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Gastro-retentive oral drug delivery systems: a promising approach for narrow absorption window drugs

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Abstract

Drugs with a narrow absorption window (NAW) are those drugs that are absorbed from the first part of the gastrointestinal tract. Therefore, typical modified/sustained release formulations of those drugs cannot provide a true long-acting drug release. Once the dosage form has passed the absorption sites at the specific regions of the small intestine; the drug is no longer absorbed from the modified release dosage form and the bioavailability is adversely decreased. While there are many pharmacological classes such as centrally acting skeletal muscle relaxants, anti-parkinsonism drugs and anti-infective belong to NAW drugs and are required to be formulated in modified release dosage forms. Modified release dosage forms based on gastroretentive technologies could hold a promise. Such dosage forms aim to release drugs in the upper part of the gastrointestinal tract especially in the stomach in a controlled release manner that might provide sustained release characteristics without sacrificing much of total bioavailability. This review provides a critical appraisal of different technologies, polymers, candidate drugs for gastroretentive technologies.

Key words

Baclofen, modified release, narrow absorption window, floating system, bioadhesive, mucoadhesive

1. Introduction

Modified release products are mainly designed to release the drug over an extended period of time to modify the release of the drug at a desired rate and/ or at a specific site of absorption. These dosage forms have the advantage of decreasing the systemic side effects, improve the efficiency of therapy by a reduction in fluctuation in drug level, improve patient compliance, in addition, to reduce toxicity associated with rapid release of some drugs by slowing drug absorption [1].

It is worth mentioning that modified release dosage forms are a broad term which can include different approaches according to their objectives as time and/or site controlled release formulations [2]. **(Figure 1)** shows the classification of modified release drug delivery systems [2].

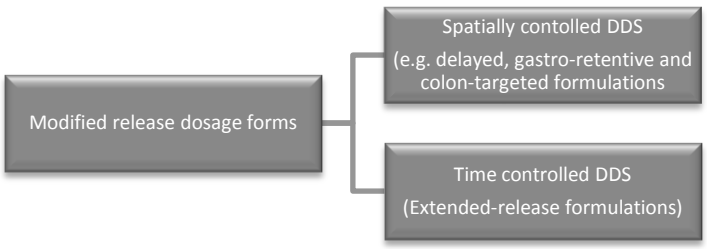

Figure 1: Classification of modified release drug delivery systems, as modified from Aulton's Pharmaceutics: The Design and Manufacture of Medicines [2]

Spatially controlled DDS; this is a type of modified release dosage form where the drug is released at a specific part of the GIT. A typical example includes delayed release dosage forms, these dosage forms aim to ensure that the drug is not released at the acidic pH of the stomach and released after passing this part [3], as ketoprofen microspheres prepared using different types of Eudragit polymers [4]. This formulation also is known as enteric coated dosage forms. Colon targeted formulations which aim to deliver the drug to the colon to treat a certain disease like ulcerative colitis as metronidazole [5]. Gastro-retentive drug delivery systems which prolong the gastric residence time of the formulations in order to improve bioavailability and/or to achieve a local effect in the stomach as nizatidine mucoadhesive tablets [6].

Extended release dosage forms; they are also known as sustained release, prolonged release or controlled release dosage forms. These dosage forms aim to prolong or sustain the drug release, and they provide a gradual release of the drug for a long period of time [7]. Different polymers can be used in such formulations these polymers include: hydroxypropyl methyl cellulose, methacrylate copolymers (Eudragit RS 100, RL 100), methyl cellulose, carbopol 934, alginates, gelatin, and methyl cellulose. various formulations were prepared as extended release using these polymers as alprazolam [8], metronidazole [9], ampicillin trihydrate [10] and ibuprofen [11].

Unfortunately, some drugs such as baclofen, levodopa, ofloxacin, and famotidine are best absorbed from the upper part of the gastrointestinal tract. These drugs can demonstrate a narrow absorption window (NAW) biopharmaceutical behavior.

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The formulation of such drugs as a modified release dosage form might pose challenges because modified release forms of these drugs might not ensure complete absorption if the modified release system passed the desired area of absorption without completing drug release out of the system [12].

Site-specific absorption of these drugs might also be related to drug solubility and stability of the drug in different parts of the gastrointestinal tract, as a result of changes in the pH or degradation under the effect of enzymes present in the lumen of the intestine. Such drugs should be formulated in such a way to maintain the drug in its preferred site of absorption. One of these techniques which have the ability to retain the dosage form in the stomach is gastroretentive drug delivery systems (GRDDS) [13, 14].

For example, famotidine was prepared as a multiple unit floating bioadhesive modified release minitablets using hydroxypropyl methylcellulose as release retardant and carbopol 971 as bioadhesive polymer. The prepared formulations were able to remain floating on the gastric fluid for more than 8 h using sodium bicarbonate as a gas generating agent, hence prolonging the gastric residence time of famotidine, in vivo studies showed that the bioavailability of famotidine minitablets was 1.62 fold compared with the commercially available tablets [15].

Controlled release gastroretentive drug delivery system of ofloxacin was prepared by conventional wet granulation using HPMC K100 as release retardant and sodium bicarbonate as gas generating agent. These formulations were able to float over the gastric contents for more than 16 h, and sustain the drug release without sacrificing the total bioavailability and the maximum therapeutic level. AUC estimated for the optimized to marketed formulation was found to be significantly different ($P < 0.05$) and it was found to be 41.80 ± 4.83 and 36.85 ± 4.77 respectively, and C_{max} was found to be 3.94 ± 0.39 and 3. 47 ± 0.70 µg/ml, respectively [16].

Famotidine was also prepared as floating microspheres by a modified solvent evaporation method. Microspheres were capable to float up to 20 h in simulated gastric fluid, The cumulative percent drug release for the prepared microspheres was found to be between 85-98 % over 20 h, compared with 5 h for pure drug [17].

2. Gastroretentive drug delivery systems

Gastroretentive dosage forms are oral dosage forms which have the ability to be retained in the GI tract and resist rapid gastric emptying. These systems are highly suitable for drugs that possess absorption window constraints. They are designed as formulations of modified release drug delivery systems which have the ability to control the release rate and site to confine the dosage form in the targeted area of the GIT (stomach) [18]. The effectiveness of gastroretentive drug delivery systems depends on several factors such as gastric transit time, food effects and site of absorption of the drug [18].

The average time required for the dosage form to traverse the stomach is 10 min to > 3 h; the wide variability in gastric emptying time depends on the type of the dosage forms and content of the stomach. For example, extremely short gastric emptying time can be recorded for liquid dosage forms in an empty stomach while relatively long gastric transit time can be assigned for solid dosage forms, as shown in (**Table 1**) [19]. The efficacy of the gastroretentive drug delivery systems depends on the drug release rate and the transit time along the GIT. Also, (**Table 1**) shows the transit time in each segment of the GIT [20].

Table 1: Shows the transit time in each segment of the GIT

Segment	Type of food	
	Liquid	**Solid**
Stomach	10-30 minutes	< 1 to > 3 hrs.
Duodenum	Short	Minutes to hrs.
Jejunum and ileum	3 hr. ± 1.5 hr.	4 hrs. ± 1.5 hr.
Colon	----------	20 hrs. – 50 hrs.

Some drugs are absorbed in a particular part of the GIT such as those drugs absorbed in the first part of the small intestine or the duodenum [21], the drug may be absorbed with the various extent in different parts of the GIT. These drugs are called drugs with a narrow absorption window (NAW) [19]. These drugs usually best absorbed in the duodenum and jejunum due to the large surface area or because of the drug shows better solubility in the upper part of the GIT than the lower part of the GIT [22]. After passing the absorption window the released drug go waste and no absorption any more in the remaining part of the GIT. This phenomenon decreases the absorption of such drugs when administered orally via immediate release drug delivery systems resulting in poor bioavailability [23]. Among these drugs with NAW is L-DOPA [24], furosemide [25], baclofen [26], riboflavin [27] and para-aminobenzoic acid [28, 29]. The prepared formulations could effectively sustain the release of such drugs but the major drawbacks in these formulations these drugs have NAW; therefore prolonging the drug release cannot be sufficient to improve drug bioavailability as these drugs cannot be absorbed after passing the desired part of the absorption [30, 31].

In general, drugs which display NAW difficult to be formulated as immediate release DDS or oral controlled release drug delivery system (CRDDS) because of the preparation of these drugs in the form of immediate release dosage forms require frequent use of a dosage form which did not improve patient compliance in addition to side effects related to the rapid release of those drugs, while sustain drug release could prolong the release time which in such cases shows no benefits because only the drug absorbed in a definite segment along the GIT [32].

Gastroretentive drug delivery systems have the ability to be retained in the stomach [33]. GRDDS remains in the stomach for several hours thus prolonging the gastric residence time which might be in favor of improving the bioavailability of NAW drugs [34, 35]. Prolonging the gastric residence time might improve the bioavailability due to the enhancement of the solubility of drugs which are more soluble at low pH [32, 36].

For example, the bioavailability of ofloxacin was improved up to 97.55 % compared with 53.90 % for the marketed product of ofloxacin (Zanocin®), when designing in ofloxacin modified release gastroretentive formulations by using different polymers as HPLC, psyllium husk, crospovidone, and its combinations [37].

Famotidine has been prepared as gastric floating calcium pectinate beads; the formulations have the ability to float over the gastric content for more than 24 h, the prepared gel beads efficiently sustain famotidine release where; 94.39 % of drug content was released over 8h from the optimized formula compared with 100 % of the drug was released over a period less than 3 h from famotidine conventional tablets [38].

2.1. Anatomical and physiological barriers for GRDDS

2.1.1. Stomach

It represents the main site for gastric retention. Its anatomy and physiology must be taken into consideration during the formulation of GRDDS. The stomach is located in the upper part of the abdomen just below the diaphragm, the size of the stomach varies according to its distension reach to 1500 ml following a meal; after emptying food it becomes in a collapsed state with a resting volume of 25-50 ml [39]. The stomach consists of three main parts; fundus, body, and pylorus (antrum). It divided anatomically into the distal and proximal part, the proximal part consists of the fundus and the body it acts as a reservoir for undigested materials, while the distal part is the main part of mixing and responsible for propelling the content to the duodenum [40].

2.1.2. Gastric motility and emptying of food

The process of gastric emptying is characterized by a definite cycle of electro-mechanical activity known as migration myoelectric complex (MMC) [41]. This is a series of event occur along the stomach and small intestine every 1.2 – 2 h and it is divided into four phases [42]:

Phase I: (45 – 60 min) is a period of few or no contractions.

Phase II: (30 – 45 min) consists of intermittent contractions, which gradually increase in intensity and frequency as the phase progresses.

Phase III: (5 – 15 min) is a short period of intense, involving both the proximal and distal gastric regions, it is also known as ('housekeeper waves'). In this phase, indigestible solids are removed from the fasted stomach.

Phase IV: (0 – 5 min) is a transition period between Phase III and Phase I of decreasing activity until the next cycle begins.

2.2. Advantages of Gastroretentive drug delivery systems

GRDDS provides various advantages over conventional dosage forms this includes:

1- Enhanced bioavailability: GRDDS improve the bioavailability of drugs having absorption in the upper part of GIT as Riboflavin, Baclofen, and L-Dopa [43-45].
2- Decrease drug level Fluctuation: the plasma level of drugs remain consistent and uniform as it improves the release and the bioavailability of the drugs [28, 46].
3- Sustained drug delivery and reduce the frequency of dosing this improves patient compliance [47].
4- Targeted drug delivery in the upper part of GIT, this suitable for drugs which mainly used in the treatment of disease of this part as antacids, drugs used in the treatment of peptic ulcer [48, 49]
5- Improve safety margin with highly potent drugs, because it releases the drug in a predictable and controlled manner [50].

2.3. Criteria for selection of candidate drugs for GRDDS

GRDDS can provide many advantages for the delivery of a wide range of drugs [23, 51]. (**Table 2**) summarizes groups of drugs that have been formulated as GRDDS:

Table 2: Categories of drugs that have been formulated as GRDDS

Drug category	Example
Drugs acting locally in the stomach [52, 53]	Misoprostol, Antacids, Antibiotics for treatment of bacterially based ulcers.
Drugs with NAW [43, 44, 54].	Levodopa, Baclofen, Riboflavin, Atenolol, Furosemide.
Drugs that are absorbed rapidly from the GIT [55]	Amoxicillin.
Drugs that are poorly soluble in the alkaline PH of the intestine such as weakly basic drugs [56, 57]	Diazepam, Propranolol, Famotidine, Verapamil.
Drugs that degrade in the colon [58]	Ranitidine, metoprolol.
Drugs that are unstable in the lower part of the GIT [52].	Captopril, Famotidine.

Using GRDDS with the aforementioned groups of drugs has been reported to enhance the absorption as well as increase the bioavailability of such drugs [59, 60]. Designing of such dosage forms allow the release of drugs to be predicted and programmed, also it ensures complete release of medicament before the dosage form reach reaches non-optimal absorption sites [61, 62].

Freeze-dried floating alginate beads of famotidine was prepared in order to enhance the bioavailability of famotidine and prolong the GRT where the drug mainly act in the stomach [53].

Riboflavin containing microballoons were prepared as GFDDS to improve the absorption of riboflavin by prolonging the GRT as the drug has NAW. So prolonging the GRT increases the time where the drug is available for absorption in the upper part of the GIT [54].

Amoxicillin is known to be effective against H. Pylori which founds mainly in the stomach, so prolonging the GRT can improve the efficacy of amoxicillin against H. Pylori. Gastric

floating calcium alginate beads of amoxicillin were prepared by *Whitehead and et.al,* which effectively prolong the GRT and improve amoxicillin activity [55].

2.4. Factors controlling the gastric residence time (GRT) of dosage forms

There are several factors controlling the gastric emptying and hence controlling GRT of oral dosage form [63]. These factors include size, density and shape of the dosage form, concomitant administered drugs, intake of food, and other biological factors such as age, gender, and body mass index, presence of disease (diabetes, Crohn's disease and gastrointestinal disease).

2.4.1. The density of dosage form

Dosage forms with a density lower than the density of the gastric fluid can experience a floating behavior and greater gastric residence time, while high density sink to the bottom of the stomach [64]. The density of the gastric fluid is reported to be 1.004 g/ml [56, 65], therefore dosage forms with density lower than 1 g/ml can float over the gastric content and carry on its journey [66]. However, the floating tendency of the dosage form usually decrease as a function of time, as the dosage form gets immersed into the fluid content of the stomach as a result of hydrodynamic equilibrium [67].

2.4.2. Size of the dosage form

The size of the dosage form is another factor controlling how long a dosage form is retained in the stomach. Gastric residence time of conventional non floating dosage forms is highly variable dependent on the size of the dosage form, which could be small, medium and large. In the fed condition, the smaller units get emptied from the stomach during the digestive phase while the larger in size emptied during the housekeeping waves. Generally, as the size of the dosage form increases, the gastric residence time increases [68], because the larger size wouldn't allow the dosage form to pass rapidly through the pyloric sphincter into the small intestine [69].

It is reported that formulations with a diameter greater than 7.5 mm can experience a better gastric residence time; however, this comes with a limitation of a size ≥ 9.9 mm due to that the formulation is prone to be too bulky to float without interference from gastric food content [66, 70]. One fact should be taken into consideration during designing of the gastro retentive drug delivery systems are that this dosage form should dissolve or erode to decrease in size to allow this dosage form to pass through the pyloric sphincter into the small intestine after achieving the required therapeutic effect [19].

2.4.3. The shape of the dosage form

It is considered one of the formulation factors affecting the gastric residence time [71]. It was found that dosage forms with ring shape and tetrahedron shape experience a greater gastric residence time compared to other shapes [72].

2.4.4. Food intake and the nature of food

It was found that ingestion of food, nature of food, caloric content, the viscosity of meals, and the frequency of feeding have a great effect on GRT. Generally, the presence of food prolongs the GRT of the dosage form and increase drug absorption by allowing it to stay at the site of absorption for longer period of time.

In general; drugs are emptied more rapidly during the fasted state than during postprandial periods [73]. In a gamma scintigraphic study of a bilayer floating capsule of misoprostol; it was found that the GRT is 199 ± 69 minutes in the fasted state compared to 618 ± 208 minutes after a light breakfast [74].

Diet component as fats, certain amino acid and peptides can slow gastric emptying thus prolongs the GRT [12]. The caloric content of the ingested food can affect the gastric emptying rate, GRT can be increased by 4 to 10 h in a meal that is high in fats and protein [18].

Generally; the increase in acidity, osmolarity, and caloric content have the ability to prolong the GRT of floating drug delivery systems (FDDS) [75].

For better gastric retention systems the caloric content should be carefully controlled and shouldn't exceed 600 Kcal, And the second meal shouldn't be given for at least 6 h after the first meal [76].

2.4.5. Effect of gender, posture, and age

It was found that female showed longer mean GRT than male, and the gastric emptying in the female is slower than male [77].

Upon studying the effect of posture on GRT it was found that when individuals rest on the left side, the floating dosage form will be toward the pyloric antrum; when the individuals rest on the right side, the floating of the dosage form will be in the opposite direction. Thus the gastric emptying of the floating dosage form is slower in individuals resting on the right side [75].

The GRT of the dosage forms also vary with age due to changes in the physiology of the GIT and hormonal response with increasing age. It has been demonstrated that GRT is prolonged in the elderly, especially in individuals 70 years or older [69].

2.4.6. Simultaneous administration of drugs

It is known that some drugs as anticholinergic agents (e.g. atropine propantheline) [78], opiates (e.g. codeine) [79, 80] and prokinetic agent (e.g. erythromycin, metoclopramide) [81] decrease the motility of the GIT so it can prolong the gastric residence time.

2.5. Approaches to gastroretentive drug delivery systems

Various techniques are currently used to prolong the gastric residence time such as bioadhesive systems, floating systems, high-density systems, swelling or expandable systems.

Based on the distribution of the drug content within the gastroretentive technology adopted, GRDDS can also be classified into a single dose (matrix system) and multiple-units

drug delivery systems. Although most gastroretentive drug delivery systems are single unite devices, they have the risk of losing their effect too rapidly due to their all-or-nothing emptying from the stomach [56]. Multiple units dosage forms can overcome this problem and increase the probability that the dosage form will remain in the stomach [82]. It also decreases the probability of dose dumping [83, 84], maximized therapeutic effect and produce better reproducibility of therapeutic effects [85]. (**Figure 2**) shows a simple diagram for single and multiple unite floating systems modified from applied biopharmaceutics and pharmacokinetics E-book [86]**.**

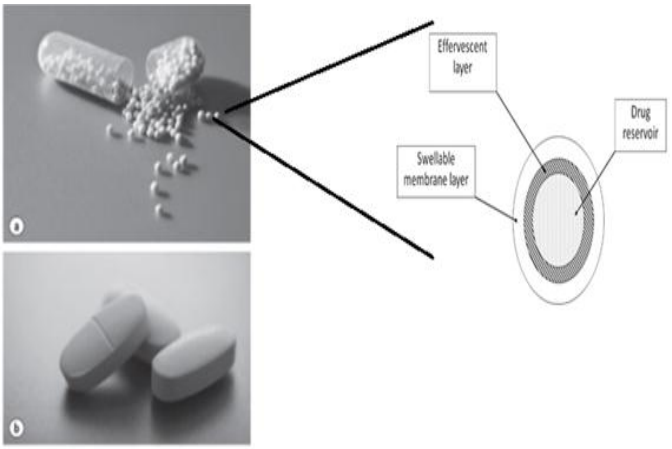

Figure 2: Schematic diagram shows (a) multiple-units floating dosage form with the detailed structure of a single unit showing different polymeric layer and (b) single dose unit floating system, modified from.

2.5.1. Bioadhesive or mucoadhesive DDS

Bioadhesive drug delivery systems are designed to be localized and bound to the mucous membrane of the gastric lumen, thus enhance drug absorption at its site of contact. Its mechanism in prolonging the GRT depend mainly on increasing the contact time of the dosage form with the biological membrane of the stomach [87, 88]. Several polymers were found to exhibit bioadhesive properties, these polymers are usually macromolecules, hydrophilic gelling substances with hydrogen bond forming groups and anionic. An example of these polymers are sodium carboxymethyl cellulose, sodium alginate, chitosan and carrageenan [87, 89, 90]. Adhesion of such polymers with biological membrane may be through hydration, H-bonding or receptor-mediated [91, 92]. Several drugs have been formulated as bioadhesive drug delivery systems such as; formulation of oral controlled release mucoadhesive compressed hydrophilic matrices of atenolol using carbopol 934P and sodium carboxymethylcellulose, Both of the polymers had a significant effect on the bioadhesive strength of the tablets [93].

Formulation of sustained-release mucoadhesive matrix tablets of simvastatin, using derivative of tamarind seed polysaccharide (Thiomer) to enhance the mucoadhesion, which allowed a good effect in the treatment of hypercholesterolemia and dyslipidemia as an adjunct to diet has an absorption window in the GI tract. The in vivo residence of thiomer placebo was more than 7 h in rabbit [94].

In addition; designing of mucoadhesive tablets of ibuprofen were prepared using chitosan and its half-acetylated derivative as mucoadhesive polymers. However, there is no in vivo study demonstrated the effectiveness of these formulations on the bioavailability of ibuprofen [95].

Mucoadhesive DDS can be also prepared using ion exchange resins. The ability of ion exchange resins to exchange ions when exposed to gastric fluids can be taken as a property in designing of floating systems. Designing of these systems depends on the loading of resin beads with bicarbonate and negatively charged drug that is bound to the resin, then these beads are coated with a semipermeable membrane of polymers such as (Eudragit RS) to avoid the rapid loss of carbon dioxide [96]. Upon exposing to acidic gastric fluid, exchange occurs between chloride ions in the gastric fluid and bicarbonate ions in the dosage form. This exchange leads to the release of carbon dioxide which is entrapped within the semipermeable membrane leading to the resin particle to float. Because the ion exchange resin must be cationic to bind with bicarbonate, the drug must be cationic. Cholestyramine is anion exchange resin with mucoadhesive character always used in designing of such formulations [76].

Riboflavin has been prepared as GRDDS using ion exchange resin; results showed that the bioavailability of riboflavin from the drug fiber was more than twice that measured after administration of the solution using urine recovery technique [97].

The major drawbacks that make this system not to be a feasible solution are bond formation is uncontrolled and may be prevented by the acidic environment of the stomach, in addition to the high rate of turnover of mucus which may also prevent mucoadhesion [98].

2.5.2. Swelling and expanding dosage forms

Another technique to prolong the GRT is by increasing the size of the dosage form after swallowing. Swelling should be above the diameter of the sphincter [99]. The diameter of the pyloric sphincter varies among individuals, it is reported 12.8 ± 7.0 mm, but because the pyloric sphincter consists of muscles so it can stretch and allow even large dosage form can pass through the sphincter during the migration myoelectric complex MMC. To avoid this defect the size of the dosage form should be greater than 20 mm [100].

Swelling/ floating gastroretentive drug delivery system of losartan has been prepared based on a combination of hydroxyethyl cellulose and sodium carboxymethyl cellulose, the results demonstrate that the mean bioavailability from formulations were approximately 164.4 ± 60.3 %, relative to the immediate-release product (Cozaar®) [101].

Freeze-drying riboflavin-containing collagen solution was prepared in the form of sponges. These sponge formulations can expand in the stomach after contact with the gastric fluid. The increases in GRT of sponges were dependent on in the swelling capacity and final size of the swollen sponges. The sponge-based tablets expanded within a few minutes after contact with simulated gastric juice and formed a drug delivery system with

a size of 8 mm, the formulations were able to sustain riboflavin release over 16 h [100].

Challenges facing designing of such dosage form are too rapid swelling or release of the drug during passing through the esophagus, this premature expansion may produce serious complications. On the other hand clearance of the dosage form from the stomach after a predetermined time interval should be taken into consideration because of too much increase in size increases the tendency to be logged in the pyloric sphincter causing serious complications [59].

2.5.3. Density controlled DDS

On contrary to gastro-retentive formulation based on gastric buoyancy (floating) which rely on using low density polymers (less than 1.00 g/cm^3), designing of such dosage forms with high density might prolong the GRT, as it settles down in the lower part of the antrum preventing it from passing through the pyloric sphincter [102]. Systems with a density of 1.3 g/ml or higher are expected to be retained in the lower part of the stomach [32]. But these dosage forms are technically difficult to be formulated and achieve the required density [103]. The in vivo data don't confirm the effectiveness of these formulations [104]. In conclusion, it has been reported that such devices did not significantly extend the gastric residence time [105].

2.5.4. Super porous hydrogels

They are highly porous systems that differ from normal swelling type systems in its degree of porosity. it has the ability to prolong the GRT [106]. It characterized by an average pore size more than 100 µm and swell to equilibrium size within a short time. The fast swelling property is based on water absorption through an open porous structure by capillary force [107]. It is intended to have sufficient mechanical strength to withstand the pressure of gastric contraction this is achieved by co-formulation of a hydrophilic particulate material, Ac-Di-Sol (croscarmellose sodium) [108, 109]. Rosiglitazone maleate, an antidiabetic drug has been prepared as super porous hydrogels as a GRDDS using Chitosan/poly (vinyl alcohol) as interpenetrating polymer, the drug release from super porous hydrogels was sustained for 6 h [110].

2.5.5. Raft-forming systems

This is a special type of floating formulations that will be discussed later in this introduction, one of the most notable examples of raft-forming systems include liquid Gaviscon®, this a widely marketed product for the treatment of hyperacidity and based on the use of potassium bicarbonate and sodium alginate. The mechanism involved in the raft-forming system includes the formation of continuous cohesive gel layer containing entrapped carbon dioxide bubble upon contact with the gastric fluids this layer is called raft [111, 112].

The raft floats on the surface of gastric content Because of its low-density compared to the gastric fluids due to the generation of carbon dioxide entrapped in the raft [113]. Various natural and synthetic polymers are used in the formulation of the raft forming drug delivery system. A natural polymer such as alginic acid, guar gum, gellan gum, chitosan and synthetic polymers such as poly (DL-lactic acid), poly (DL-lactide-co-glycolide), poly-caprolactone and HPMC are used for formulation development of the raft forming drug delivery systems [114].

Due to the advantage of this dosage form in its ability to float over the GIT fluid, these systems have received much attention in the delivery of antacids and delivery of drugs used in the treatment of gastro-esophageal reflux disease (GERD). Liquid Gaviscon is an example of a dosage form designed on the basis of raft formation and used in the treatment of GERD [103, 115].

2.5.6. Magnetic systems

This system based on the dosage form contains a small magnet and another magnet is placed on the abdomen over the position of the stomach using an extracorporeal magnet, this system can prolong the GRT [116, 117]. Peroral acyclovir depot tablets with internal magnets have been prepared to prolong the GRT of acyclovir. An external magnet was used to prolong the gastric residence times of the dosage forms and the duration of absorption of acyclovir. The magnetic depot tablets contained 200 mg acyclovir, the mean area under the plasma concentration-time-curve ($AUC_{0–24h}$), was 2802.7 ng/ml.h in the presence of the extracorporal magnet, compared with 1598.8 ng/ml.h Without the extracorporal magnet as a mean $AUC_{0–24h}$ [117].

2.5.7. Floating drug delivery systems (FDDS)

From all the gastroretentive drug delivery systems known the floating type of GRDDS is the prominent one [118, 119]. Such systems that float immediately upon contact with the gastric fluid are characterized by its low bulk density which must be below 1.00 g/cm^3 providing sufficient buoyancy to remain float over gastric fluid for a prolonged period of time while the drug release at the desired rate and site [120, 121]. This low density can be achieved by either entrapment of air as a hollow chamber [122] or by the incorporation of low-density materials as oils or a fatty substance [123, 124] or foam powder [56].

Based on the mechanism of floating, FDDS can be classified into two distinctive systems; Effervescent systems and non-effervescent systems as shown in (**Figure 3**).

2.5.7.1. Effervescent floating DDS

The effervescent systems are matrix type system including gas-generating systems and volatile liquid containing systems. These systems are classified according to the mechanism of floating into:

A. Gas generating systems

The mechanism of floating of these systems depends on the production of carbon dioxide due to the reaction between carbonate or bicarbonate incorporated in the formulation and the gastric acid or co-formulated acids as citric or tartaric acid, and

the gas retained in the gel hydrocolloid matrix due to the incorporated polymer as methyl cellulose, chitosan and Carbomer [66, 125].

Floating multi-layer tablet of anhydrous theophylline has been prepared using sodium bicarbonate as a gas generating agent; in vitro studies revealed that the optimized formulations were able to float over the gastric content for 8 h with sustained release properties using different types of Eudragit polymer, but unfortunately, there was no data about the bioavailability of theophylline [126].

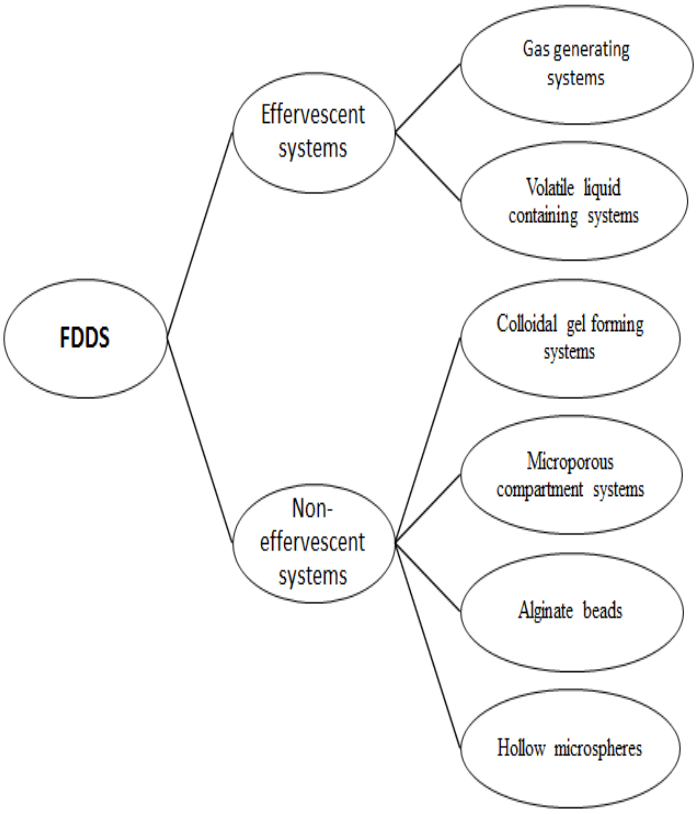

Figure 3: Types of floating dosage form based on the mechanism of buoyancy.

B. Volatile liquid systems

The floating bases on the incorporation of volatile liquid as Ether or cyclopentane, introduced inflatable chamber which volatilizes at body temperature allowing the system to increase in size and float over the gastric fluids [127, 128].

2.5.7.2. Non-effervescent floating systems

The floating of non-effervescent systems relies on two possible mechanisms, the first one; depends on the incorporation of high swelling and gelling capacity polymer as cellulose type hydrocolloid, polysaccharides, and matrix-forming polymers, like hydroxypropylmethylcellulose, polycarbonate, polyacrylate, sodium alginate, and polymethacrylate are used [69]. After oral administration of these dosage forms swells upon contact with the gastric fluids forming a gel layer with entrapped air around the system core, the entrapped air within the swelling matrix imparts buoyancy of the dosage form [66, 69].

The second mechanism may be related to floating of such systems depend on incorporating a gas-filled chamber of specific gravity into a microporous component that allows the system to float [129]. They are further classified into:

A. Hydrodynamically balanced gel systems

Formulation of hydrodynamically balanced systems depends on the incorporation high level (20-75% w/w) of gel-forming hydrocolloid together with the drug that allows the drug to remain buoyant over the gastric fluids. These systems may contain one or more gel-forming cellulose type hydrocolloid as; hydroxypropyl methyl cellulose, ethyl cellulose, and alginic acid. It also contains matrix forming polymers as Polycarbophil, polyacrylate [130]. Such systems upon contact with gastric fluids the hydrocolloid hydrate and form a colloid gel barrier around its surface [131, 132].

Hydrodynamically balanced system of metformin has been prepared like a single unit floating capsule using various polymers as HPMC K4M and ethyl cellulose, the prepared formulations remained buoyant of 6 h using gamma scintigraphic studies; It was also observed that the drug release from the optimized HBS formulations could be sustained for a prolonged period, with C_{max} and T_{max} being 76.97% in 7 h, compared with C_{max} and T_{max} being 97.21% in 3 h in immediate release capsules [133].

B. Microporous compartment systems

In these systems, the drug is encapsulated into microporous compartment having pores along its top and bottom surface, this chamber containing entrapped air which causes the system to float. Gastric fluid can pass through the pores and dissolve the drug which can be released through the pores of the floating chamber [28, 134]. Controlled porosity osmotic pump tablets for salvianolic acid (SA) have been prepared using an artificial network method, in vitro release studies showed sustain drug release for 12 h [135].

C. Alginate beads

In this approach, a solution of sodium alginate is dropped into an aqueous solution of calcium chloride and caused the precipitation of calcium alginate. These beads are then separated and air dried or freeze-dried. This results in a porous system which can float over the gastric content [136]. These beads can prolong the GRT for more than 5.5 h [137]. Combination of famotidine and quercetin for the treatment of peptic ulcer have been prepared in the form of freeze dried calcium alginate beads with floating properties for more than 8 h [53].

D. Microballoons/ hollow microspheres

The technique used in the preparation of these systems includes solvent evaporation or solvent diffusion methods which create hollow inner core [138]. Polymers such as polycarbonate, chitosan, Eudragit S and polyvinyl acetate are commonly used in the preparation of such systems [139]. The amount of drug

released can be controlled by optimizing the polymer quantity and the polymer plasticizer ratio. Riboflavin has been prepared as hollow microspheres to prolong the GRT and improve its bioavailability [54]. Hollow microspheres of theophylline have been prepared by using a solvent evaporation method using cellulose acetate butyrate and Eudragit RL 100 as polymers, the prepared formulations could remain float for more than 24 h [140].

2.6. Polymers commonly used to formulate GRDDS

Various polymers have been used in the formulation of GRDDS, these polymers are commonly used for the preparation of gastroretentive DDS. This is because these polymers show many favorable properties such as mucoadhesion, inherent sustained release polymer properties by increasing the viscosity and tortuosity in the diffusion layer, swelling and hydrophilic. The polymeric particles absorb water causing the system to swell, which lead to retention of the dosage form in the stomach allowing the drug to release from the system [141]. Examples of commonly used biocompatible polymers are:

2.6.1. Sodium alginate

Alginates are biodegradable hydrophilic polymers consisting of β-D-mannuronic acid and α-L-glucuronic acid residues joined by 1, 4-glycosidic linkages [142]. These polysaccharides found in brown seaweed and marine algae such as Laminaria Hyperborea, Ascophyllum nodosum, and Macrocystis pyrifera [143]. Several alginate salts are commercially available as sodium alginate, calcium alginate, ammonium alginate, and potassium alginate. Specially; sodium alginate has been commonly used in the formulation of GRDDS. Alginates can be chosen in such formulations as it exhibits good characters as biocompatibility, biodegradable, nontoxic in addition to it experience mucoadhesive properties [144]. These polymers form a viscous gel layer upon contact with gastric fluids to form low-density dosage form. Alginate can form cross-linking with polyvalent cations which result in the formation of stable gel-like matrices [145]. Sodium alginate has been used as a polymer in the preparation of gastroretentive drug delivery tablet of domperidone [146]

2.6.2. Carbopol

It is pH dependent polymer used in the preparation of GRDDS due to its ability to swell upon contact with gastric fluid forming low-density dosage form which can prolong the gastric residence time [147]. HPMC is commonly used with carbopol in order to impart its viscosity [148].

Numerous enhancements have been made to the Carbopol polymer family to address formulation requirements and improve product handling during processing. For example, the solvent system used to synthesize the polymers has evolved. Specifically, the traditional polymers are synthesized in benzene and the toxicologically preferred polymers are synthesized in either ethyl acetate or a co-solvent ethyl acetate/cyclohexane mixture; these variations in formulation parameters produce polymers with different characters as viscosity, degree of crosslinking and molecular weight. Carbopol 934 NF, 940 NF, 971 NF, and 5984 EP are examples of these polymers with different properties. Carpobol 934 has been used as a polymer in the formulation of mucoadhesive tablets of atenolol [93].

2.6.3. Hydroxypropylmethylcellulose (HPMC)

It is a water-soluble polymer, available in a wide range of molecular weights and viscosity grades. In addition, it has a unique swelling/erosion characteristics which reflect its ability to control drug release [149, 150]. HPMC K4M has been used as a polymer in the preparation of gastroretentive floating tablet of ibuprofen, and the tablet remains float for more than 13 h [151].

2.6.4. Polymethacrylate (Eudragits®)

Eudragits are commonly used in controlled release DDS as release retardant [152]. They are classified into polycations as Eudragit E, Eudragit RS, and Eudragit RL; while Eudragit L, and Eudragit S are polyanions [153]. A novel raft forming systems of curcumin have been prepared using curcumin-Eudragit® EPO solid dispersion to prolong the GRT of curcumin and provide a controlled release therapy to treat gastric ulcer [154].

2.7. Drug classes with NAW biopharmaceutical behavior that can benefit from Gastroretentive DFs

2.7.1. Skeletal muscle relaxants

Baclofen is primarily absorbed from the upper part of the GIT especially at the duodenum. It has been reported that preparation of baclofen as modified release super porous hydrogel (SPH) systems using different polymers as gellan gum, guar gum, polyvinyl alcohol, and gelatin can improve the bioavailability of baclofen relative to commercially available lioresal®. The area under Curve obtained with the floating SPH was approximately 1.8 times those of conventional baclofen tablets [155].

Chlorzoxazone is a benzoxazinone derivative with a mild sedative and centrally acting muscle relaxant activity. Chlorzoxazone belongs to the biopharmaceutics classification (BCS) class II, i.e. low solubility and high permeability, Chlorzoxazone is a good candidate to be formulated as a gastroretentive dosage forms as it belongs to BCS II classification which characterized by low solubility, therefore The increase in gastric residence time helps increase its solubility and hence its absorption. It has been reported that the formulation of chlorzoxazone as floating tablets using HPMC K100 may enhance the bioavailability as well as decreasing side effects. Results showed that the prepared formulation can be float over the gastric content for more than 12 h with 98.23 % released over this period of time. Unfortunately, there is no in vivo data support the effectiveness of results obtained from this study [156].

2.7.2. Antiparkinsonism

Due to its narrow absorption window, levodopa has to be administered continuously to the upper parts of the GIT in order to maintain sustained therapeutic levels. Formulation of levodopa in the form of modified release gastroretentive dosage forms may help in enhancing bioavailability and decreasing the frequency of administration thus improving patient compliance.
Levodopa has been formulated as gastric floating minitablets by melt granulation and subsequent compression using different polymers as precirol®, compritol® and methocel®; sodium bicarbonate or calcium carbonate were used as gas generating agents.
In-vitro results showed that levodopa minitablets can float for more than 13 h with floating lag time equal to 1 min; formulations have the ability to sustain drug release for more than 8 h. there is no in vivo data support the results obtained from in vitro studies [83].

2.7.3. Anti-infective

Ciprofloxacin is a fluoroquinolone antibiotic which is primarily dissolved and absorbed from the upper part of the GIT. Ciprofloxacin floating tablets have been prepared by direct compression using carbomer 971, hydroxypropyl methylcellulose, xanthan gum, and crospovidone. The prepared formulations were able to float for more than 24 h with floating lag time less than 20 sec using sodium bicarbonate as a gas generating agent. Prolong drug release for 24 h allow the drug to be administered once daily thus improve patient compliance. In vivo studies showed that C_{max} and T_{max} of optimized gastroretentive formulation were found to be 0.945 ± 0.29 µg/ml and 6.0 ± 1.41 h, respectively. C_{max} and T_{max} for the conventional product were estimated to be 2.1 ± 0.46 µg/ml and 1.42 ± 0.59 h, respectively. The $AUC_{0-\infty}$ for optimized gastroretentive formulation and conventional product were 8.12 ± 1.8 and 9.45 ± 2 µg/ml/h, respectively [157].
Ofloxacin is an antibacterial which is widely prescribed for the treatment of duodenal ulcers. Ofloxacin exhibit pH-dependent solubility which is more soluble in acidic pH and slightly soluble in alkaline or neutral pH. The bioavailability of ofloxacin decreased upon increasing pH; therefore this drug is better to be formulated as modified release gastroretentive dosage forms.
Gastric floating beads of ofloxacin have been prepared using low methoxy pectin with gellan gum, karaya gum, and xanthan gum as release retardant polymer. The prepared formulations can float over the gastric content for 24h with zero lag time. Ofloxacin floating beads showed prolonged drug release for more than 8 h. Unfortunately, no in-vivo data confirm the results obtained from in vitro studies [158].

2.8. Examples of different GRDDS and market products prepared using gastroretentive drug delivery techniques

Various studies have been done to develop gastroretentive drug delivery systems, (**Table 3**) demonstrates some of drugs prepared with this technique. While (**Table 4**) demonstrates market products prepared as gastroretentive drug delivery systems.

Table 3: Examples of drugs formulated as a gastroretentive drug delivery systems

Drug	Gastroretentive dosage form	Ref.
Ranitidine	Tablet	**[58]**
Famotidine	Calcium pectinate gel beads	**[38]**
Ciprofloxacin HCl	HDB Tablet	**[159]**
Ofloxacin	Tablet	**[160]**
Propranolol HCl	Tablet	**[161]**
Norfloxacin	Tablet	**[162]**
Furosemide	Minitablets	**[163]**
Metoclopramide HCl	Tablet	**[164]**
Antidiabetic drugs (Metformin,glipizide)	Tablet	**[165]**
Pregabalin	Tablet	**[166]**
Aluminum hydroxide and magnesium carbonate	Floating liquid alginate preparations	**[167]**
Fluconazole	Mucoadhesive nanoparticle	**[168]**

Table 4: Examples of a marketed product of gastroretentive drug delivery systems

Product Name	Active Ingredient
Liquid Gaviscon®	Aluminum hydroxide and magnesium carbonate
Cifran OD®	Ciprofloxacin
Cytotec®	Misoprostol
Topalkan®	Alginic acid plus aluminum an Mg salts
Almagate Flot Coat®	Antacids
Madopar HBS®	Levodopa plus Benserazide
Valrelease®	Diazepam
Cefaclor LP®	Cefaclor
Metformin GR®	Metformin hydrochloride
Baclofen GRS®	Baclofen
Zanocin OD®	Ofloxacin

2.9. Limitation of gastroretentive drug delivery systems

Despite the variety of drugs that can be formulated as GRDDS and enhancement of its activity and bioavailability there are also drugs which are not suitable to be formulated as GRDDS. From the theoretical point of view, these instances are few and depend on the characteristics of the drug substances. Examples of drugs that can be considered a poor candidate for GRDDS include:

- Aspirin and other NSAIDs drugs are known to cause gastric lesion thus prolonging the GRT with a slow release of the drug may increase the susceptibility of gastric lesions [34].
- Drugs that are unstable at the acidic pH of the stomach [169].
- Drugs exhibit low solubility at low pH may experience dissolution problems and may not completely release the drug.
- Drugs which absorbed equally along the GIT such as isosorbide dinitrate, nifedipine (these drugs undergo first-pass hepatic metabolism); so designing of such drug in the form of GRDDS is likely to show extensive loss of the drug due to hepatic metabolism [20, 170].

Conclusive remarks

This review systematically summarizes a growing body of research to indicate that gastroretentive drug delivery systems can provide a potential pathway for delivering NAW drugs in modified/sustained release drug delivery systems. These systems can be more patient-friendly than conventional immediate-release dosage forms. Minimizing the frequency of drug administration for chronic diseases like Parkinsonism; minimizing side effects due to rapid plasma peaking and consequently enhancing patient compliance are among benefits that can be claimed. Help to improve the bioavailability of drugs which characterized by narrow absorption window. Further, recent reports elucidate the effectiveness of these formulations in improving the bioavailability and the pharmacological activity of such drugs.

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