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

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ABSTRACT

Nearly half of the world’s population suffers from Helicobacter pylori (H. pylori) and gastric disorders. It is 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 Gastrointestinal 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 gastroretentive 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 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 GRT 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 preparing 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 [8-10], 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 particular 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 erratic gastric emptying time (GET).
- 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 like captopril, cyclosporine, ranitidine, ciprofloxacin, amoxycillin, 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]. Finally, another study highlights that biodegradable, multi-layered controlled release gastro-retentive dosage form of zaleplon provides adequate sleep maintenance and minimizes next-day residual consequences [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](image-url)
**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, GRRDS: 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 works as a reservoir for unassimilated 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 via the stomach and small intestine, known as the inter-digestive myoelectric cycle of relocating myoelectric complex (MMC). 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, 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 severe contraction, affecting proximal and distal parts; also known as (housekeeper waves), involving undigested removal food from the fasted stomach.
- **Phase IV**: It has a duration of 0-5 min. It is a transition period between Phase III and Phase I, showing decreased movement till the beginning of the subsequent cycle [31].

![Fig. 2. Various phases of inter-digestive myoelectric cycle of migrating myoelectric complex](image.png)
| 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 | [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]    |
| Drugs             | Polymers                                      | Method of preparation | GRDDs       | Purpose of Study                                                                 | Ref.  |
|-------------------|----------------------------------------------|-----------------------|-------------|----------------------------------------------------------------------------------|-------|
| 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]  |
| Drugs               | Polymers                    | Method of preparation | GRDDs            | Purpose of Study                                                                 | Ref. |
|--------------------|-----------------------------|----------------------|------------------|----------------------------------------------------------------------------------|------|
| Aceclofenac        | Eudragit S 100.             | Emulsion dehydration | Floating         | Microspheres coated with Eudragit-pectin delivered aceclofenac (24 h with       | [52] |
|                    |                             |                      | microspheres     | significant anti-inflammatory effect) in colon for treatment of rheumatoid        |      |
|                    |                             |                      |                  | arthritis                                                                        |      |
| Cimetidine         | HPMC and EC                 | Solvent evaporation  | Floating         | Microspheres prolonged drug release (8 h), buoyancy for 10 hr                   | [53] |
|                    |                             |                      | microspheres     |                                                                                  |      |
| Cephalexin         | EC                          | Emulsion Solvent     | Floating         | Results showed stirring speed and polymer concentration affected with size and   | [54] |
|                    |                             |                      | microspheres     | prolonged the drug release and floating time of more than 12 h                  |      |
| Metoprolol Tartrate| HPMC (K4M)/(K100M)          | Direct Compression   | Floating         | The floating tablets extended drug release up to 8 h, increased the gastric      | [55] |
|                    |                             |                      | microspheres     | retention and to improve the bioavailability of the drug                        |      |
|                    |                             |                      |                  |                                                                                  |      |
| Stavudine          | HPMC (K4M)/(K15M)/(K100K)   | Melt Granulation     | Floating Matrix  | Matrix system of hydrophobic and hydrophilic polymer decreased the burst release  | [56] |
|                    | and EC                      |                      | Tablet           | of drug from the floating tablet (floating time less than 3 min) and prolonged   |      |
|                    |                             |                      |                  | the drug release up to 12 h.                                                    |      |
| Valacyclovir       | EC                          | Solvent Evaporation  | Floating         | Floating microspheres prolonged the drug release 94.03% at 12 h and localizing  | [57] |
| Hydrochloride      |                             | and Water-In-Oil     | Microspheres     | the drug at upper GIT.                                                          |      |
|                    |                             | Emulsification       |                  |                                                                                  |      |
| Venlafaxine        | Carbopol 971P, EC, Eudragit  | Direct Compression   | Mucoadhesive     | Mucoadhesive tablet having adhesion time up to 12 hours showed better GI        | [58] |
| Hydrochloride      | RS-PO                       |                      | Tablets          | residence and 99.85% drug release at 12 h                                       |      |
| Metformin          | HPMC (K4M), EC              | Solvent Evaporation  | Floating         | Floating microballoons exhibited excellent floatability (>10 h) and prolonged    | [59] |
|                    |                             |                      | Microballoons    | drug release (8 h).                                                             |      |
| Ciprofloxacin      | Sodium Alginate, HPMC (K15M)| Direct Compression   | Floating         | Floating Matrix Tablets exhibited excellent floating behaviour (5.5 h), and     | [60] |
| Hydrochloride      |                             |                      | Matrix Tablets   | sustained the drug release.                                                     |      |
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 significant gastro retention than other shapes. These devices with a 22.5-48 KSI (keto pound/ inch²) 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 (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.

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 longer. Due to the buoyancy effect on the gastric contents, the drug liberated slowly, showing increased GRT and controlled plasma drug concentration. In addition, the device forms a cohesive gel barricade and maintains specific gravity less than gastric contents (1.004-1.010), discussed in (Table 3 and Figs. 3 and 4 (A-E)) [62-84].

Table 3. GRDDS approaches, methods and polymers for delivery

| Approaches                             | Description                                      | Polymers /Excipients                          | Ref.  |
|----------------------------------------|--------------------------------------------------|------------------------------------------------|-------|
| Hydrodynamically balanced systems      | Drugs are added in combination with hydrocolloids, provides floating | Contains hydrophilic polymers Polycarbophil, Alginic acid sodium carboxymethyl cellulose, HPMC, agar and Polyacrylates | [62]  |
| (HBS)                                  |                                                  |                                                |       |
| 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                           | Based on hypothesis, dense pellets               | Barium sulphate, zinc                          | [67-69] |
| Approaches                          | Description                                                                 | Polymers /Excipients                                      | Ref.       |
|------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------|------------|
| Swelling type systems              | 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 floating, increases GRT | Poly(acryl)starch, DEAE cellulose and Poly(acryl) dextran | [78,79]    |
| 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]    |

Fig 3. GRDDs approaches for delivery of drugs.
A. Hollow microspheres approach

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] |
| Patent No. | Formulation                                                                 | Approaches                                                                 | Publication year | Ref. |
|-----------|------------------------------------------------------------------------------|-----------------------------------------------------------------------------|------------------|------|
| 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 | pharmaceutical composition for gastrointestinal drug delivery                 | Bio-adhesion promotes controlled release.                                    | 2015             | [112]|
| US200500 63980A1 | Gastric raft composition                                                      | Floating raft promotes controlled release                                   | 2005             | [113]|
| US80677 700OB2 | In situ gel formation of pectin                                               | In situ formation of floating raft, promotes release                         | 2004             | [114]|
| US663528 1 | The gastric retaining liquid dosage form                                     | Bio-erodible carrier facilitates retention of within stomach, erodes rapidly | 2003             | [115]|
| US679728 3 | Gastric retaining dosage form having multiple layers                         | Multilayered active agent shows swellable properties, promotes controlled release | 2004             | [116]|
| US858608 3 | GRDDS comprising an extruded hydratable polymer                             | Involves extrusion, improved gastric retention                               | 2013             | [117]|
| US911979 3 | GR dosage form of doxycycline                                                | Combination of floating, swelling and bio-adhesive promotes drug release.    | 2015             | [118]|
| US201503 66832 | GR dosage form for carbidopa/levodopa                                         | Carbidopa Shows swelling properties.                                        | 2015             | [119]|
| US201502 31084 | Osmotic floating tablets                                                      | Outer osmotic core achieves gastro-retention.                               | 2015             | [120]|
| US201603 38949 | Stabilized gastro-retentive tablets of pregabalin                            | Gastro-retention increased due to swelling                                   | 2016             | [121]|
| EP314851 4 | The expandable gastro-retentive dosage form                                  | Unfolding increases GRT and prolong release                                 | 2017             | [122]|
| EP257579 8 | 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                                |
| Gaviscon       | Alum. Hydroxide and MgCO$_3$ | Liquid, P.O. | GlaxoSmithKline                                   |
| 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        | 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.                                    | Sun pharm industri Stries                         |
| Baclofen GRS   | Baclofen          | SDF, P.O.                                    | Sun pharm industri Stries                         |
| Zanocin OD     | Ofloxacin         | SDF, P.O.                                    | GlaxoSmithKline                                   |
| Coreg CR       | Carvedilol        | Gastro-retention with osmotic system (SDF), P.O. | Sun Pharma, Japan                                |
| Inon Ace Tablets® | 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® proQuin XR | Rifampicin               | Bio-adhesive tablets, P.O. | Lupin, India                                      |
|                | Ciprofloxacin     | Polymer based swelling technology: AcuFormTM, P.O. | Depomed, USA                                     |

**SDF:** Solid dosage form

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**8. 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 GRDD 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.

**DISCLAIMER**

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.

**CONSENT**

It is not applicable.

**ETHICAL APPROVAL**

It is not applicable.
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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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