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Review Article

Current progress of oral site-specific dosage forms: Emphasis on gastroretentive drug delivery systems

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ABSTRACT

The oral route of administration is considered the easiest, most convenient, and most widely used drug delivery route. One of the hardest challenges facing oral drug delivery systems (DDS) is the erratic absorption of drugs through the gastrointestinal tract (GIT). The conventional oral dosage forms usually suffer from low bioavailability, especially in the case of drugs with narrow absorption windows (NAW). The oral controlled-release dosage forms could overcome the previous limitation by providing predicted and calculated drug release, resulting in an improvement of the efficacy of drugs. One of the most promising types of oral controlled-release dosage forms for this purpose is the gastro retentive drug delivery system (GRDDS), which was found to improve the gastric retention of the dosage form and maximize the absorption and bioavailability of the drugs with NAW. In this review, we summarize the different GRDDS techniques used for improving drug absorption, their methods of preparation, and their mechanisms of action.

Keywords: *Oral route; Controlled release; Narrow absorption window; Gastroretentive delivery systems; Tablets.*

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1. INTRODUCTION

The oral route of administration is considered the most convenient route among other routes. It offers many advantages including the ability to offer immediate or controlled release. In addition, the gastrointestinal tract (GIT) offers a large surface area for drug absorption (>300 m^2) owing to the presence of enterocytes (the major intestinal cells that facilitate the absorption of elements by special transporters). One of the challenges facing oral drug delivery systems (DDS) is the ability to control the release and maximize the absorption of drugs at specific sites along the GIT. One of the most significant drawbacks of oral DDS is the erratic absorption of some drugs through the GIT segments, which necessitates the formulation of DDS that target specific absorption sites. Furthermore, the presence of other factors affecting drug stability and solubility throughout the GIT such as gastric pH and the enzymatic action of the gastric

enzymes affect drug absorption **[1, 2, 3]**. Moreover, many drugs are only absorbed in the primary region of the small intestine, which is classified as narrow absorption window (NAW) drugs. The absorption in this site is controlled by several biochemical and physiological factors, and the formulation of these drugs in conventional immediate-release dosage forms results in incomplete absorption of drugs, and hence low bioavailability **[4, 5, 6]**. Many researchers have attempted the formulation of oral controlled dosage forms to localize the drug at the site of absorption, control the variability of drug release, and maximize its absorption. One of the most promising approaches to oral controlled DDS is the gastro retentive drug delivery system (GRDDS). GRDDS results in improvement of the gastric retention of the dosage form, hence maximization of drug absorption of some drugs, with decreased frequency of administration and increased patient compliance **[7-10]**.

2. Gastric Emptying

The gastric emptying rate is the time spent by the dosage form till it passes through the stomach. It is variable for different oral pharmaceuticals and was proven to depend on the dosage form itself and the state of the stomach (fed or fasted state). The reported gastric emptying time ranges from 2 min to 2 h. The GIT motility involves two modes; the first one is called inter-digestive motility which takes place during the fasting state to evacuate the upper GIT, and the second one is the digestive motility which occurs during the fed state. The GIT motility during the fasting state is controlled by a pattern called migrating motor complex (MMC), which is a pattern of movement and silence controlled by the motilin hormone and subdivided into four phases:

(A) Phase I (basal phase) which ranges from 40 to 60 min with rare contractions.

(B) Phase II (pre-burst phase) which ranges from 40 to 60 min with intermittent action potential and contractions. As the phase progresses, the intensity and frequency also increase gradually.

(C) Phase III (burst phase) which ranges from 4 to 6 min. It includes intense and regular contractions for a short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine.

(D) Phase IV which ranges from 0 to 5 min and occurs between phases III and I of 2 consecutive cycles **[10, 11].**

The presence of food stops the MMC cycle and starts the digestive phase activating the postprandial motility every 5-10 min. It was reported that oral dosage forms such as disintegrating tablets, pellets, and liquids evacuate rapidly during the fed state. On the other hand, the sustained release or controlled release dosage forms have a slower stomach emptying rate, and they tend to stay for longer periods **[4]**.

To improve the gastric retention of drugs, the prepared dosage form must have the ability to resist the gastric emptying effect of the stomach and to stay despite the force of peristatic movement, until complete and effective delivery of the drug, followed by gradual removal from the GIT. **Table 1** illustrates the transit times of

various conventional dosage forms across the GIT as reported elsewhere **[12, 13]**.

Oral-controlled drug delivery systems (OCDDS) are usually used to achieve a uniform and accurate supply of the drug by continuous release at a certain period. It is considered beneficial and effective in the case of drugs that require repetitive and frequent dosing, by serving to decrease the dosing frequency and improve the patient's compliance. Also, OCDDS result in an improvement of the drug's bioavailability, reduction of its adverse side effects, and significant reduction of the overall health care cost **[14, 15, 16]**. One of the most promising OCDDS designed to delay drug release is GRDDS, which increases the gastric residence of the dosage form and improves the encapsulated drug bioavailability **[17]**.

Table 1. Transit times of various dosage forms across the GIT [12, 13]

	Transit time (h)		
Dosage form	**Stomach**	**Small intestine**	**Total**
Tablets	2.7 ± 1.5	3.1 ± 0.4	5.8
Pellets	1.2 ± 1.3	3.4 ± 1.0	4.6
Capsules	0.8 ± 1.2	3.2 ± 0.8	4.0
Solution	0.3 ± 0.07	4.1 ± 0.5	4.4

3. Gastro-retentive Drug Delivery System (GRDDS)

A GRDDS is a dosage form designed to reside for a longer time inside the stomach, which is beneficial for active drugs having a NAW. A GRDDS is not only designed to control the time of drug release but also to accurately define the targeted area of the drug release in the GIT. GRDDS helps to increase the gastric residence time (GRT), thus it helps to improve drug bioavailability through several factors **[4, 17, 18]**. A GRDDS could withstand the in *vivo* peristaltic movement, and remain intact despite the GIT disturbance. Accordingly, the GI transit time is expected to prolong for an average of 5.8 h to 25 h **[4, 19]**.

3.1. Factors affecting GRT

There are several factors controlling the GRT of dosage forms such as dosage form characteristics (size, shape, and density), presence or absence of food, concomitantly administrated drugs, and the patient's profile (gender, other diseases, age, etc.) **[9, 20, 21]**.

3.1.1. Dosage form characteristics

Dosage forms with a density less than the density of gastric fluid float on the gastric fluid surface, hence their gastric residency increases. The reported density of the gastric fluid is 1.004 g/mL so any dosage form with a density less than 1 g/mL is considered a GRDDS through its floating behavior **[10]**.

In addition, the GRT is directly proportional to the size of the dosage form. As the size increases, the GRT increases exponentially as the relatively large size prevents the dosage form from passing through the pyloric sphincter. Dosage forms with a diameter of more than 7.5 mm have longer residence time **[15]**.

The non-disintegrating/undigested gastro-retentive dosage form is unable to pass through the pyloric sphincter due to the retropulsion reflex that activates the delivery of the undigested materials from the pylorus to the body's stomach **[22]**, while small particles like food and other dosage forms which have diameters smaller than 5 mm, they can mix into the chyme and are emptied from the stomach by passing through the pyloric sphincter **[7, 13]**.

Among the different shapes of oral dosage forms designed, it was reported that the ring or tetrahedron shape is the shape that achieves longer residence time **[6]**.

3.1.2. Food intake and nature of food

Food intake with an oral dosage form generally increases gastric retention, and hence improves gastric absorption. Also, the nature and type of food affect gastric retention. For example, a diet rich in fats and protein increases the GRT of the oral dosage form **[10]**.

3.1.3. Biological factors (gender and age)

It was reported that there is a significant decrease in GRT in males than in females. Moreover, with aging, some physiological and hormonal changes affect the GRT, in which a prolongation in GRT and slowing in the gastric emptying rate occurs in old age **[15]**.

3.2. Formulation techniques of gastroretentive drug delivery systems

Several techniques have been reported for formulating GRDDS, including low-density or floating systems, high-density systems, expandable systems, super porous hydrogel systems, bio-adhesive/mucoadhesive systems, magnetic systems, and ion-exchange resin systems **[9, 23, 24, 25]**.

3.2.1. Low-density/floating systems

The floating technique is one of the most promising techniques for the formulation of a GRDDS, which is widely used to prolong the GRT. It relies on the immediate floating of the dosage form owing to its low bulk density, which allows the dosage form to float for a long period over the gastric fluid until complete drug release occurs with a specific rate, as shown in **Fig. 1.** The techniques used to decrease the bulk density of a dosage form depend on either creation of a hollow chamber through air entrapment or incorporation of low-density substance like oil or fat or foam powder **[10, 17]**. According to the technique applied for the formulation, floating drug delivery systems (FDDS) are classified into two systems; effervescent systems and non-effervescent systems**,** as detailed below and displayed in **Table 2.**

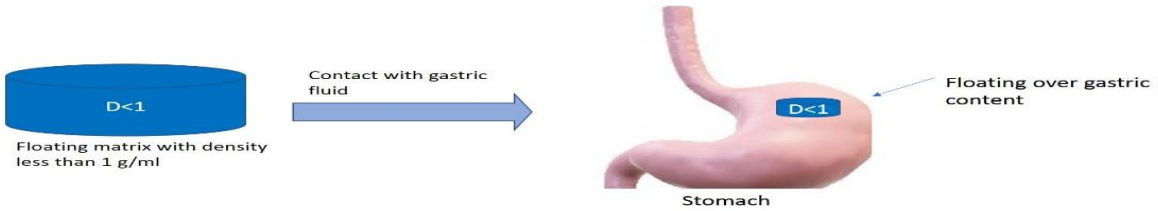

Fig. 1. Illustrative photo of a floating system

Table 2. List of drugs fabricated in various floating GRDDS

GRDDS	Drugs	Polymers	Outcomes	Ref.
Effervescent FDDS	Metronidazole	HPMC K4, XG and NaHCO3	• The prepared matrix tablets floated in a pH 1.2 buffer solution and retarded the drug release for up to 12 h.	**[26]**
	Loxoprofen sodium	XG, guar gum, HPMCK4M, with NaHCO3 and citric acid.	• The results revealed that XG had the highest swelling ability. • The optimized formulation retarded the drug release and maintained floated up to 12h.	**[27]**
Non- effervescent FDDS Hydrodynamically balanced gel systems (HBS)	Metronidazole	Hydroxypropyl cellulose (HPC), HPMC, hydroxyl methylcellulose (HMC), and Avicel	• The results showed that HPMC was the polymer that gave the best buoyance behavior of tablets, while HPC alone did not achieve buoyancy. • The tablet buoyancy depended on formulating an HBS with a density less than gastric content by trapping the air within the swollen polymer and the release controlled by the diffusion of the drug from the boundary gel layer formed by hydration of the hydrocolloid polymer. • The in *vivo* study revealed significantly improved bioavailability after a single oral dose of selected formulations compared with conventional tablets of the same dose strength.	**[33]**
Floating beads systems	Ivacaftor	SA, calcium chloride Polyethylene glycol, urea, and mannitol Chitosan, HPMC k100M	• The formulations were prepared by applying the ionotropic gelation technique. • The optimized formulation was successfully prepared to retain the drug in the stomach, it showed entrapment efficiency of 96.23% and in-vitro drug release of 95.62% at 12 h.	**[37]**
Floating micro balloons/ hollow microspheres	Lopinavir	Eudragit S-100	• The floating hollow micro balloons are prepared by the non-aqueous solvent evaporation method. • The selected formulation showed an entrapment efficiency of 91.82% and prolonged the drug release by about 86.35% at 12 h.	**[40]**
	Rilpivirine HCl	Ethyl cellulose and carbopol.	• The study formulated floating microspheres by emulsion solvent diffusion technique. • The results showed that the optimized formulation had good encapsulation efficacy with favorable buoyancy and prolonged drug release accounting for 98% at 12 h.	**[42]**

Floating raft-Forming Systems	Amoxicillin	Guar gum, glyceryl monostearate (GMS), calcium carbonate.	• The formulation was prepared by dispersion and homogenization techniques. • The results showed that the increase in the quantity of both guar gum and GMS lead to an increase in the gelation duration and the release up to 24 h with a minimum floating lag time. • *In vivo* pharmacokinetic studies showed that the prepared formulations exhibited greater AUCo-t, Cmax, t_{max}, and $t_{1/2}$ when compared to the marketed formulation.	**[45]**
	Bupropion	Pectin and alginate as in-situ gel-forming polymer Sodium Citrate, Calcium Carbonate Compritol 888 ATO & Precirol	• The liberation of CO_2 upon contact of the formulation with acidic pH leads to the formation of an ionic intermolecular crosslinking between polymers and divalent ions resulting in the gels network causing the system to float and this caused a decrease in the density system. • The selected formulation showed excellent floating behavior with prolonged drug release reached 54.17% at 8 h and could control the release for more than 12 h.	**[46]**

3.2.1.1. Effervescent floating systems

The construction of an effervescent floating system comprises two different techniques: either the incorporation of a gas-generating agent or the inclusion of volatile liquids. The most popular ingredients used in gas-generating systems are sodium bicarbonate and calcium carbonate, usually used in combination with hydrophilic polymers. This system depends on the entrapment of carbon dioxide gas generated after a chemical reaction with gastric HCl in the hydrocolloid matrix, accompanied by effervescence, which aids in the floating of the dosage form **[26, 27, 28]**. As for effervescent floating systems depending on volatile liquids such as ether and cyclopentane, the volatile liquid is designed to be entrapped inside an inflatable chamber, and the gas produced from their volatilization at body temperature helps the dosage forms to float. Therefore, it is considered an inflatable system and an intra-gastric osmotically controlled drug delivery system **[24, 25]**. Many studies have developed different effervescent floating systems. Ahmed *et al.* formulated floating tablets of itopride hydrochloride using different hydrocolloid polymers such as hydroxypropyl methylcellulose (HPMC), ethyl cellulose, and/or methacrylic acid polymers such as Eudragit, carbopol 934P, with sodium bicarbonate and anhydrous citric acid as an effervescent mixture. The study revealed that the sodium bicarbonate was essential to achieve optimum *in vitro* buoyancy (floating lag time of 3–6 min and floating duration of 24 h.). The *in*

vitro results showed that a formulation composed of 28.5% Eudragit, 3% sodium bicarbonate, and 7% citric acid achieved sustained drug release up to 96.51% after 24 h, and the pharmacokinetic results indicated that the area under the curve of the prepared sustained-release floating tablets achieved 93.69 μg h/mL compared to 49.89 μg h/mL for the reference formulation (Ganaton®); indicating that the formulation successfully increased the bioavailability of itopride by 1.89-folds. Additionally, the plasma concentration of the drug after 24 h was equal to that of the commercial tablet after 8 h **[29]**. Additionally, Rashmitha *et al.* formulated fenoverine floating tablets using sodium bicarbonate and citric acid as effervescent and gas-generating agents, with different hydrophilic polymers such as xanthan gum (XG) and sodium alginate (SA). The *in vitro* buoyancy study revealed that all the prepared formulations remained buoyant for 6-12 h due to the gas generated from sodium bicarbonate and citric acid upon contact with an acidic medium. The gas generated was trapped and protected within the gel formed upon hydration of the hydrophilic polymer, thereby lowering the density of the tablet below 1 g/cm3; where the tablet became buoyant to float and exhibited desired sustained release time for 12 h **[16]**.

3.2.1.2. Non-effervescent floating systems

The mechanism of a non-effervescent floating system depends on air entrapped inside the dosage form to decrease the bulk density. Air is usually entrapped inside the dosage form through two mechanisms. The first one is by using a polymer with high swelling and gelling properties, such as colloidal cellulose type (HPMC, SA) and matrix-forming polymers like polyacrylate, and polymethacrylate. These polymers tend to swell once they meet the gastric fluid; forming a gel with air entrapped inside the core of the dosage form. The air entrapped through swelling improves the floating properties **[10, 30]**. The second floating mechanism of air entrapment is through the incorporation of the microporous component containing a chamber filled with gas with a specific gravity to induce the floating behavior of the dosage form known as drug-loaded micro balloons/hollow microspheres **[17]**. Types of the non-effervescent floating system include hydrodynamically balanced gel systems, alginate beads, and micro balloons/hollow microspheres.

The hydrodynamically balanced gel system depends on using a gel-forming hydrocolloid at a high level (20-75% w/w) mixed with the drug, to improve the floating behavior. The most frequently used gel-forming colloids are cellulose-type hydrocolloids as HPMC, and ethyl cellulose as matrix-forming polymers **[11, 31-33]**. Upon contact with the gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air entrapped by the swollen polymer provides a density of less than one and induces floating**.** Kim *et al.* prepared non-effervescent gastroretentive tablets containing pregabalin for once-daily administration using HPMC and cross-povidone. They reported that the formulation showed good buoyancy after contact with water due to the hydrophilic property of the used polymers, which exhibited rapid swelling capacity and decreased buoyance lag time, which

consequently minimized the risk of premature gastric emptying. The release was prolonged over 24 h as the drug diffusion from the core to dissolution media was inhibited by a viscously hydrated layer. The selected formulation-maintained buoyancy for over 24 h and expanded above the fed-state pyloric sphincter diameter (12.8 mm). In *vivo* results in beagle dogs indicated that the optimized formulations were suitable as once-daily dosage forms [**34]**.

For the second system, the formulation of alginate beads depends on the precipitation, separation, and drying of calcium alginate through a chemical reaction between a solution of SA and calcium chloride. Calcium alginate beads are porous, which gives them the ability to float over the gastric fluid and increase the GRT for more than 5.5 h **[6, 35-37]**. Bangun *et al.* developed alginate beads containing turmeric extract-solid dispersion or turmeric extract. The turmeric extract solid dispersion was prepared by the solvent method using polyvinylpyrrolidone as a carrier. The turmeric extract solid dispersion was encapsulated with alginate gel by the gelation method. The in *vivo* study in rats revealed that the alginate beads containing solid dispersion were more effective in the treatment of induced ulcer and gastric retention up to 12 h after oral administration. The beads were attached to the gastric mucosa due to the mucoadhesive properties of alginate, which was attributed to the richness of the mucosa lining of the stomach with mucin. This mucin contains an oligosaccharide chain with terminal sialic acid, and the alginate polymer contains a carboxylic group and hydroxyl groups, which serve as powerful “ligands” for mucin through the formation of hydrogen bonds. This results in excellent gastroretentive properties for alginate beads **[38]**.

Micro balloons-based system is a non-effervescent GRDDS. Micro balloons (hollow microspheres) are spherical empty particles without a core. Different methods have been used in the preparation of these micro balloons including evaporation, diffusion, polymerization, and spray drying techniques**.** This system is considered a multiple buoyant unit dosage forms with good floating properties because of the central hollow space inside the microsphere. The most commonly used polymers in the preparation of this system are chitosan, polycarbonate, polyvinyl acetate, and Eudragit. By controlling the type of polymer, plasticizer, and solvents employed in the preparation, drug release can be controlled **[39-43]**. Gupta *et al.* developed pantoprazole sodium non-effervescent floating micro balloons, which were spherical in shape with an internal cavity and porous walls. The formulations were prepared using ethanol, dichloromethane, and a suitable plasticizer; DBT (Dibutylphthlate), magnesium stearate, and different grades of Eudragit by adopting the emulsion solvent diffusion method. Evaluation of the prepared loaded micro balloons revealed that the optimized formulation prolonged the drug release by 99% over 12 h. Also, the *in vivo* study proved the efficacy of the pantoprazole-loaded microballoons in stomach ulcer healing **[44]**.

A raft-forming system consists of an effervescent liquid with *in situ* gel properties and buoyancy capability. It combines effervescent and gel-forming techniques for the formation of

floating GRDDS. The operation of this system depends on the formation of a viscous cohesive gel layer upon the contact of the dosage form with gastric content, resulting from polymer swelling. This layer is called a raft, and it can remain intact and buoyant over the gastric content for a long period. This system is usually formulated by using a gel-forming agent and gas-generating materials such as alkaline bicarbonates or carbonates, which make the system buoyant due to their low bulk density. The aforementioned system has been extensively used in the treatment of gastroesophageal reflux disease **[21, 45-47]**. El Nabarawi *et al.* developed a floating raft system of mebeverine HCl consisting of alginate, calcium carbonate as an effervescent agent, a hydrophilic for swellability (HPMC K100M), in combination with lipid or wax polymers eg. Compritol 888, and Precirol as glyceride base for the preparation of controlled-release dosage forms. Results of this study showed that formulations with a higher concentration of alginate formed a rigid gel with a short gelation time, and the incorporation of HPMC in the system resulted in adequate gel strength. Furthermore, increasing lipid polymer content enhanced the floating ability of the dosage form due to the low density of the used lipids in addition to the three-dimensional network of the cubic phase of the used lipids, which further reduced the permeability of the formed gel, leading to a reduction in the diffusion of the entrapped CO_2, thus resulting in excellent buoyancy. The pharmacokinetic study performed for the selected formulation and marketed Duspatalin retard® (200 mg) as reference in beagle dogs revealed that the mean peak drug concentration of the selected formulation was higher than that of the market product, indicating higher bioavailability accounting for 116.01% compared to marketed product. Conclusively, the study demonstrated that the raft systems would be promising as GRDDS for prolonging drug action **[48]**.

3.2.2. High-Density systems

A high-density system relies on designing a dosage form with higher density than gastric fluid (A density close to 2.5 g cm^{-3} is considered optimal for significant prolongation of GRT). Barium sulfate, iron powder, zinc oxide, and titanium dioxide are the most frequently used excipients to prepare this system, but this system is technically difficult to manufacture, and its clinical significance is still questionable **[24, 49]**. It was reported that designing high-density pellets could resist gastric movement and prolong GRT up to 25 h. Few clinical studies attempted this system with no significant improvement in effectiveness in humans, so further studies are required to investigate the clinical significance of such dosage forms **[50, 51]**. Nur *et al.* formulated gastro retentive high-density tablets of theophylline using SA and polyvinylpyrrolidone by the wet granulation method. Results revealed that all prepared formulations had a density that exceeded that of gastric fluid, which is ~1.004 g/mL, and the used hydrophilic polymers gave a fairly good swelling property which resulted in a prompt formation of an inner layer. *In vitro*, drug release results showed that the cumulative release percentage for all formulations was ≈ 90% at 12 h. It was assumed that the slow-release action of the high-density system resulted from the

entrapment of the drug in the folds of the antrum, thus resisting peristaltic waves from the stomach wall, with residence in the lower part of the stomach for a long period **[52]**.

3.2.3. Swelling/expanding and unfolding dosage forms

An expandable dosage form expands upon contact with GIF and swells to a size larger than the diameter of the pyloric sphincter. The reported diameter of the pyloric sphincter is 12.8 ± 7.0 mm, hence it is recommended that the final diameter of the designed dosage form after swelling is larger than this diameter as shown in **Fig. 2.** This system is also termed "plug type system" because it can block the pyloric sphincter. This design includes three stages; the first one is the small configuration of the dosage form to be easily swallowed by the patient, the second one is the expansion inside the stomach to stop the dosage form from passing through the pyloric sphincter, and finally, the return of the dosage form to the normal small configuration to be easily evacuated from stomach after drug release. The expansion inside the stomach occurs by one of two mechanisms: either by unfolding or swelling **[22]**.

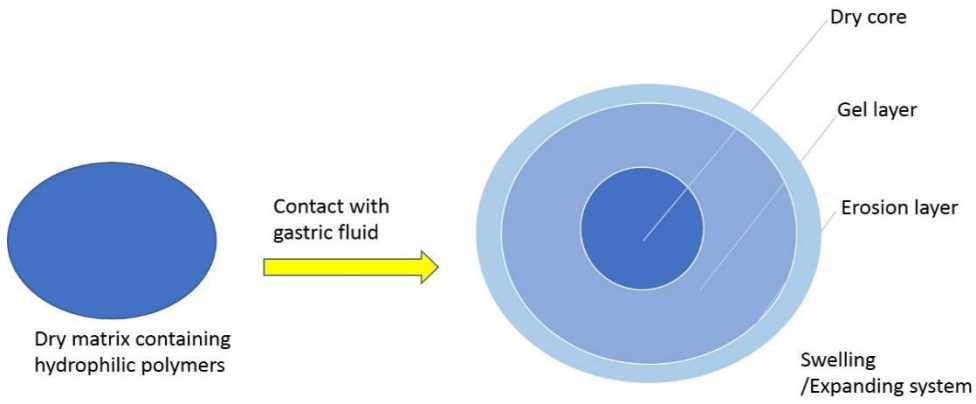

Fig. 2. Illustrative photo of a Swelling / Expanding system.

As for the swelling system, diffusion is the main mechanism through which the dosage form starts swelling followed by drug release from the system. This can be accomplished by the utilization of hydrophilic polymers that can absorb water from the gastric fluids and increase the volume of the system, resulting in swelling to the desirable size, hence causing retention of the expanded formulation inside the stomach for a prolonged time. This mechanism carries a challenge in controlling the swelling and erosion of dosage form so that rapid swelling and premature expansion are avoided. Moreover, the evacuation of the dosage form from the stomach after drug release should be monitored to avoid unwanted side effects such as bowel obstruction, intestinal adhesion, and gastropathy **[24, 53-55]**. Swelling/ floating GRDDS of losartan has been prepared based on a combination of hydroxyethyl cellulose and sodium carboxymethyl cellulose, and results demonstrated that the mean bioavailability from the optimized formulation

was approximately 164.4 ± 60.3 %, relative to the immediate-release product **[56]**. In addition, Jadhav *et al.* formulated expanding gastroretentive tablets of diltiazem hydrochloride using HPMC and sodium carboxymethylcellulose, in which tablets achieved good expansion within the first hour and remained swollen with sustained drug release up to 12 h **[57]**.

As for the unfolding systems, they operate by mechanical shape memory. When the polymer and drug encapsulated inside the small-sized gelatin capsule meet the gastric fluid, gelatin dissolves and releases the mechanically expanded configuration. Different geometrical forms of biodegradable polymers can be prepared and compressed within a capsule. The selection of suitable biodegradable polymer is based on its molecular weight, viscosity grade, and swelling properties to maintain the sustained release profile of the dosage form. However, there are a few drawbacks of the expandable systems such as relatively low storage stability due to easy hydrolysis, the biodegradability of the polymers which results in difficulty in manufacturing, high cost, the inability of some polymers to keep their structural integrity, and liability to cause bowel obstruction, intestinal adhesion, and gastropathy **[9, 24, 58]**. Sivaneswari *et al.* developed and characterized an expandable GRDDS of levetiracetam based on the unfolding mechanism. In their study, the drug was loaded onto a polymeric patch made of HPMC, carbopol 934 P, and XG, which was designed to adhere to the gastric mucosa, from which the drug was released in a sustained manner **[59].** Moreover, Ullah *et al.* developed an unfolding gastro retentive dosage form of enalapril maleate, in which the drug-loaded films were prepared by solid dispersion technique using methodical K15 and Eudragit RSPO and Eudragit RLPO as polymers and polyethylene glycol 400 (PEG 400) as a plasticizer, after which the film was folded in a capsule shell. Results delineated that the formulations provided satisfactory unfolding behavior, allowing the expanded form to remain in the stomach, and sustaining the drug release up to 12 h in gastric fluid, which was attributed to the drug release retarding ability of the polymeric film **[60]**. Furthermore, Kaewkroek *et al.* formulated expandable unfoldable films made from starch and chitosan containing ginger extract, as a solid dispersion. The film was inserted into a hard gelatin capsule and employed as a gastroretentive device. The study revealed that the formulation exhibited high expansion and that it unfolded completely within 15 min in simulated gastric fluid, resulting in a 2.8-fold increase in area, with sustained release up to 90% over 8 h **[61]**.

3.2.4. Superporous hydrogel systems (SPH)

This system is differentiated from the previously mentioned swelling/expanding GRRDS by its higher water uptake capacity and faster swelling ability. The larger surface area and intra- or inter-porous void space help in withstanding a larger amount of water in its framework, resulting in quick swelling capacity. The average pore size of SPH is >100 μm as compared to conventional hydrogel (ranging from 10 nm to 10 μm), and this makes it superior to withstand pressure build-up by gastro retentive

contraction, thus increasing GRT**.** Currently, there are many interpenetrating highly swellable polymers used in this system such as Ac-Di-Sol (croscarmellose sodium) and chitosan/polyvinyl alcohol (PVA). However, the variability in pH has a great influence on the sensitivity of this system and could reverse the swelling, as the change in pH may lead to a change in the mechanical strength of the polymer structure **[15, 17, 24, 62, 63]**. Jihad *et al.* formulated carvedilol gastro-retentive capsule as an SPH system. The formulations were prepared by gas blowing technique from various kinds and concentrations of materials such as monomers (polyvinyl alcohol and acrylamide), cross-linkers (methylene bisacrylamide (Bis), and glutaraldehyde), hybrid agent (chitosan), foaming agent (sodium bicarbonate) and foam stabilizer (tween 80). The introduction of non-soluble hydrophilic polymers enabled the dosage form to take up great amounts of water in a short time due to the existence of interrelated microscopic holes. The hydrogel with its characteristic pore size was considered SPH and was characterized by a larger surface area than the traditional hydrogels due to its porous structure. These properties caused dried SPH to swell very rapidly in contact with water to very large sizes, and the enlarged hydrogel was able to stay in the stomach for an extended time and slowly release the loaded drug. Results showed that formulations varied in their swelling ratio, floating time, density, and drug release according to the different compositions. The best formulation which was composed of chitosan (2%), Bis (1%), PVA (150 mg), and sodium bicarbonate (100 mg) showed a drug release of 79% at 12 h. The study revealed that carvedilol SPH is a promising system to improve the floating time and increase GRT **[64].** Moreover, Kiran *et al.* developed **an** interpenetrating polymer network-based SPH of esomeprazole, using different concentrations of PVA, chitosan, and crosslinking agent glutaraldehyde. The SPH loaded with the drug was compressed to prepare SPH gastroretentive tablets, and results showed that the optimized formulation exhibited good swelling capacity with a total floating time of up to 24 h and sustained release manner of up to 12 h, which might be attributed to the high swelling ability and the porous network of the used hydrophilic polymers **[63]**.

3.2.5. Bio-adhesive/mucoadhesive systems

Bio-adhesive/mucoadhesive systems prolong the GRT of the dosage form by increasing the time of adhesion/contact between the mucosal surface and the dosage form thus, enhancing the drug absorption in a specific site. These systems are usually developed using mucoadhesive polymers such as polyacrylic acid (carbopol\polycarbophil), chitosan, (polymethyl vinyl ether/maleic anhydride copolymers), HPMC, SA, polyethylene glycol, dextran, and polylactic acid. The adhesion may be explained by different theories. The absorption theory suggests that Vander Waals and hydrogen bonding forces help in binding the dosage form to biological membranes. The electron theory relates adhesion to the presence of attractive electrostatic forces between the mucosal surface and the bioadhesive polymers. The wetting theory also explains the adhesion of dosage form by the development of intimate contact between

the polymer and the mucous layers. On the other hand, the diffusion theory assumes the existence of physical entanglement between the mucin strands and the polymer chains. One of the largest drawbacks of this system is the difficulty in controlling the bond between the dosage forms and mucus due to the change in the stomach environment **[15, 17, 65, 66]**. Gunda *et al.* prepared gastro retentive bioadhesive moxifloxacin tablets utilizing mucoadhesive polymers; semisynthetic-HPMCK 100M and natural lannea coromandel gum, which acted also as drug release rate modifiers. Results of this study showed that all the prepared formulations exhibited high mucoadhesive strength (force of detachment) of about 211.73- 494.71 mN, which resulted in an increase in its GI residence time up to 26 h and eventually improved the extent of drug bioavailability. The *in vitro* drug release study revealed that the polymer amount and viscosity had an inverse relation to the release rate of the drug. The study hypothesized that the strong adhesion of the prepared formulations is ascribed to the hydrogen bond formation with the mucus membrane **[67]**.

3.2.6. Magnetic systems

In this system, a small internal magnet is incorporated in the dosage form along with a magnet that is positioned concomitantly over the stomach to retain the loaded drug in the stomach. This system is not preferred as it has many drawbacks such as poor patient compliance and difficulty in determining the accurate position of the external magnet, hence, the clinical applicability of such systems is hindered and only a few studies have been conducted on these systems **[15, 21, 31]**. Fujimori *et al.* tested the gastric retention capability of acetaminophen magnetically controlled release bilayer tablet with the application of an external magnetic field. The bilayer tablet consisted of two layers; one layer containing the drug (drug layer) and the other one containing ferrite (magnetic layer). The *in vitro* study revealed that the tablets sustained the drug release over 12 h. The in *vivo* study was performed on beagle dogs using a permanent magnet applied on the stomach for 8 h after administration of the magnetic tablets, and it was shown that GRT and bioavailability of the drug were improved by magnetic tablets as the tablets remained in the stomach for a prolonged period in the presence of the extracorporeal magnet, and the drug plasma concentration values were significantly increased about 2-folds as compared to tablets administration without the application of external magnet **[9, 68]**.

3.2.7. Ion-exchange resin systems

This system is developed by combining an ionic drug and ion exchange resin loaded with bicarbonate ions in a polymeric matrix. The target of adding an ion exchange resin is to allow the complexation of the drug with the resin in the gastric medium so that the drug is released gradually afterward from the complex. The system is usually coated with a semipermeable membrane to delay the CO_2 release till reaching the acidic environment of the stomach and thus decreasing the density of the system and maintaining a floating system which increases the gastric retention of the drug with poor bioavailability for a prolonged time **[15, 21, 47]**. Daihom *et al.* developed GRDDS of

domperidone resinate complex. The study reported that among the different types of resins used, a Dowex ion exchange resin has exhibited the slowest drug release owing to the high binding efficacy and the ionic interaction of the drug with the dowex resin, resulting in a slow controlled release profile of 64% after 18 h **[69]**.

Conclusion

This article discussed the potential of gastro retentive drug delivery systems for controlled release with various mechanisms. Gastro retentive drug delivery systems are promising for overcoming the low bioavailability of drugs with narrow absorption through retaining the dosage form in the stomach for a definite time with a sustained release manner, thus reducing the frequency of administration of the drug and increasing patient compliance.

Declarations

Ethics approval and consent to participate

Not applicable

Consent to publish

Not applicable

Competing interests

No competing interests were declared by the authors.

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