic system

In this system, by using a strong magnet with a powerful magnetic field onto the body surface, the movement of gastroretentive formulation with a small internal magnet is controlled. Several reports tell about the positive results of this system, but the success of this system depends upon the selection of the magnet position with very high precision.[48] Gröning et al.[49] developed peroral acyclovir depot tablets with an internal magnet. An extracorporeal magnet was used to prolong the GRT of the dosage form and to influence the duration of absorption of acyclovir. They performed an *in vivo* study with five healthy male subjects and determined the plasma concentration-time profiles of acyclovir. Computer simulations were carried out to display the influence of GRT of acyclovir depot preparations on the plasma concentration-time profiles of acyclovir. Figure 4E displays a magnetic system of GRDDS.

In vitro assessment

For GRDDS, *in vitro* assessment is very essential to predict gastric transit behavior. Following are the parameters, which should be considered for designing novel gastroretentive formulations.

i. Buoyancy lag time

It is the time taken for gastroretentive formulations to move onto the surface of the dissolution medium. It is determined using a USP dissolution apparatus containing 900 mL of 0.1 N HCl solution as a testing medium maintained at 37°C. The time required to float different dosage forms noted as floating lag time.[50]

ii. Floating time

This determines the buoyancy of dosage form. In this test, a specific dissolution apparatus is used depending upon the type of dosage form with 900 mL of dissolution medium kept at 37°C. The floating time or floating duration of the dosage form is determined by visual observation.[51,52]

iii. Specific gravity/density

Specific gravity estimates are essential for both low-density and high-density GRDDS. Specific gravity is determined using the displacement method.[53]

iv. Swelling index

Swelling index is determined by immersing the tablets in 0.1 N HCl at 37°C and their periodic removal at regular intervals.[54]

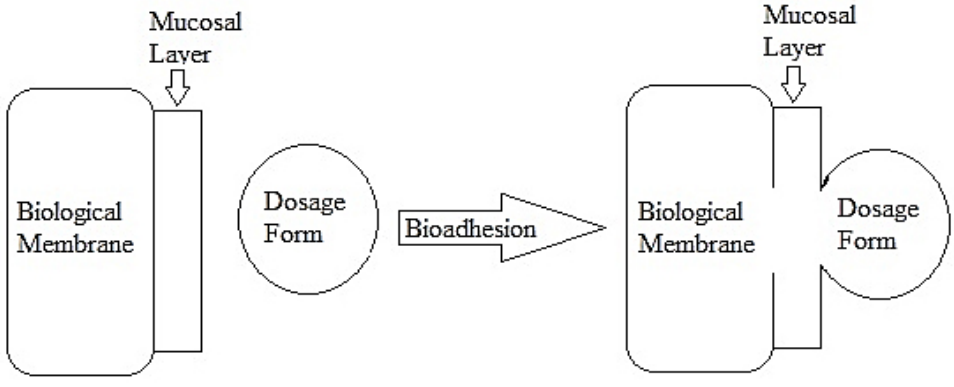

Figure 8. Principle of mucoadhesive drug delivery system

v. Water uptake

In this study, the dosage form is removed from the dissolution medium after the regular interval and a weight change is determined.[55]

Water uptake (WU) = $(W_t - W_o) * 100/W_o$

where W_t= weight of the dosage form at time t, W_o= initial weight of the dosage form

vi. Weight variation

Various official methods are recommended by pharmacopeias to calculate the weight variation. Usually, the individual and average weight of 20 tablets are recorded. From these data, average weight and weight variation is calculated.[56,57]

iii. Hardness and friability

Hardness or crushing strength is determined using a Monsanto tester, Strong cobb tester, Pfizer tester, *etc.* Friability (strength) of tablets is determined using a Roche friabilator.[58,59]

viii. In vitro dissolution tests

This test is performed to determine drug release from GRDDS in gastric fluid and intestinal fluid maintained at 37°C at a definite time using USP dissolution type II apparatus (paddle).[59,60]

Here, after *in vitro* assesment, Table 1 represents the recent trends in GRDDS, while Table 2 represents the names of drug candidates for GRDDS.

Evaluation of microsphere and beads

An optical microscope was used to measure the particle size of beads and microspheres. Surface morphology and cross-sectional morphology are evaluated with the help of a scanning electron microscope.

In vivo assessment

a. Radiology

This technique is mainly used to determine the position of gastroretentive dosage form filled with barium sulfate (radio-opaque marker) inside the body system concerning time using

Table 1. Showing some recent trends in GRDDS

Drug	Requirements for development	Dosage forms	References
Diltiazem HCl	a) Low solubility b) Short half-life c) Low bioavailability (40-50%)	Osmotic tablet (pump)	63
Theophylline	a) Short half-life b) Low bioavailability	Floating capsule	64
Metformin HCl	a) Short half-life b) Low bioavailability	Beads	65
Ciprofloxacin hydrochloride	a) Low bioavailability b) Short elimination half-life	CR floating tablet	66
Acyclovir	a) Short half-life b) Oral bioavailability is poor (15-30%) due to poor water solubility c) Degrade at high pH	SR floating microsphere	67
Ranitidine HCl	a) Short half-life b) Absorption window in a part of GIT c) Poor bioavailability	Floating (pulsatile) DDS	68
Ciprofloxacin HCl	a) Short elimination half-life (about 4 h) b) Narrow absorption window and absorbed in proximal SI c) Freely soluble in water	Floating tablet (matrix)	69
Ziduvudine	a) Dose dependant solubility b) Short biological half-life c) Poor bioavailability	Tablet	72
Cephalexin	a) Acidic drug b) Short half-life c) Poor bioavailability	Floating tablet	73

GRDDS: Gastroretentive drug delivery systems

X-ray. X-ray pictures are taken at different intervals to record the correct position of the dosage form.[61,62]

b. Scintigraphy

Similar to radiology, it is used to determine *in vivo* floating behavior of the gastroretentive dosage form. In scintigraphy, 99mTc pertechnetate is used as an emitting material instead of an X-ray to engulf the formulation to record the image.[63,64]

c. Gastroscopy

Gastroscopy is widely used for visual examinations of gastroretentive dosage forms. In this technique, an illuminate optical, tubular, and slender instrument called "endoscope" is used to look deep inside the body parts such as the stomach, esophagus, and small intestine.[65,66]

d. Ultrasonography

It is a diagnostic imaging technique, in which ultrasound is used for imaging internal body structures. The main disadvantage of this test is non-detectability at entrails.[1,66,67]

e. ^{13}C octanoic acid breath test

Radioactive ^{13}C octanoic acid is used to assess the extent of absorption of drugs from GRDDS. This compound gets absorbed

Table 2. Some of the drug candidates for GRDDS

Drug	Pharmacological and/or therapeutic class	Solubility	Stability in gastric and intestinal	Absorption and oral bioavailability	Half-life (h)	References
Itraconazole	Antibiotics	Low water solubility	-	70-80% absolute bioavailability	4	66
Acyclovir	Antiviral	Slightly soluble in water	-	Rapidly absorbed	3.0 ± 1.4	67
Ranitidine	Histamine H2-receptor antagonist	Low solubility at alkaline Ph	Colonic metabolism	50% absolute bioavailability	2.5-3	68
Ciprofloxacin	Fluoroquinoline	Freely soluble in water	-	Mainly absorbed in proximal areas	4	69
Furosemide	Loop diuretic	Poor water solubility	-	Mainly absorbed from stomach	1.3 ± 0.8	70
Tacrolimus	Immunosuppressant	Poor water solubility	-	Low oral availability	-	71
Captopril	Angiotensin converting enzyme inhibitor	Freely soluble in water	Stable at gastric pH but unstable in intestine	-	2	72
Repaglinide	Oral hypoglycemic agent	Poorly soluble in water	-	Low bioavailability	1	73
Metformin hydrochloride	Antidiabetic	Freely soluble in water	-	Absolute bioavailability (50-60%)	1.5-1.6	74
Alfuzocin HCL	Alpha adrenergic receptor blocker	Highly water soluble	-	Absorbed from upper GIT	5	75
Cephalexin	Cephalosporin type antibiotic	-	Degrade in alkaline pH	-	1	76
Ofloxacin	Fluoroquinoline	-	-	Highly soluble in Absorption occurs	9	77
	Antidiabetic	-	-	Acidic media and precipitate in upper GIT alkaline media	-	-
Verapamil hydrochloride	Calcium channel blocker	Soluble in water	-	Low bioavailability (10-20%) due to first pass effect	4	78
Domperidone	Prokinetic agent	Good solubility in acidic pH but reduced	-	Rapidly absorbed from stomach & upper part of GIT	7	79

GRDDS: Gastroretentive drug delivery systems

from the duodenum, and, when it is radiolabelled, then after its metabolism, the CO_2 exhaled in breath can be correlated with the amount of octanoic acid absorbed. The radiolabelled CO_2 was measured by isotope ratio mass spectroscopy.[65,66]

f. Magnetic marker monitoring

Compared with radiology and scintigraphy, this method is radiation-less, and thus is non-hazardous.[67,68] It involves real-time tracking of the dosage form in the gastrointestinal tract.[69,70] This technique is mainly used for the determination of the gastrointestinal motility and dissolution behavior of pharmaceuticals. In this technique, the dosage form is labeled as a magnetic dipole by incorporating a trace of ferromagnetic particles and recording the magnetic dipole field by an apparatus responsive to bio-magnetic measurement.[71-73]

Advantages and applications of gastroretentive delivery systems

Gastroretentive dosage forms release the drug in a controlled manner to their specific site of action.[74] These systems help increase the bioavailability of drugs that get metabolized in the upper part of the gastrointestinal tract, such as riboflavin and levodopa, *etc*.[75,76] For drugs that have a short half-life, gastroretentive dosage forms help reduce the dosing frequency and improve patient compliance by enhancing GRT. Also, they provide a sustained and prolonged release of drugs in the stomach and intestine, which are helpful in local therapy.[77-79] Lastly, Table 3 depicts the gastroretentive technologies adopted by various pharmaceutical companies, and Table 4 represents the list of commonly used drugs for various floating systems.

Table 3. Gastroretentive technologies adopted by various pharmaceutical companies

Technology	Company	Product	API	References
Bioadhesive tablets	Lupin, India	Xifaxan	Rifaximin	80
			Ofloxacin	
Effervescent floating system	Ranbaxy, India	Zanocin OD	Metformin HCl	81
		Riomet OD	Ciprofloxacin	
	-	Cifran OD		
Colloidal gel forming floating system	Ranbaxy, India	Conviron	Ferrous sulphate	82
Foam-based floating system	Sato Pharma, Japan	Inon ace tablets	Simethicone	83
	-	-	Gabapentin	
Polymer-based swelling technology: AcuFormTM	Depomed, USA	Gabapentin GR	Ciprofloxacin	84
	-	ProQuin XR	Metformin HCl	
Effervescent and swelling-based floating system	Sun Pharma	Prazopress XL	Prazosin HCl	85
Swelling-based floating system	Japan	Metformin Hcl	Metformin HCl	86
	Galenix, France	Cafeclor LP	Cefaclor	
	-	Tramadol LP	Tramadol	
Floating CR capsule	Roche, UK	Madopar	Levodopa and benserzide	86
	-	Valrelease	Diazepam	
Expandable system (unfloading)	Intec Pharma, Israel	Accordion PillTM	Carbidopa/levodopa	86
Erodible matrix-based system	Bayer, USA	Cipro XR	Ciprofloxacin HCl and betaines	87
Coated multi-layer and swelling system	Sun Pharma, India	Baclofen GRS	Baclofen	88
Gastroretention with osmotic system	GlaxoSmithKline, UK	Coreg CR	Carvedilol	89
Effervescent floating liquid alginate preparation	Reckitt Benckiser Healthcare,UK	Liquid gaviscon	Alginic acid and sodium bicarbonate	89
Bilayer-floating capsule	Pfizer, UK	Cytotec	Misoprostol	90
Raft-forming system	Pierre Fabre	Topalkan	Aluminium magnesium	90
	Medicament, France	Almagate flatcoat	Aluminium magnesium antacid	

Table 4. List of commonly used drugs for various floating system[82,83,85,87-90]

Type of system	Drugs used
Microspheres tablets/pills	Rosiglitazone maleate, verapamil, orlistat, aspirin, griseofulvin, acetylsalicylic acid, ibuprofen, ampicillin, captopril, sotalol, isosorbide dinitrate, terfanadine
Tablets	Losartan, furosemide, ciprofloxacin, captopril, cinnarazine, sotalol, ampicillin, florouracil, metformin hydrochloride, atenolol, baclofen
Films	Cinnarizine, peritanide, quinidine gluconate, albendazole, *p*-aminobenzoic acid, prednisolone
Granules	Ranitidine HCl, diclofenac sodium, cinnarizine, indomethacin, fluorouracil, diltiazem, isosorbide dinitrate
Powders	Riboflavin, sotalol, theophylline
Capsules	Verapamil HCl, chlordizepoxide, diazepam, misoprostol, furosemide, L-DOPA, pepstatin, nicardipine

CONCLUSION

GRDDS are unique systems and have become important in the last three decades. It offers various advantages, *viz*., site-specific, slow, and controlled release of drugs from different types of gastroretentive dosage forms, thus improving patient compliance and reducing the side effects by minimizing dosing frequency. Therefore, it is expected that in the future, various pharmaceutical companies will come forward to initialize gastroretentive drug delivery technology to create excellent advantages, prolonging patents, and a better outcome for their marketed formulations.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: K.V., S.M., P.D., Design: K.V., S.M., J.S., P.D., Data Collection or Processing: K.V., S.M., P.D., Analysis or Interpretation: K.V., S.M., Literature Search: K.V., S.M., Writing: K.V., S.M., M.A.K., D.K.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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