Review

Gastro-retentive drug delivery systems and their in vivo success: A recent update

Uttam Kumar Mandal *, Bappaditya Chatterjee, Faria Gias Senjoti

Department of Pharmaceutical Technology, Kulliyyah of Pharmacy, International Islamic University Malaysia (IIUM), Kuantan 25200, Malaysia

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ABSTRACT

Gastro-retentive drug delivery system (GRDDS) has gained immense popularity in the field of oral drug delivery recently. It is a widely employed approach to retain the dosage form in the stomach for an extended period of time and release the drug slowly that can address many challenges associated with conventional oral delivery, including poor bioavailability. Different innovative approaches like magnetic field assisted gastro-retention, plug type swelling system, muco-adhesion technique, floating system with or without effervescence are being applied to fabricate GRDDS. Apart from in vitro characterization, successful GRDDS development demands well designed in vivo study to establish enhanced gastro-retention and prolonged drug release. Gama scintigraphy and MRI are popular techniques to evaluate in vivo gastric residence time. However, checking of their overall in-vivo efficacy still remains a major challenge for this kind of dosage form, especially in small animals like mice or rat. Reported in vivo studies with beagle dogs, rabbits, and human subjects are only a handful in spite of a large number of encouraging in vitro results. In spite of the many advantages, high subject variations in gastrointestinal physiological condition, effect of food, and variable rate of gastric emptying time are the challenges that limit the number of available GRDDS in the market. This review article highlights the in vivo works of GRDDS carried out in the recent past, including their limitations and challenges that need to be overcome in the near future.

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1. Introduction

Oral formulations have earned a significant place among the various dosage forms developed so far for human administration. In most of the cases, the conventional oral delivery systems show limited bioavailability because of fast gastric-emptying time among many other reasons involved [1,2]. However, the recent technological development has resulted to many novel pharmaceutical products, mainly the controlled release drug delivery systems to overcome this problem. Gastro-retentive drug delivery system (GRDDS) is one such
example where the attribute like gastric retention time coupled with the drug release for extended time has significantly improved patient compliance. Some inherent limitations of the conventional oral drug delivery systems have ignited the interest to this new delivery system. Fast gastric emptying associated with conventional oral medications leads to a bioavailability issue for many drug molecules (e.g. pranlukast hydrate, metformin HCl, baclofen, etc.), of which the main principal site of absorption is the stomach or the proximal part of the small intestine, or have the absorption issue in the distal part of the intestine [3–5]. Solubility can also be improved by prolonging the gastric retention of drugs that are less soluble in an elevated pH environment of the intestine [2]. There are many drugs (e.g. captopril, metronidazole, ranitidine HCl, etc.) that are prone to degradation in the colonic area [2,6]. To attain required therapeutic activity, recurrent dosing is needed for the drugs with short half-lives as they have the tendency of getting eliminated quickly from the systemic circulation. However, an oral sustained-controlled release formulation with additional gastric retention property can avoid these limitations by releasing the drug slowly in the stomach along with maintaining an effective drug concentration in the systemic circulation for an extended period of time [7]. Apart from the systemic action, GRDDS has proved to be effective locally to treat gastric and duodenal ulcers, including esophagitis, by eradicating the deeply buried Helicobacter pylori from the submucosal tissue of the stomach [2,5,8–10]. The history of GRDDS formulations dates back to almost three decades [11]. The basic fabrication techniques, including their in vitro characterizations, are also well established. Even in recent times, quite a few reviews have been published on GRDDS [5,12–18]. These reviews are more focused on the formulation aspects or in vitro characterization studies done by various researchers or overall GRDDS. The industrial aspects covering physicochemical, biopharmaceutical and regulatory considerations of GRDDS have been reviewed by Pawar et al. [19]. Still, the number of marketed gastro-retentive formulations is not significant. So, it is very important to look through the in vivo studies done with GRDDS in order to find out the pharmacokinetic performances of the developed systems considering their significant roles in successful commercialization of any dosage form. As per our literature search, there is no review available to date focusing on in vivo performances of GRDDS, especially on recent works. In this context, the aim of this review is to summarize the in vivo studies of GRDDS in terms of pharmacokinetic parameters as well as gastro-retention times and the inherent challenges or constraints for in vivo evaluations recorded by various researchers.

2. Stomach physiology

Success of GRDDS relies on the understanding of stomach physiology and related gastric emptying process. Structurally the human stomach is composed of three anatomical regions: fundus, body and antrum (pylorus), as depicted in Fig. 1. After a meal, the average volume of a stomach is about 1.5 l, which varies from 250 to 500 ml during the inter-digestive phases [18]. The part made of the fundus and the body acts as a reservoir of any undigested material, while the antrum performs as the principal site for the mixing action. Being the lower part, the antrum works as a pump for gastric emptying by a propelling action. Pylorus acts to separate the stomach from the duodenum and plays a major role in gastric residence time of the ingested materials. However, the pattern of the gastric motility is different for the fasting and fed state [20]. The gastric motility pattern is systematized in cycles of activity as well as quiescence. The duration of each cycle is 90–120 min and it contains four phases, as mentioned in Table 1 [21]. The motility pattern of the stomach is usually called migrating motor complex (MMC) [17].

3. Approaches to fabricate gastro-retentive systems

Different approaches have been adopted by researchers to enhance gastric residence time with the prolonged drug release. The concept of high density formulation is one such approach (Fig. 2). The developed dosage form was made heavy (density: 2.5 to 3.0 g/ml) to withstand in vivo peristaltic movement and remained intact in spite of the GIT disturbance. Accordingly, the GI transit time was expected to prolong for
an average of 5.8 h to 25 h [7,22]. Barium sulfate, iron powder, titanium oxide, and zinc oxide were incorporated in the formulation to increase the density of the dosage form. Increased dose size required to achieve that high density was one of the major drawbacks of this kind of system, as reported by Chawla et al. [23]. Another novel idea was postulated to retain the dosage form within the stomach by the application of a magnetic field. The dosage form would contain magnetically active elements. One external magnet was required to position on the abdomen over the location of the stomach to retain the administered drug in place (Fig. 3). Though innovative in design, lack of patient compliance was one of the major setbacks for in vivo design of this delivery system [24].

With the introduction of swelling and expanding system (Fig. 4), GRDDS managed to achieve significant success both in vitro and in vivo in order to retain the dosage form in the stomach [25,26]. Bolton and Desai [27] reported one such system that was designed to increase in size bigger than the diameter of pyloric sphincter and remain logged there (Fig. 4). Alternatively, the system was named as ‘plug type systems’ due to their pyloric sphincter blocking attribute. Once the polymer came in contact with the gastric fluid, it absorbed water and swelled [18,28–30]. The selection of a suitable polymer (or combination of polymers) with an appropriate molecular weight/viscosity grade and swelling properties enabled the dosage form to attain sustained-release characteristic. Further advancement of such kind of dosage form has taken place with the introduction of novel polymers with super-porous nature, causing them to swell to an equilibrium size within a minute. This characteristic rapid swelling property (swelling ratio is 1:100 or more) of the polymer with an average pore size of more than 100 μm occurs due to capillary wetting through several interrelated open pores when the dosage form comes in contact with GI fluid [31].

Another type of GRDDS has been designed utilizing buoyancy (floating) property of any dosage form experienced in GI fluid [32]. The bulk density of the dosage form attains less than the density of gastric fluid (1.004 to 1.010 g/ml) after a certain lag time. This lag time depends on the rate of swelling of the polymer used in the formulation, which again depends on the type, viscosity grade, presence of wicking agent or swelling enhancers, etc. [33–35]. The said parameters of the formulation also determine the duration of floating as well as in vitro drug release rate. The efficacy of the floating behavior also depends on the physiological conditions of the patients, like fed-state or fasting state, amount of gastric fluid, etc. [1]. After the required drug release, the used dosage form is emptied out from the stomach [36]. One additional attribute such as effervescence was incorporated within this swelling-based floating delivery system to improve the floating behavior (floating lag time as well as floating duration), as shown in Fig. 5 [37–41]. Various effervescent components (e.g. sodium bicarbonate,
tartaric acid and citric acid) were mixed within the dosage form. When these components come in contact with the gastric contents, carbon dioxide (CO\textsubscript{2}) is liberated as a result of a chemical reaction and it becomes trapped within the gelified hydrocolloid system. These combinations of effervescence and swelling help the dosage form achieve effective density less than the gastric fluid and result in an upward motion onto a dosage form which maintains the buoyancy for a prolonged period of time \[37\]. In addition to the single unit systems, the bi-layers and tri-layers design of this combination approach has also been considered to incorporate two different drugs with different release profiles \[37\]. One of the drugs and excipients is individually formulated as sustained release layer containing the gas generating unit, whereas the outer layer includes the second drug for immediate release profile \[42\]. Bio-adhesive or muco-adhesive drug delivery systems were also tried as gastro-retentive systems. The dosage form was made to be attached inside the lumen of the stomach wall and survive the gastrointestinal motility for a longer period (Fig. 6). It was also beneficial as a site specific design to promote local drug absorption in an infected area of the stomach. Muco-adhesive excipients like polycarbophil, lectins, carbopol, chitosan, carboxymethylcellulose (CMC), pectin and gliadin were reported as formulation compositions for this kind of design \[43–45\]. The combination of muco-adhesion and floating or swelling mechanism is being adopted as another novel approach for improved gastro-retention attributes \[9,46,47\].

In-situ gelling technique (also known as raft forming system) in combination with carbon dioxide bubble entrapment was also reported as another patient compliance design for gastro-retention. This type of delivery system, initially as a solution form, contains sodium alginate as in situ gel forming polymer along with carbonates or bicarbonates as effervescent agents. When they come in contact with the gastric fluid, they swell and generate a viscous cohesive gel that contains entrapped carbon dioxide bubbles, causing the drug delivery systems to float. For gastroesophageal reflux treatment, raft forming systems are frequently used because of their tendency to produce a layer on the upper part of the gastric fluid \[48,49\].

4. In vitro assessment of GRDDS

In vitro evaluations of GRDDS are prerequisite to ensure the in vivo performance with respect to floating lag time and floating duration, as well as selection of right formulation composition. In case of tablet dosage form, the routine evaluation tests include general tabletting parameters like hardness, friability, general appearance, drug content, uniformity of content, weight variation, and in vitro drug release \[37\]. For evaluation of floating behavior like floating lag time and the duration of floating for any GRDDS, deionized water and simulated gastric fluid have been used in the literature \[50\]. These two media are used to observe possible differences in buoyancy capabilities of the dosage forms. Additionally, swelling property and the rate of swelling of the polymeric dosage forms placed in a dissolution medium (0.1N HCl) are tested for at least 8 h to ensure drug release and floating mechanism. This is done by measuring the size of the swollen tablet or the weight gain after collecting them at the end of the study \[46\]. For in vitro drug release test, simulated gastric fluid is used as the test medium. Samples are withdrawn from the dissolution baskets with a predetermined time interval and are diluted appropriately to be analyzed for the drug content \[51\]. Microscopic observation, preferably scanning electron microscopy (SEM), is used at different magnification powers for visualization of the surface morphology of the dosage form. For the gastro-retentive beads and microspheres, some other additional tests like drug loading, particle size analysis and drug entrapment efficiency are performed to optimize formulation composition and related processing parameters \[52,53\]. Spectrophotometer, optical microscope and particle size analyzer are routinely used in these types of in vitro evaluation tests.
5. In vivo gastric retention as a surrogate of pharmacokinetic study

A well-designed in vivo study in appropriate animal model or healthy human subjects is required to prove the in vivo efficacy of any GRDDS. However, handling smaller animals like mice, rats, guinea pigs or rabbits for checking the gastric retention along with bioavailability study is difficult, especially for a big size tablet dosage form, as reported by Turner et al. [54]. That’s why most of the literatures on formulation of GRDDS had shown the proof of in vivo gastric retention in relatively bigger sized animals like dog or human subjects, together with important in vitro characterization studies such as dissolution study, estimation of floating lag time and floating duration. The extended in vivo gastric retention was hypothesized that the GRDDS was supposed to give improved therapeutic efficacy as compared to the conventional dosage form. Many sophisticated visualization techniques are helpful in this regard. Gamma scintigraphy is one such popular and elegant technique to provide appropriate assessment of gastro-retentivity in humans. A small amount of radioisotope with short half-life is incorporated within the dosage form. The formulation is exposed to a neutron source that can cause it to release the characteristic gamma rays to be captured as an image after processing by a computer [55]. Badve et al. [56] formulated hollow calcium pectinate beads of diclofenac sodium for its chronopharmacological action. The floating beads were structurally hollow spheres with a bulk density of less than 1 g/ml and 34% porosity. An in vivo study was done on rabbits by gamma scintigraphy, which showed gastro-retention of beads up to 5 h. There are many other recent reports of success in vivo gastric retention of floating tablets and microspheres containing versatile drug molecules like ascaridole, calcium-disodium edentate, and repaglinide [57–59]. Magnetic Resonance Imaging (MRI) is another technique to prove in vivo gastro-retention of a GRDDS. This is comparatively a safe technique that uses magnetic fields and radio waves to view the complete anatomical structure along with the location of the ingested dosage form. The compounds with super paramagnetic properties (e.g. ferrous oxide) are incorporated for the visualization purpose [51]. Steingeetter et al. [60] used this technique to report the in vivo gastric retention of gadolinium chelates (Gd-DOTA) floating tablet containing Fe₃O₄ as a super-paramagnetic agent and succeeded in analyzing intra-gastric tablet position and residence time in human volunteers. Radiology or X-ray is another alternative technique where a radio-opaque material is incorporated with the GRDDS. This technique has been reported in the evaluation of gastro-retentivity, the disintegration rate of dosage forms and their esophageal transit [61]. However, the safety issue is associated with this technique as repetitive exposure to X-ray may incur health hazard [62]. In spite of that, the technique has the advantage of using it successfully in human volunteers, dogs, and rabbits [63–67]. To diagnose and monitor the GIT, gastroscopy is another commonly used technique. Fiber optics or video system is used to locate the dosage form by this technique. As this procedure is less convenient, sometimes it is applied with minor anesthesia in human to assess gastric retention of any dosage form [68]. But in case of dogs, complete anesthesia is required, as reported by Dhiman et al. [51].

6. In vivo success of GRDDS in the background of pharmacokinetic attributes

Based on a huge volume of literatures, it is quite established that oral gastro-retentive drug delivery system has been widely explored within the last three decades of research in drug delivery. However, only a handful of them have been evidenced with in vivo proofs. The following sections contain a glimpse of them arranged chronologically for animal and human subjects separately:

6.1. Animal study

Klausner et al. [18] developed a novel controlled release GRDDS of Levodopa by using unfolding polymeric membranes with extended dimensions and high rigidity. In vivo study was done with the beagle dogs pretreated with carbidopa. The developed formulation was administered and the location of the dosage form in the gastrointestinal tract was determined by X-ray. Also, serial blood samples were collected and examined for the active drug. It was found that the optimized controlled release GRDDS of Levodopa was able to maintain the therapeutic concentrations of Levodopa (>500 ng/ml) over 9 h. The mean absorption time was considerably prolonged compared to non-GR controlled release-particles and oral solution.

Jain et al. [57] formulated floating microsphere of repaglinide (hypoglycemic agent) where calcium silicate was used as porous carrier and Eudragit as polymer. Sprague Dawley male rats were subjected to the organ distribution study and suspension of 99mTc-labeled floating microspheres were administered to albino rabbits orally with water. After the gastric residence time of 6 h as confirmed by gamma scintigraphy, the rats were sacrificed and organs were isolated (stomach and intestinal region). Organ distribution of the test compound was found to be uniform and the relative bioavailability was 3.17 times compared to marketed tablets.

In vivo anti-tumor study was carried out by Shishu and Aggarwal [69] to check the therapeutic efficacy of floating calcium alginate beads of 5-flouracil. It was found that the multiple unit floating system was able to reduce gastric tumor incidence by 74% in mice where the reduction of this incidence was found to be only 25% in the case of a conventional tablet dosage form.

Pande et al. [70] prepared cefpodoxime proxetil microspheres as GRDDS. The solvent evaporation technique was used for the development of the drug loaded microspheres where ethyl cellulose and HPMC were used as the release retarded materials. Two groups of male albino rats were subjected to oral ingestion of the cefpodoxime proxetil microspheres and cefpodoxime proxetil suspension at a dose of 10 mg/kg. Blood samples were collected at a pre-determined time intervals from retro-orbital region and centrifuged for separating plasma samples, which were finally analyzed by HPTLC. This study resulted in an increase of the relative bioavailability of the drug formulated into the microspheres which was 1.5 times more compared to the suspension.

Guan et al. [71] confirmed the efficacy of a gastro-retentive floating osmotic capsule containing famotidine as compared
to its marketed formulation. The developed capsules were based on novel asymmetric membrane technology where the membrane was composed of glycerin and diethyl phthalate. Polyethylene oxide WSR N-80 (molecular weight 200,000) was used to prepare the sustained release floating granules encapsulated within the capsule shells. The optimized formulation provided in vitro zero-order drug release profile and floating time both for 12 h. Six healthy male beagle dogs were administered the optimized 40 mg floating capsules (Test) and famotidine 20 mg commercial tablets (two tablets per administration as Reference) in a well-designed in vivo study and blood samples were withdrawn for 36 h. Peak plasma concentration ($C_{\text{max}}$) for the Reference formulation was found to be 0.334 μg/ml as compared to 0.187 μg/ml for the Test formulation capsule. Similarly, the time to reach peak plasma concentration ($T_{\text{max}}$) for the Reference tablet was 2.083 h as against 4 h for the Test capsule. Elimination half-life ($t_{1/2}$) was found to be approximately double for floating capsule (23.634 h) as compared to that of commercial tablet (13.178 h). As expected, the area under the curve (AUC$_{0-\infty}$) for the Reference tablet was found to be 31.411 μg/ml, whereas for the Test capsules it was 50.4 μg/ml. Accordingly, the relative bioavailability of developed capsule was about 1.605 times higher than the commercial formulation. This in vivo study clearly proved the advantage of gastro-retentive formulation over conventional one.

Khan and Dehghan [72] reported enhanced bioavailability of atorvastatin calcium, a hypolipidemic drug, administered in albino rabbits as floating tablets. With an in vitro floating lag time of $56 \pm 4.16$ s and floating duration of 6 h, the tablets could enhance the bioavailability 1.6 times compared with that of the conventional tablets.

The stomach is the major absorption site for cephalixin and gastro-retentive formulation could achieve its enhanced bioavailability as confirmed by Yin et al. [73]. Cephalexin loaded gastro-floating tablets were prepared by hydroxypropyl methylcellulose (HPMC K100M) as a matrix and sodium bicarbonate as a gas-forming agent. The developed tablets had a floating lag time below 15 s and floating duration of more than 12 h with a satisfactory in vitro sustained-release profile for 12 h. An in vivo pharmacokinetic study was conducted in fed and fasted beagle dogs comparing with conventional capsules and sustained release tablets. Cephalexin floating tablets resulted in a relative bioavailability of 99.4% with an extended drug release profile, while the reference formulations gave a relative bioavailability of only 39.3%. However, the study had shown a significant effect on the pharmacokinetics of sustained-release tablets.

Thakar et al. [4] reported an in vivo study on rabbits for the floating tablets containing baclofen. Composed of Polyox WSR 303 and HPMC K4M as swelling polymers and sodium bicarbonate as gas generating agent, the tablets showed favorable gastro-retentive properties like a floating lag time of 4 to 5 s and floating duration of more than 12 h. In line with the in vitro properties, the optimized floating dosage form provided prolonged gastric residence time and showed a 2.34 times increase in bioavailability as compared to the commercial formulation.

Combination of floating and bioadhesion was found to provide improved in vivo efficacy of famotidine mini-tablets fabricated by Zhu et al. [74] with HPMC K4M as release retarding and swelling polymer together with carbopol 971P (bioadhesive materials) and sodium bicarbonate (gas-forming agent). Tested in rat models, the mini-tablets could result in a 1.62-fold enhancement in bioavailability.

Qi et al. [75] reported in vivo success of the compression coated floating tablet of ofloxacin. The tablets were prepared by hydroxypropyl cellulose as compression coating agent, sodium alginate as a drug release modifier, and sodium bicarbonate as an effervescent agent. In vitro attributes of the tablets like a floating lag time of 30 s and floating duration of 12 h were well correlated with its relative bioavailability of 172% against the market formulation studied in New Zealand rabbits.

The combination of effervescence and swelling floating mechanism as a mean of superior gastro-retentivity and in vivo efficacy was proven by Kadivar et al. [67] for imatinib mesylate sustained release tablet prepared with HPMC K4M, sodium alginate and carbomer 934P. Studied in New Zealand rabbits, the gastro-retentive tablets could increase the bioavailability around 1.5 times compared to the conventional tablets (Gleevec).

### 6.2. Human study

Chen et al. [76] developed a gastro-retentive tablets based on swelling/effervescence mechanism with a combination of hydroxyethyl cellulose, sodium carboxymethyl cellulose, and sodium bicarbonate for administering antihypertensive drug losartan. Tablets were found to remain floating in vitro for more than 16 h with a swelling to 2 cm in diameter within 3 h. Additionally, the tablets showed pH-dependent drug release with an extension for 24 h. When tested in healthy human volunteers, the optimized tablets achieved an enhanced bioavailability of approximately 164% relative to the immediate release market formulation named Cozaar®. As expected, the gastro-retentive floating tablets produced favorable pharmacokinetic parameters: maximum residence time (MRT) and $T_{\text{max}}$ values were greater and $C_{\text{max}}$ values were lower as compared to the commercial formulation.

Bomma and Veerabrahma [66] established efficacy of antibiotic treatment with gastro-retentive tablets of cefuroxime axetil over conventional tablets, Zocef®. Developed and optimized tablets were based on a combination of swelling (HPMC and Polyox WSR 303) and effervescence (citric acid, calcium carbonate) mechanism. In line with in vitro floating duration of more than 12 h with a floating lag time of less than 30 s, the optimized tablets could be retained 225 ± 30 min in human subjects as confirmed by in vivo radiographic studies. The same tablets were tested on eight healthy human volunteers. The developed floating tablets showed superior bioavailability than Zocef tablet. Based on in vivo performance, a significant difference was observed in $C_{\text{max}}$, $T_{\text{max}}$, $t_{1/2}$, AUC$_{0-\infty}$, and mean residence time between test and reference ($P < 0.05$). As compared to the reference tablets, the floating tablets of cefuroxime axetil resulted in an increase of 1.61-fold relative bioavailability.

In vivo efficacy of GRDDS containing a high load of nico tinamide (600 mg) as an active drug was patented by Meijerink et al. [77]. Hypromellose was used as a swellable agent in that formulation. Eight healthy adult volunteers were used to explore their pharmacokinetic profiles. Blood samples as well as urine were collected at a pre-determined time intervals. The developed dosage form was capable of maintaining an increased
nicotinamide plasma levels in vivo for a period of at least 8 h after ingestion by the volunteers.

Ranade et al. [78] studied ellagic acid and aloe vera gel powder as a bilayer floating tablet prepared with HPMC K15M and sodium bicarbonate to treat stomach ulcer. The researchers reported 75% ulcer inhibition in comparison to 57% ulcer inhibition with ellagic acid alone. This efficacy was resulted from the tablets that showed in vitro floating duration of only 4 h with a cumulative 92% drug release.

In another study, efficacy of gastro-retentive emulsion gel calcium pectinate beads containing cinnarizine prepared by the ionotropic gelation method was established by Abouelatta et al. [79]. The researchers reported improved in vivo efficacy with a mean AUC$_{0-24}$ and AUC$_{0-\infty}$ enhancement of 1.79 and 3.80 times, respectively, compared to a conventional tablet in healthy human volunteers. Interestingly, the beads composed of pectin (base), glyceryl monooleate and labrafac lipophile WL 1349 (oil phase) had instant in vitro floating capacity.

Although many GRDDS with various novel fabrication options have been reported for their in vitro success, their commercialization success is not significant. A glimpse of a few new candidates together with the old ones is summarized in Table 2 [5,19,80].

7. Challenges ahead with GRDDS

The retention time of the dosage forms in the GIT is one of the determinants of the bioavailability of oral drug delivery systems. In case of GRDDS, it is rather specific to the stomach only. Therefore, for developing a GRDDS, the main challenge is retaining the delivery system in the stomach or the upper part of the small intestine for a long time until all the drugs have been released at a predetermined rate [74]. The process of gastric emptying time is highly variable. Among many other factors, it mainly depends on the dosage form as well as fed or fasted state of the stomach. The gastric retention time is extended in the fed state, whereas shortened by the fasting state [81]. Other physiological barriers and factors like the type of food, caloric content, gender and age play significant roles in the variation of gastric emptying time [82]. Because of high caloric content, high fat meal strongly prolongs the process of gastric emptying. Indigestible polymers or fatty acid salts also modify the motility pattern of the stomach under fed state and help in reducing gastric emptying rate [1]. Additionally, patients have variable GRT depending on gender and age, as reported by Mojaverian et al. [83]. The pylorus limitation plays an important role in gastric retention of any GRDDS. The pylorus size is about 2 to 3 mm during the digestion and the diameter becomes 12.8 ± 7.0 mm during the inter-digestive phase. Thus, all particles must have a diameter lower than 5 mm so that they can pass through the pylorus into the duodenum [84]. Another factor to consider here is the variation in pylorus size and its peristaltic movement of the animal (e.g. dog, rabbit model) from that of the human [85]. So, in vivo efficacy results need to be concluded carefully. Size and shape of the dosage form, individual’s disease state, and body mass index are some other factors on which gastric residence time is dependent and related to the efficacy of the dosage form [84]. However, it has been reported that sometimes multiple-unit GRDDS shows an improved and predictable drug release compared to a single-unit GRDDS. Due to a combination of the lag time and the gastric emptying process, a single unit gastro-retentive dosage form (GRDF) may ultimately exit the stomach before the dosage form becomes functional [5]. Hence, to develop an optimum GRDDS, the main challenges are to overcome the problems associated with the gastric emptying rate of the stomach together with maintaining an appropriate drug release rate for an extended period of time before it gets metabolized in the system [86].

Table 2 – List of commercialized gastro-retentive drug delivery system (GRDDS).*

<table>
<thead>
<tr>
<th>Product</th>
<th>Drug</th>
<th>Company</th>
<th>Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid Gaviscon®</td>
<td>Ciprofloxacine and sodium bicarbonate</td>
<td>Reckitt Benckiser Healthcare, UK</td>
<td>Effervescent floating</td>
</tr>
<tr>
<td>Cipro XR®</td>
<td>Ciprofloxacine HCl and betaine</td>
<td>Bayer, USA</td>
<td>Erodible matrix-based system</td>
</tr>
<tr>
<td>Prazopress XL®</td>
<td>Prazosin hydrochloride</td>
<td>Sun Pharma, Japan</td>
<td>Effervescent and swelling-based floating system</td>
</tr>
<tr>
<td>Conviron</td>
<td>Ferrous sulfate</td>
<td>Ranbaxy, India</td>
<td>Colloidal gel forming floating system</td>
</tr>
<tr>
<td>Cefaclor LP®</td>
<td>Cefaclor</td>
<td>Galenix, France</td>
<td>Floating system</td>
</tr>
<tr>
<td>Tramadol LP®</td>
<td>Tramadol</td>
<td>Galenix, France</td>
<td>Floating system</td>
</tr>
<tr>
<td>Baclofen GRS®</td>
<td>Baclofen</td>
<td>Sun Pharma, India</td>
<td>Coated multi-layer floating and swelling system</td>
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<tr>
<td>Gabapentin GR®</td>
<td>Gabapentin</td>
<td>Depomed, Inc., USA</td>
<td>Polymer-based swelling technology</td>
</tr>
<tr>
<td>Proquin XR®</td>
<td>Ciprofloxacine</td>
<td>Depomed Inc., USA</td>
<td>Polymer-based swelling technology</td>
</tr>
<tr>
<td>Glumetza®</td>
<td>Metformin HCl</td>
<td>Depomed Inc., USA</td>
<td>Polymer-based swelling technology</td>
</tr>
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<td>Levodopa and benserazine</td>
<td>Roche, UK</td>
<td>Floating capsule</td>
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<td>Diazepam</td>
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<td>Floating capsule</td>
</tr>
<tr>
<td>Topalkan®</td>
<td>Aluminum and magnesium</td>
<td>Pierre Fabre Medicament, France</td>
<td>Floating liquid alginate</td>
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<tr>
<td>Xifaxan®</td>
<td>Rifaximin</td>
<td>Lupin, India</td>
<td>Bioadhesive tablets</td>
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<td>Coreg CR®</td>
<td>Carvediol</td>
<td>GlaxoSmithKline</td>
<td>Gastro-retention with osmotic system</td>
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<tr>
<td>Inon Ace®</td>
<td>Simethicone</td>
<td>Sato Pharma, Japan</td>
<td>Foam-based floating system</td>
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<tr>
<td>Cytotec®</td>
<td>Misoprostol</td>
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* Prinderre et al. [5], Pawar et al. [19], and Kotreka and Adeyeye [80].
8. Conclusions

According to the review of different published literature and detailed investigations on commercial products, it can be concluded that no single gastro-retentive system could be marked as the best suited for any drug candidate. However, several advantages of GRDDS for patients have been evidenced in the majority of them. Individual drug candidate or a combination of the drugs needs to be assessed case by case regarding the necessary dose and the ease of manufacturing process. Polymer selection remains a critical factor for the formulations that contain high dose. This selection is essential for the compressibility needed to exploit the high doses of the APIs. However, the criteria of ideal polymer should be based on its amount in the dosage form; a minimum quantity that provides a substantial gastric retention should be preferred [5]. Although several approaches like floating, bio-adhesion, efervesence, sinking, magnetic, swelling, etc. have been proposed over the years, reports on their in vivo success have not been captured significantly. Formulation wise, the major trend has been shifted toward the use of swelling polymer matrix together with efervesence in the design of floating delivery systems. Commercially it is emerging slowly as an important novel drug delivery due to many inherent challenges associated with it in spite of the numerous potential benefits offered by this delivery system. In terms of delivering drugs to the systemic circulation along with enhanced effectiveness, it is expected that GRDDS will become more popular in the near future. However, it is necessary to establish their efficacy by properly designed in vivo studies for a specific drug because of the complexity in pharmacokinetic and pharmacodynamic parameters.

References


