Miracle of Gastroretentive Drug Delivery Systems: Approaches for Treatment of Gastric Disorders and Their Future Perspectives

ABSTRACT

Nearly half of the world's population suffers from *Helicobacter pylori* (H. pylori) and gastric disorders. It is one of the most common pathogenic bacteria that cause gastritis, gastroduodenal ulcer disease, and gastric cancer. Because short residence period, a narrow absorption window in the upper small intestine results in poor bioavailability with standard dosage forms. In addition, combination therapies develop antibiotics, undesirable responses, and poor patient compliance. Therefore, these drawbacks may overcome by Gastro retentive drug delivery systems (GRDDs). A site-specific drug delivery system comes into force for boosting the therapeutic oral bioavailability, prolonging the residence site, effective medication through a small absorption window of GIT, and stimulating local effect in the stomach and duodenum. This review highlighted anatomy and physiology of gastric barrier, various GRDDS approach, merits, demerits for improving drug delivery, and future perspectives. Finally, this review may benefit researchers and industrialists working in this field.

Keywords: H. pylori, Gastroretentive, Floating systems, Gastritis, Buoyancy

1. INTRODUCTION

The oral route is the most popular drug delivery administration due to the ease of administration [1]. In addition, the patient compliance and ease of administration make them readily available in the market and widely used delivery system [2]. However, the bioavailability of drugs in oral dose forms is affected by various circumstances. Although, this route has limitations, such as short gastric residence time (GRT) and requiring time for contents to enter the intestine, and reduced absorption [3]. Further, gastric retention has gotten attention due to quick gastric emptying time. Drugs with a short half-life are rapidly absorbed and easily removed from the bloodstream, thus requiring frequent dosing. Further, the limitation can be overcome by developing oral sustained-controlled-release formulations to modify drug release time; this slowly releases the medication in the Gastro intestinal I tract (GIT) and maintains effective drug concentration in blood [4]. However, such oral drug delivery devices encounter physiological restriction during variable GRT showing the inadequate medicament release from the drug delivery system. Although it is essential to deliver the therapeutic drug at a specific site to maintain drug concentration, due to variable GRT, concentration in the bloodstream is altered.

Innovative drug delivery devices overcome the drawback of poor oral drug delivery as gastro-retentive dosage forms. Further, this increases the stay of the drug for an extended period in the stomach and increases the GRT of medicines, improving drug absorption. In addition to this, this further improves drug bioavailability, prolongs the duration of drug release, reduces drug wastage at high pH. The prolonged gastric emptying approach also treats peptic ulcer patients and reduces GI side effects by modifying drug delivery release. In addition to this, it improves the gastric residence of drugs in the stomach [5].

Gastro retentive drug delivery systems (GRDDs) effectively delivered weakly acidic drugs like domperidone and papaverine to enhance solubility and reduce the dose. In

addition to this, the Gastro-resistant tablet dosage form intentionally delays drug release to allow the tablet to pass after some time from one part to another. Prolong-release delivery systems are modified-release systems that show delayed drug release. Enteric-coated system designed to combat the stomach acidic environment and provide site-specific release of drugs in the intestine. Drugs like Proton pump inhibitors, H-2 blockers, insulin delivery, and NSAIDs are suitable candidates for developing delayed release dosage forms [6].

GRDDs are fruitful approaches that prolong GRT, targeting site-specific drug release for local and systemic effects. Over the last few decades, GRDD approaches designed and developed and further includes: High density (sinking) systems that show retention in the bottom of the stomach [7], low density (floating) systems [8, 9, 10], mucoadhesive systems offer adhesion to stomach mucosa [11] and Swellable systems through the pyloric sphincter [12, 13], super porous hydrogel systems [14], and magnetic systems [15]. This review highlights various GRRDs approaches and methodologies for site-specific delivery of drugs at controlled release.

2. NEED FOR GRDDS

- Drugs absorbed at a specific site only require that maximum drug reaches a particular site.
- Drugs absorbing from the proximal part of the GIT.
- Drugs show low solubility and degradation at basic pH and variable gastric emptying time.
- A local or sustained drug delivery system treats certain conditions [16].

2.1. Merits of GRDDS

- Drugs with narrow absorption window.
- Longer stomach residence time, useful for treatment of peptic ulcer.
- For improving the bioavailability of drugs such as cyclosporine, ciprofloxacin, ranitidine, Amoxycillin, captopril, and absorption from stomach.
- Improves patient compliance and therapeutic efficacy by reducing dosing frequency.
- Targeted therapy for local ailments in the upper GI tract and avoids first pass.
- GRDDs prolong drug release, utilized for stomach and small intestine disorders.
- Site-specific drug delivery and excellent accessibility.
- Rapid absorption shows good blood flow rates.
- Minimize mucosal irritation due to controlled release, e.g., NSAIDs
- Decreased fluctuations in plasma drug concentration prevent adverse effects. [17]

Further, a study highlights the importance of several patents reported where the development of GRDDS has shown significant improvements in drug delivery over conventional formulations. The gastro retentive pulsatile pharmaceutical delivery of Valsartan improves solubility and enhances residence time [18].

Another study suggested minocycline enhances bioavailability. In addition to this, this further reduces severe gastrointestinal side effects, such as reflux, vertigo, dizziness, and nausea [19]. Another study highlights that biodegradable, multi-layered controlled release gastroretentive dosage form of zaleplon provides good sleep maintenance and minimizes next-day residual effects [20].

2.2. Demerits of GRDDS

- Floating dosage systems show limitations and require increased fluid content in the stomach to work efficiently.

- Due to contractile waves, the floating dosage form quickly swipes away in supine or sleeping posture. So, patients should avoid taking floating dosage forms before sleep.
- In an acidic environment, drugs with stability and low solubility irritate the gastric mucosa.
- Bio/mucoadhesive systems show a high turnover rate due to layered and soluble mucus.
- Bio-adhesive drug delivery systems show esophageal binding. In addition to this, the hydrogel-based swelling requires a longer time to swell.
- Upon multiple administrations, increased size drug delivery systems cause stomach hazards, resulting in permanent retention in the stomach [16, 17].

3. GRDDS ACTING DRUGS

The gastro retentive drug delivery systems are suitable for the following types of drug therapy that helps in prolonging GRT, depicted in Fig. 1 [21-27], and their impact over conventional delivery, summarized in Table 1 [28].

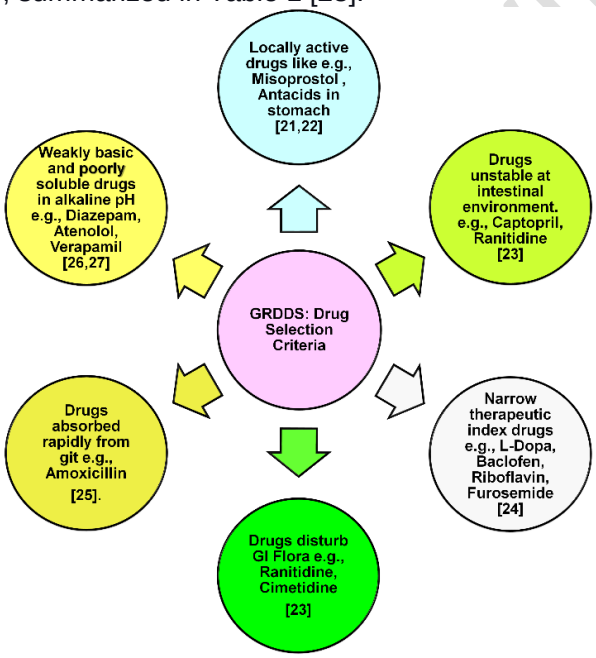


Fig 1. Drugs candidates for GRDDs.

Table 1. Impact of Gastro-retentive drug delivery in comparison to Conventional [28].

Parameters discussed	CDDS effect	GRRDS effect
Patient compliance	Poorly controlled	Shows better control
Dose Dumping	Higher dose dumping	Risk is less
Drugs locally acting on stomach	Not useful	More significant
Toxicity	High susceptibility	Less susceptibility
Poorly water-soluble drugs (high pH)	Not useful	More significant
Drugs degradation (colon)	Not useful	More significant
Drugs with fast GIT Absorption	Not useful	More significant
Drugs less absorption (small Intestine)	Not useful	More significant

*CDDS: Conventional drug delivery system, GRDDs: Gastro-retentive drug delivery system

4. ANATOMICAL AND PHYSIOLOGICAL BARRIERS FOR GRDDS

4.1. Stomach

The stomach, the leading site of gastric retention, physiology, and anatomy, plays a significant contribution during the formulation of GRDDs. It is present in the upper abdomen and leads to distension due to a meal. Further, it comes at a resting state with 25-50 ml [29]. It has three parts: fundus, body, and pylorus (antrum). The body acts as a reservoir for undigested food; the proximal part consists of the fundus and the distal part responsible for propelling contents into the intestine [30].

4.2. Gastric motility and emptying of food

Gastric emptying mainly happens during fed and fasted states, but the mortality pattern differs in both states. The inter-digestive cycle occurs every 2-3 hrs in a fasting state through the stomach and small intestine, known as the inter-digestive myoelectric cycle of migrating myoelectric complex (MMC). It is further divided into four phases, shown in Fig. 2 [31]. First, the activities occur during gastric emptying, shown in Table 2 [32-60].

- **Phase i:** Basal phase, having a 45-60 min duration, showing no or few contractions.
- **Phase ii:** Pre-burst phase, having a duration of 30-45 min, involves intermittent contractions with a gradual increase in intensity.
- **Phase iii**: Burst phase, with a duration of 5-15 min, short period intense contraction, involving proximal and distal regions; this is also known as (‘housekeeper waves’), involving undigested removal food from the fasted stomach.
- **Phase iv**: It having a duration of 0-5 min. It is a transition period between Phase III and Phase I, showing decreased activity till the beginning of the next cycle [31].

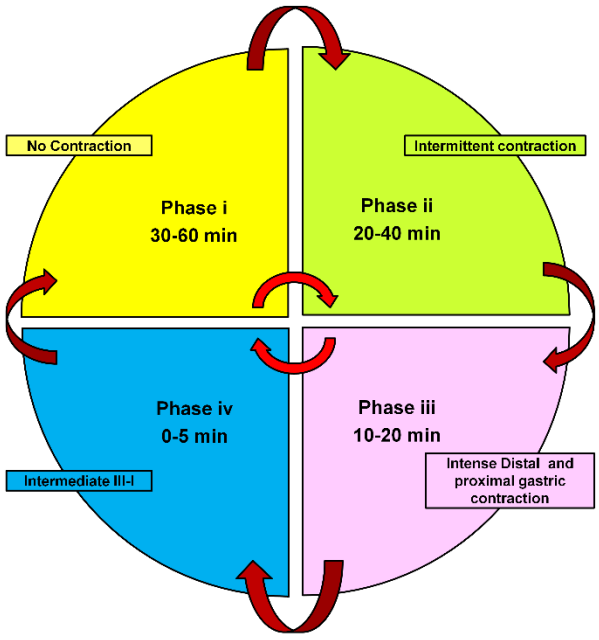


Fig. 2. Various phases of inter-digestive myoelectric cycle of migrating myoelectric complex.

Table 2. GRDDs of various drugs and their purpose.

Drugs	Polymers	Method of preparation	GRDDs	Purpose of Study	Ref.
Ranitidine Hydrochloride	Sodium carboxy methyl cellulose, HPMC K-100	Osmotic method involves swelling and floating	Floating tablet	Optimized formulation, Batch IVA/CT3 showed 35 sec lag time and floated till 19hrs. Batch IV, showed desired release	[32]
Famotidine Calcium pectinate	HPMC K15M, polycarbophil and Carbopol	Gelatin-emulsion	Gel beads	Floating beads showed prolong release with copolymer and float up to 1 days.	[33]
Ciprofloxacin HCl	Sodium alginate and HPMC K15M	Direct compression	Floating tablet	Tablet float due to effervesce nature and sustained the drug release for prolong period of time	[34]
Ofloxacin	HPMC K100M and Isabgol husk	Wet granulation	Tablet	Swelling property of tablet indicated water holding capacity results in floating and provide sustain drug release up to 24 h	[35]
Propranolol HCl	HPMC (K4M)/(E15) LV, and HPC. Xanthan gum and sodium alginate	Direct compression	Floating tablets	Formulation containing HPMC K4 M, showed in-vitro release (92%, 18 h)	[36]
Norfloxacin	Xanthan gum and HPMC (K4M)/(K100M)	Wet granulation	Floating tablet	Due effervescent nature, table floated in gastric medium for prolong period and released the drug 94.3 ± 1.5 % (9 h) containing HPMC (K4M)	[37]
Furosemide	Polymethacrylates and Eudragit RL30D	Direct compression	Mini tabs	Combination of Polymethacrylates Eudragit RL30D, maintained buoyancy within acceptable time and drug release over a period of 12 h.	[38]
Metoclopramide HCl	Karaya gum, guar gum, HPMC (E15) alone and in combination with HPMC (K15M)	Direct compression	Floating-matrix tablets	Tablet floated up to 24 h without erosion and prolonged the drug release.	[39]
Pregabalin	Cross povidone and HPMC	Wet granulation and compaction	Swelling and non-floating effervescent tablet	Buoyancy behavior over 24 h sufficient for significant amount of drug release	[40]
Fluconazole	Eudragit RL and Eudragit RS	Spontaneous emulsification	Mucoadhesive nanoparticles	Mucoadhesive nanoparticles contain fluconazole once-a-day showed significant local antifungal against candidiasis in gastric medium	[41]

Gabapentin	Hydroxy ethyl cellulose (HEC)	Direct compression	Floating tablets	Matrix tablets containing gabapentin enhanced GRT (up to 12 h) and prolonged the drug release (99.75 percent, at 12 h).	[42]
Verapamil	MCC, Eudragit L30D 55 and Eudragit NE 30D	Wet granulation for pellet preparation	Floating capsules	Multiple-unit floating pellet dosage form delivered significantly drug than conventional tablet due to buoyancy effect.	[43]
Metoprolol Succinate	Sodium alginate, NaCMC	Direct compression	Floating tablets	Controlled release Metoprolol Succinate, showed floating (16 h)	[44]
Acyclovir	HPMC	Compressed coating	Magnetic depot tablets	Extracorporeal magnet prolonged the GRT and influenced the duration of absorption of drug.	[45]
Metronidazole	HPMC E5 and Hydroxypropyl cellulose Mf50, MC, Carbopol 934P and κ-carrageenan	Ionotropic gelation	Chitosan-treated alginate beads	Beads showed 92.09% entrapment efficiency and immediate buoyancy behaviour results in drug release (100%) after 4 h), and completely eradicate *H. pylori*.	[46]
Clarithromycin	HPMC (K4M)	Wet granulation	Floating tablets	Floating behaviour up to 12 h of tablets indicated increase in GRT and localized action of drug for Peptic ulcer due to H. pylori infection.	[47]
Amoxycillin	Gellun gum	In-situ gelation	In-situ gel solution	Prolongs ten times drug release	[48]
Silymarin	HPMC (K4M)/(K15M) and psyllium husk	Wet granulation	Floating tablets	Provides drug release up to 24hrs	[49]
Riboflavin	Eudragit S 100	Emulsion solvent diffusion	Micro-balloons	Micro-balloons showed inverse relationships between the buoyancy and the level of release of riboflavin from it.	[50]
Diltiazem HCL	Eudragit S 100 and Ethyl cellulose (EC)	Non-aqueous emulsion Solvent evaporation	Floating microspheres	Drug loaded mucoadhesive floating microspheres using calcium carbonate (gas generating agent) help in floating and released the Drug up to 8 h.	[51]
Aceclofenac	Eudragit S 100.	Emulsion dehydration	Floating microspheres	Floating microspheres coated with Eudragit- pectin delivered aceclofenac (24 h with significant anti-inflammatory effect) in colon for treatment of	[52]

				rheumatoid arthritis	
Cimetidine	HPMC and EC	Solvent evaporation	Floating microspheres	Microspheres prolonged drug release (8 h), buoyancy for 10hr	[53]
Cephalexin	EC	Emulsion Solvent	Floating microspheres	Results showed stirring speed and polymer concentration affected with size. The drug release and floating time of more than 12 h	[54]
Metoprolol Tartrate	HPMC (K4M)/(K100M)	Direct Compression	Floating tablets	The floating tablets extended drug release up to 8 h, increased the gastric retention and to improve the bioavailability of the drug	[55]
Stavudine	HPMC (K4M)/(K15M)/ (K100K) and EC	Melt Granulation	Floating Matrix Tablet	Matrix system of hydrophobic and hydrophilic polymer decreased the burst release of drug from the floating tablet (floating time less than 3 min) and prolonged the drug release upto12 h.	[56]
Valacyclovir Hydrochloride	EC	Solvent Evaporation and Water-In-Oil Emulsification	Floating Microspheres	Floating microspheres prolonged the drug release 94.03% at 12h and localizing the drug at upper GIT.	[57]
Venlafaxine Hydrochloride	Carbopol 971P, EC, Eudragit RS-PO	Direct Compression	Mucoadhesive Tablets	Mucoadhesive tablet having adhesion time up to 12hours showed better GI residence and 99.85% drug release at 12 h	[58]
Metformin	HPMC (K4M), EC	Solvent Evaporation	Floating Micro-balloons	Floating microballoons exhibited excellent floatability (>10 h) and prolonged drug release. (8 h).	[59]
Ciprofloxacin Hydrochloride	Sodium Alginate, HPMC (K15M)	Direct Compression	Floating Matrix Tablets	Floating Matrix Tablets exhibited excellent floating behaviour (5.5 h), and sustained the drug release.	[60]

5. FACTORS AFFECTING GASTRIC RETENTION TIME OF THE GRDDS [61]

The following are the factors which affect the stability and performance of GRDDs.

- **Density of dosage form**: Good floating property is often exhibited by the dosage forms having a thickness less than that of gastric fluids (~1.004g/ml). In contrast, a density closer to 2.7g/ml is needed for high-density systems to achieve good gastro-retention.
- **Size of the dosage form**: Due to larger particle size, the dosage form having a diameter of more than 7.5mm, shows more GRT because it does not quickly pass from the pyloric antrum to the intestine.
- **Shape of the dosage form**: Ring and tetrahedron-shaped devices show better gastro retention than other shapes. These devices with a 22.5-48 KSI (keto pound/ inch^2) deliver more GRT (90-100 %).
- **Fed or unfed state:** GI motility characterized through MMC occurs every 1.5 to 2 hours, responsible for sweeping unprocessed material from the stomach. In addition to it, if it coincides with the drug administered along with MMC, GRT is predicted to be short during the unfed state. However, MMC delay during the fed state, and GRT is considerably longer.
- **Nature of meal**: Consumption of fatty acids like starch and cellulose, indigestible polymers, changes stomach motility pattern and delays MMC. This further decreases gastric emptying rate (GER) and prolongs the drug release.
- **Caloric Content:** Protein-rich and fat diet increases GRT to 4 to 10h.
- **Frequency of meal**: GRT improved more than 6 to 7 h with continuous meals compared to a single meal because of the low frequency of MMC.
- **Age**: People with age more than 70 years have significant longer GRT, although GRT is less in children and new born infants.
- **Gender**: Males showed less GRT (3.4h) than female counterparts (4.6h).
- **Posture**: No significant effect of posture was found on GRT for individuals in the upright, ambulatory, and supine state
- **Concomitant drug administration**: Anticholinergic drugs like atropine, propantheline, and opiate-like codeine can prolong GRT.
- **Circadian rhythms**: During the daytime, cardiac rhythms are increased, and night rhythms are less, affecting GRT.
- **Diseased state**: Pathological conditions like ulcers, spasm, and flatulence affects the GIT environment.
- **Exercise**: Retards gastric emptying time [61].

6. GASTRIC RETENTION APPROACHES

GRDDs concept was described in early 1962 and shows less bulk density than gastric fluids, so it stays in the stomach for a prolonged time. Due to the buoyancy effect on the gastric contents, the drug is released slowly, showing increased GRT and controlled plasma drug concentration. The device forms a cohesive gel barricade and maintains specific gravity less than gastric contents (1.004-1.010), discussed in (Table 3 and Fig. 3 and 4 (A-E)) [62-84].

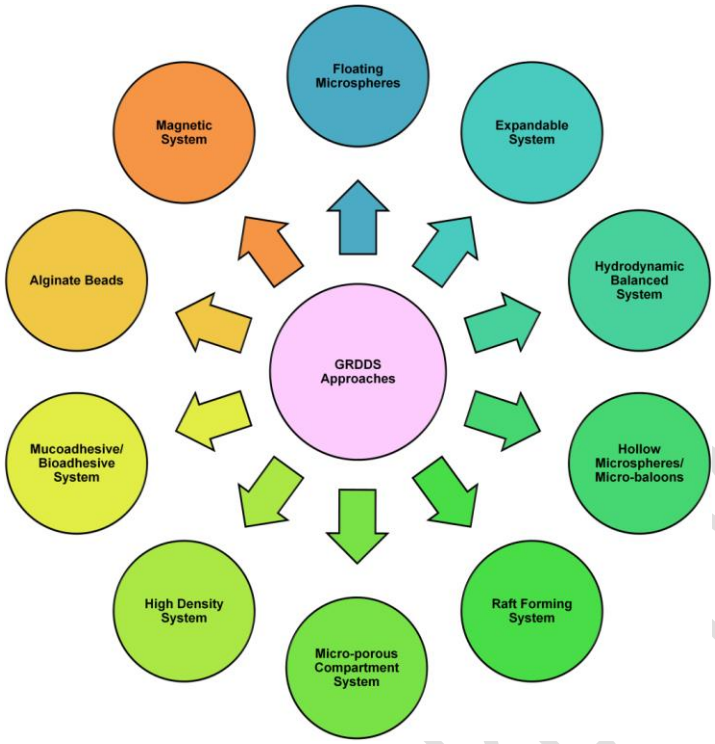
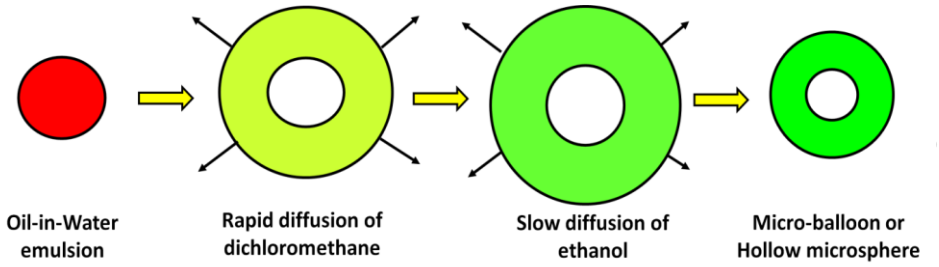


Fig 3. GRDDs approaches for delivery of drugs.

Table 3. GRDDs Approaches, Methods and Polymers for Delivery.

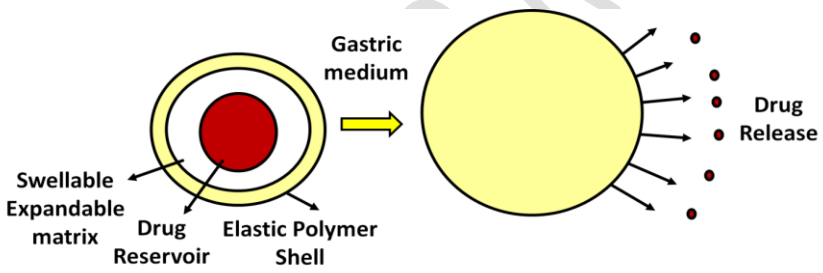
Approaches	**Description**	**Polymers /Excipients**	**Ref.**
Hydrodynamically balanced systems (HBS)	Drugs are added in combination with hydrocolloids, provides floating	Contains hydrophilic polymers Polycarbophil, Alginic acid sodium carboxymethyl cellulose, HPMC, agar and Polyacrylates	[62
Raft systems	Carbonate due to chemical reaction, forms bubbles, provides floating	Sodium alginate, Sodium bicarbonate, Acid neutralizer.	[63-65]
Bio-adhesive/ Mucoadhesive systems	Bio-adhesive systems forms electrostatic bonds at stomach interface.	Bio-adhesive polymers like Sucralfate, dextrin, HPMC and Tragacanth	[66]
High density systems	Based on hypothesis, dense pellets remain for longer duration	Barium sulphate, zinc oxide and Fe are used	[67-69]
Swelling type system	Swelling systems provides swelling property increases GRT	Biodegradable polymers and Swelling agents like Sodium starch glycolate and cross povidone	[70-72]
Magnetic systems	External stimuli as magnetic field used for targeted drug delivery	-	[73,74]
Hollow microspheres/ Microballoons	Useful for prolonged release containing captured air as microspheres, promotes floating	Poly D and PVA	[75-77]
Floating microspheres	Useful for prolonged release containing captured air as microspheres, promotes	Poly(acryl)starch, DEAE cellulose and Poly(acryl)	[78,79]

	floating, increases GRT	dextran	
Microporous Compartment System	Drug pool enclosed within compartment with pores, trapped air promotes floating and buoyancy in stomach	Cellulose, PVP, MC, PVA and HPMC	[80,81]
Alginate beads	Floating alginate linear anionic block Co-polymer shows hydrogel formation inotropic gelation, showing retention more than 5.5 h	Sodium and Calcium alginate and Low Methoxylated pectin	[82-84]

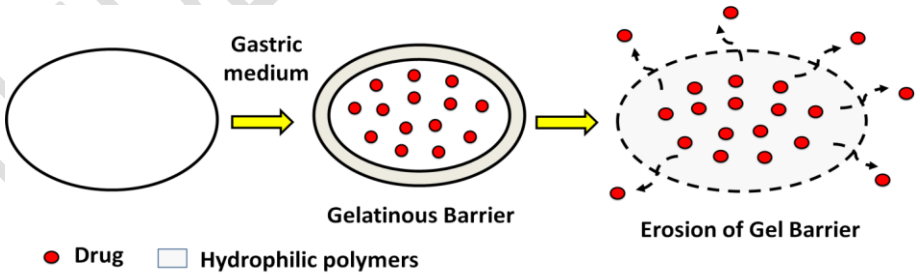


A. Hollow microspheres approach

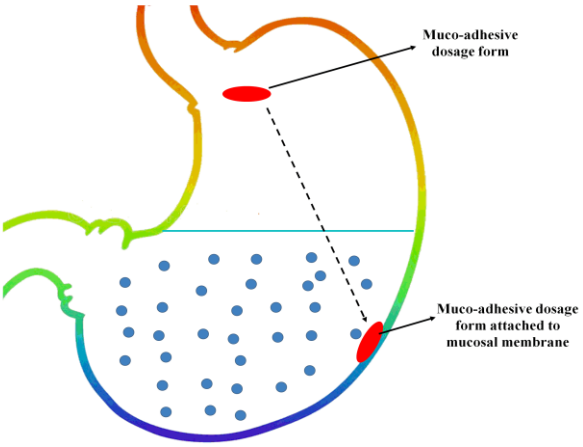
B.



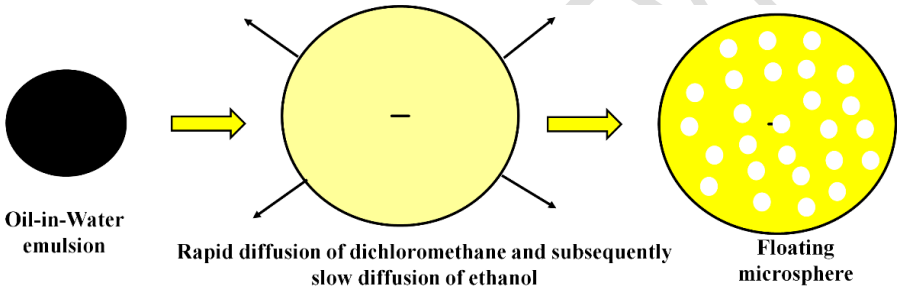
B. Swelling System approach



C. Hydrodynamically balanced system approach



D. Muco-adhesive system approach



E. Floating system approach

Fig. 4. Drug release from various approaches of GRDDS (A-E).

7. Future Perspectives

The rationale for GRDDS and its importance in industries are discussed in Fig 5 [85-86], along with the list of patents and marketed formulation of GRDDS showing prolonged residence time in Table 4 [87-123] and Table 5.

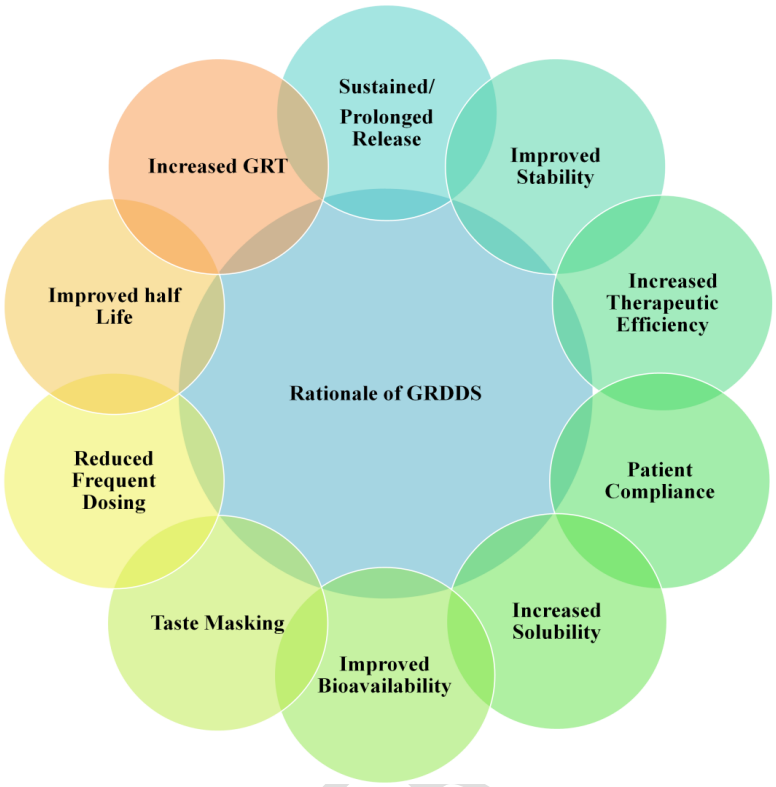


Fig 5. GRDDS Rationale for selection of Drugs

Table 4. Patents on GRDDS and their approaches.

Patent No.	Formulation	Approaches	Publication year	Ref.
US 4767627	GRDDs for controlled delivery of drugs	Swelling drug delivery showed control release.	1988	[87]
US 5443843	GRDDs drug for controlled release of drug	Shows more retention attached to controlled release device prevent GI transit.	1995	[88]
US 5780057	Tablet showing increased contact with gastric fluids	Two- or three-layer tablet, swells rapidly After imbibition prolongs GRT allows slow drug release	1998	[89]
US 597289	GRDDs for controlled release of sparingly soluble drugs	Tablets or capsules once ingested, swells and release the drug slowly	1999	[90]
US 6488962	Tablet shapes to enhance gastric retention	Specifically shaped oral swellable dosage forms, resist GI transit	2002	[91]
US 6548083	Prolonged release used for gastric retention	Polymer matrix, and swells and comes in contact with gastric fluids, increases the retention in stomach.	2003	[92]
US 6635280	GRDDs involving extended drug release in fed state	Diffusion method is used for release of polymer and dosage remains intact for longer duration until drug release	2003	[93]
US 2723340	Optimal polymer mixtures for gastric retentive tablets	Swelling facilitates controlled release of drug and gastro-retention	2004	[94]
US 6776999	Expandable GR therapeutically active system with a prolonged GRT	Drug release depends upon medicament form and not on polymer, prolongs GRT	2004	[95]

US 7976870	GRDDs showing with restricted drug release in lower GIT	Biocompatible polymers swell and erode rapidly, prolongs GRT, drugs release at controlled rate	2011	[96]
US 9393205	GR tablets	Monolithic tablets cause imbibition of gastric fluids, tablet floats, drug release is controlled	2016	[97]
US 9801816	GR dosage form for extended release of acamprosate	Acamprosate showed extended release due to swelling and erosion	2017	[98]
US 5769638	Buoyant controlled release powder formulation	Capsules floats and releases drug at controlled rate	1992	[99]
US 5198229	Self-retaining GIT delivery device	Drug delivery device with low density delivers the drug and provides floating in stomach	1993	[100]
US 5232704	Sustained release bilayer buoyant dosage form	Capsule made of non-compressed bi-layer promotes controlled release and floats in GI	1993	[101]
US 5626876	Floating system for oral therapy	Floatable and oral lighter than the gastric fluid is used, provides floating	1997	[102]
US 6207197	Gastro-retentive controlled release microspheres	Microsphere containing an active ingredient controls rate of drug release	2001	[103]
US 8277843	Programmable buoyant delivery technology	Drug-coated over coat is used, forms hollow space, provides programmable drug delivery	2012	[104]
US 8808669	GR extended-release composition of the therapeutic agent	Controlled release, shows floating and swelling effect at acidic condition, prolongs drug release	2014	[105]
US 9314430	Floating GR dosage form	Cylindrical shaped elongated form is used, shows floating	2016	[106]
US 9561179	Controlled-release floating pharmaceutical compositions	Microparticles containing drug deposited on floating core surface, shows control release	2017	[107]
US 5472704	Pharmaceutical CR composition with bio-adhesive properties	Mucoadhesive agents used for different routes like rectal, periodontal, vaginal, nasal, and ocular	1995	[108]
US 5900247.	Mucoadhesive pharmaceutical composition for the controlled release	Bio-adhesion facilitates the prolonged release in the buccal cavity	1999	[109]
US 6303147	Bio-adhesive solid dosage form (SDF)	Bio-adhesive shows prolonged release for locally or systemically acting drugs.	2001	[110]
US 6306789	Mucoadhesive granules of carbomer suitable for oral administration of drugs	Mucoadhesive granules, provides sustained release of the drug	2001	[111]
US 8974825 A	pharmaceutical composition for gastrointestinal drug delivery	Bio-adhesion promotes controlled release.	2015	[112]
US20050063980A1	Gastric raft composition	Floating raft promotes controlled release	2005	[113]
USOO67770OOB2	In situ gel formation of pectin	In situ formation of floating raft, promotes release	2004	[114]
US6635281	The gastric retaining liquid dosage form	Bio-erodible carrier facilitates retention of within stomach, erodes rapidly	2003	[115]
US6797283	Gastric retaining dosage form having multiple layers	Multilayered active agent shows swellable properties, promotes controlled release	2004	[116]
US8586083	GRDDS comprising an	Involves extrusion, improved gastric	2013	[117]

	extruded hydratable polymer	retention.		
US9119793	GR dosage form of doxycycline	Combination of floating, swelling and bio-adhesive promotes drug release.	2015	[118]
US20150366832	GR dosage form for carbidopa/levodopa	Carbidopa Shows swelling properties.	2015	[119]
US20150231084	Osmotic floating tablets	Outer osmotic core achieves gastro-retention.	2015	[120]
US20160338949	Stabilized gastro-retentive tablets of pregabalin	Gastro-retention increased due to swelling	2016	[121]
EP3148514	The expandable gastro-retentive dosage form	Unfolding increases GRT and prolong release	2017	[122]
EP2575798	Gastro-retentive systems of gaba analogs	Swelling act as a release retardant	2017	[123]

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Table 5. Marketed formulation of GRDDs

Brand Name	Active Ingredient	Dosage Form & Route	Manufacturer
Valrelease	Diazepam	Capsule, extended release	Roche Laboratories
Madopar	Benserazide and L-dopa	Dispersible Tablets, Per oral (P.O.)	Roche Laboratories
Liquid Gaviscon	Alum. Hydroxide and $MgCO_3$	Liquid, P.O.	GlaxoSmithKline Consumer Healthcare Holdings (US) LLC
Topalkan	Alum.-Mg antacid	SDF, P.O.	Pierre Fabre Drug, France
Conviron	Ferrous Sulphate	SDF, P.O.	Conviron
Cytotech	Misoprostol	SDF, P.O.	Pfizer
Cifran OD	Ciprofloxacin	SDF, P.O.	Sun pharmaceutical industries ltd
Glumetza	Metformin	SDF, P.O.	Salix Pharmaceuticals
Coreg CR	Carvidilol Phosphate	SDF, P.O.	Sun pharm industries
Inon Ace Tablets	Simethicone	SDF, P.O.	Sato Pharmaceutical Co., Ltd.
Almagate flatcoat	Aluminium magnesium antacid	Floating liquid form, P.O.	Pierre Fabre Drug, France
Cefaclor LP	Cefaclor	SDF, P.O.	
Baclofen GRS	Baclofen	SDF, P.O.	Sun pharm indu Stries
Zanocin OD	Ofloxacin	SDF, P.O.	Sun pharm industries
Coreg CR	Carvedilol	Gastro-retention with osmotic system (SDF), P.O.	GlaxoSmithKline
Inon Ace Tables®	Simethicone	Foam based floating system, P.O.	Sato Pharma, Japan
Prazopress XL®	Prazosin hydrochloride	Effervescent and swelling based floating system, P.O.	Sun Pharma, Japan
Accordion Pill®	Carbidopa/levodopa	Expandable system (unfolding), P.O.	Intec Pharma, Israel
Xifaxan®	Rifampicin	Bio-adhesive tablets, P.O.	Lupin, India
proQuin XR	Ciprofloxacin	Polymer based swelling technology: AcuFormTM, P.O.	Depomed, USA

SDF: Solid dosage form

CONCLUSION

Gastro retentive drug delivery offers potential advantages in delivering drugs at enhanced solubility and bioavailability. On the other hand, the drawbacks of poor solubility, bioavailability, and high first-pass effect promote ideas for designing newer techniques for improving drug delivery at a controlled rate. In recent years, the Gastro retentive drug delivery system has been explored to ensure optimized drug delivery. Newer technologies adopted in gastro retentive drug delivery offer swellable, absorbable, floating, and high-density systems, promoting the controlled release. In addition, it offers to improve patient

compliance and promote industrial growth. GRDDs will provide newer leads that promote improved efficiencies for various pharmacotherapeutics in the coming future.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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