

Review on Gastroretentive Drug Delivery System

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Abstract

The oral delivery in English way was the very popular method, due to the ready taking of medicine and administration process. After oral administration of a drug, the process of its bioavailability being influenced by its stay in stomach are imperative. Lately, gastroretentive drug delivery systems (GRDDS) have been extensively used for drugs with a narrow absorption window, an inability to formulate the dose at high pH due to decreased stability and increasing solubility at low pH level. Such drugs are the part of the design of medicine system that keeps for a while in the stomach and upon release of its active components causes the desired effect in the stomach. Achieving the desired result of gastric retention of drugs may be done through the use of agents of effervescence, mucoadhesive polymers, magnetic matter, bouncy enhancing carriers, along with a method which is effective in forming plug-like substances that are resistant to emptying of the stomach. Such conclusion records a concise viewpoint about the essential attributes of the latest individually addressed procedures on GRDDS.

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

Introduction

Oral administration is still the most administrated approach notwithstanding continuous improvement in drug delivery approaches since patients still find it easy to use and comfortable with this method. The point release drug delivery systems, by the way, are meant to be as an oral medication.[1] Those delivery systems deliver the medications in one after another, pre-determined, predictable and controlled dose. Such drugs do not make a good oral candidate having its challenges on stability and absorption. This drawback of the drug can be solved by the use of modern technologies, which facilitate these drugs to stay in the stomach for a longer period at -3 time. The

drug delivery system example of which has got the name of gastroretentive drug delivery (GRDDS) ranks high among the drug delivery methods. GRDDS are proper for those pharmaceuticals, such as albuterol:[2] which are absorbed in the stomach; are unstable in an alkaline environment (e.g. ranitidine and metformin);[3] are poorly soluble in an alkaline environment (e.g. furosemide and diazepam) [4]; and have conditions within an absorption zone (e.g. riboflavin) [5]

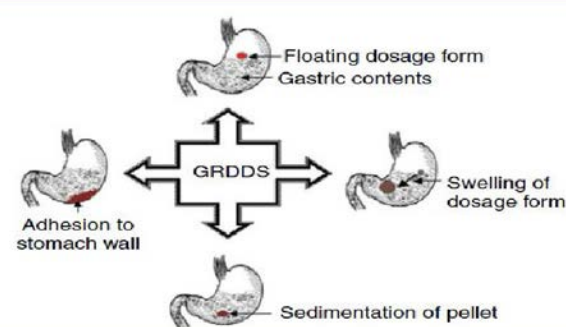
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Some of the common advantages associated with use of GRDDS include improved patient compliance by reducing the frequency of dosing; improved therapeutic efficacy of drugs with a short half-life; site-specific delivery of medications; sustained and 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 superporous 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

Comprehending the structure and operation of the stomach is crucial to the development of effective gastroretentive dosage forms. Anatomically, the stomach is composed of three parts: the fundus, which is located closest to the esophagus and serves as a storage area for food that has been swallowed; the body; and the antrum, which is the last portion and connects the body to the small intestine. Antrum aids in stomach emptying and churning.⁹ During a fast, the stomach and intestine go through a cycle of contractions known as the migrating myoelectric cycle every 120 to 180 minutes. It is separated into four additional phases. The term "digestive motility pattern" refers to the pattern of contraction alterations in a fed state.¹⁰ Phase 1 (basal phase) and Phase 2 make up this pattern.



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/cm³. 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 gastroprotective properties.¹²

Physiological factors affecting retention of GRDDS in the stomach

The fed or unfed state, the type of meal, the calorie content, and the frequency of feeding are the main variables influencing the gastric retention time of dosage forms. Because of the increased GI motility during fasting, there is a reduction in gastric retention time. Peristalsis is the cause of the emptying of the stomach contents. The gastric residence is brief if the onset of peristalsis aligns with the administration of the dosage form. Peristalsis, on the other hand, is delayed after meals and could contribute to the formulation's longer gastric residence. A meal rich in calories that includes proteins, fats, and fibrous materials prolongs the period of gastric retention. Because peristalsis is persistently inhibited when there are multiple meals, the gastric retention is greater than that of a single meal. Additionally, a few other elements, like age and sex,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.

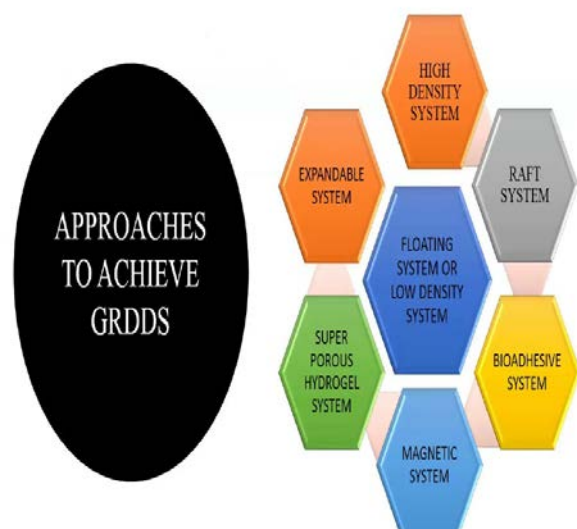
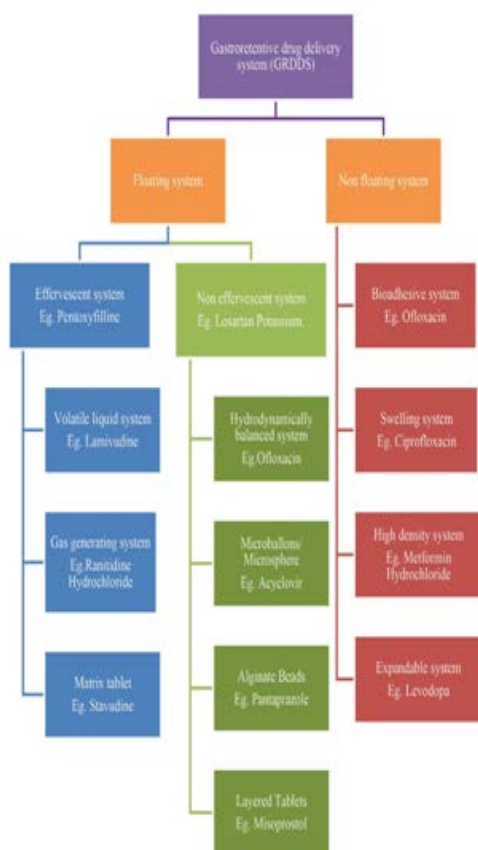


Figure 2: Approaches of gastroretentive drug delivery system

Classification of GRDDS



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 are 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 gastrointestinal transit of placebo pellet systems of varying densities using gamma scintigraphy. They reported that at 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.

(A) Effervescent system

This system uses carbonates (e.g. sodium bicarbonate) to generate *in situ* carbon dioxide (CO₂).^{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) **Volatil liquid/vacuum type:** These are further classified into three types.

i) *Inflatable system*

It consists of a pull out 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, 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 hours than 12.48 hours of the reference tablet and deliver the drug in an approximately zero-order manner for 24 hours.

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 hours.

X-ray imaging study in albino rabbits indicated the residence of tablet in the stomach even after a period of 12 hours.

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 nifedipine 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 CO₂, 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 resins. 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 CO₂ gas when it comes in contact with the gastric fluid and

causes the beads to float. Atyab *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 2x10, 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 form 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 Malakar³³ 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 formula

tion. 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 Radhi³⁵ 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 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 Radhi³⁵ 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 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.

iv. Layered tablets

Layered tablets are more popular due to ease of their preparation, low cost, and high stability. *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 croscopolldone were found to be critical factors affecting *in vitro* dissolution and floating properties of the prepared tablets.

Figure 7 depicts a schematic of single-layered floating tablets.

a. **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 croscopolone were used as superdisintegrants. 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

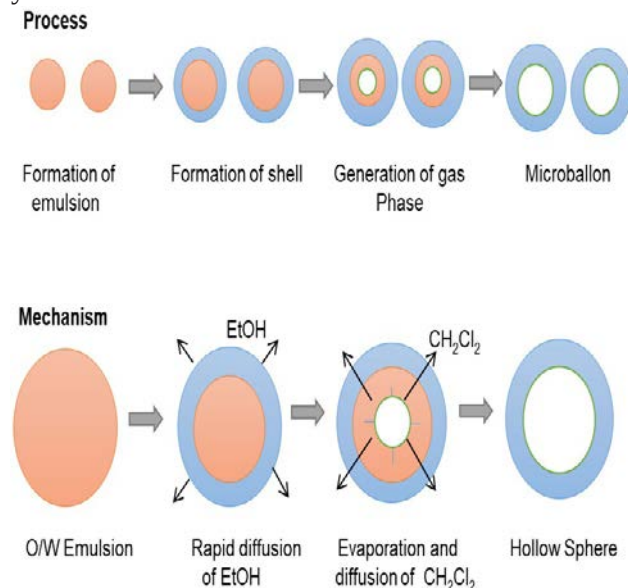


Figure 6. Preparation technique and mechanism of microballoon formation

are mainly used.⁴⁰ Natural polymers such as sodium alginate, gelatin, guar gum, etc., and semi-synthetic 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 HP MCK4M.

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- Swellings 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 lodged 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*-tetramethylethylenediamine 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 formulation to move onto the surface of the dissolution medium. It is determined using a USP dissolution apparatus containing 900 mL of 0.1N 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

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

$$\text{Water uptake (WU)} = (W_t - W_0) \times 100 / W_0$$

where W_t = weight of the dosage form at time t , W_0 = 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 definite time using USP dissolution type II apparatus (paddle).^{59,60}

Here, after *in vitro* assessment, 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 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
	a) Low solubility		
Diltiazem HCl	b) Short half-life	Osmotic tablet (pump)	63
	c) Low bioavailability (40-50%)		
	a) Short half-life		
Theophylline		Floating capsule	64
	b) Low bioavailability		
	a) Short half-life		
Metformin HCl		Beads	65
	b) Low bioavailability		
Ciprofloxacin hydrochloride	Low bioavailability Short elimination half-life	CR floating tablet	66
Acyclovir	Short half-life b) Oral bioavailability is poor (15-30%) due to poor water solubility Degrade at high pH	SR floating microsphere	67
Ranitidine HCl	Short half-life Absorption window in a part of GIT Poor bioavailability	Floating (pulsatile) DDS	68

Ciprofloxacin HCl	Short elimination half-life (about 4h) Narrow absorption window and absorbed in proximal SI Freely soluble in water	Floating tablet (matrix)	69
Zidovudine	Dose dependent solubility Short biological half-life Poor bioavailability	Tablet	72
Cephalexin	Acidic drug Short half-life 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, ^{99m}Tc 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 illuminated 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 atentrails.^{1,66,67}

e. ¹³C Octanoic acid breath test

Radioactive ¹³C octanoic acid is used to assess the extent of absorption of drugs from GRDDS.

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

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.

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