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Review

Overview on gastroretentive drug delivery systems for improving drug bioavailability

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ABSTRACT

In recent decades, many efforts have been made in order to improve drug bioavailability after oral administration. Gastroretentive drug delivery systems are a good example; they emerged to enhance the bioavailability and effectiveness of drugs with a narrow absorption window in the upper gastrointestinal tract and/or to promote local activity in the stomach and duodenum. Several strategies are used to increase the gastric residence time, namely bioadhesive or mucoadhesive systems, expandable systems, high-density systems, floating systems, superporous hydrogels and magnetic systems. The present review highlights some of the drugs that can benefit from gastroretentive strategies, such as the factors that influence gastric retention time and the mechanism of action of gastroretentive systems, as well as their classification into single and multiple unit systems.

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1. Introduction

The oral administration route has always assumed a role of prominence in therapy due to its well-established advantages. Several factors make this route preferable to patients, and these formulations are also less expensive, easy to transport and store, flexible in terms of the constituents, and ready to administer (Pinto, 2010).

However, oral administration faces some physiological constraints due to the heterogeneity of the gastrointestinal system. In addition, several variables change throughout the gastrointestinal tract and greatly influence drug absorption. Among these factors, pH, the commensal flora, gastrointestinal transit time, enzymatic activity and surface area are the most important (Rouge et al., 1996).

Conventional systems are not enough to overcome all the difficulties imposed by the gastrointestinal tract. For instance, they are inappropriate for drugs that are preferentially absorbed in the upper part of the digestive system since conventional formulations do not possess the capacity to face gastric emptying; therefore, they cannot be released in the colon where they stay during the final period of their release time. Therefore, the incomplete release of drugs and the concomitant reduction of dose effectiveness are consequences of the incapacity of the conventional systems to be retained at the stomach level (Kagan and Hoffman, 2008). In order to overcome these adversities, technological researchers have developed pharmaceutical systems that control drug release and the residence time, some of which are already available on the market.

The failure in gastric retention with conventional systems has led to the development of oral gastroretentive systems. Such delivery systems were designed to be retained in the upper gastrointestinal tract for a prolonged period of time, during which they release the drug on a controlled basis. The extended contact of gastroretentive systems with the absorbing membrane allows an increase in drug bioavailability (Boldhane and Kuchekar, 2010). Additional advantages of these systems include (Garg and Gupta, 2008): (i) an improvement in therapeutic effectiveness, (ii) a reduction in drug loss, (iii) an increase in drug solubility in cases with low solubility in a high pH environment, and (iv) benefits due to the delivery of drugs that act locally in the stomach and duodenum.

Several strategies have been studied to formulate successful controlled drug delivery systems that increase the gastric residence time such as bioadhesive or mucoadhesive systems, expandable systems, high-density systems, floating systems, superporous hydrogels, and magnetic systems (Friedman et al., 2004, 2005; Garg and Gupta, 2008; Gerard et al., 2014; Grenier et al., 2015; Hassan, 2014; Pathak et al., 2015; Tsabari et al., 2013). This review compiles relevant information about the drugs that can benefit from gastroretention strategies, the factors that influence their gastric retention time, the mechanism of action of gastroretention, as well as their presentation as single and multiple unit systems.

2. Suitable drug candidates for gastroretention

Table 1 lists the most common drugs that are good candidates to be formulated with gastroretention strategies. Many physiological conditions lead to the need for development gastroretentive systems such as a narrow upper gastrointestinal absorption window, a short drug half-life, drug instability in the gastrointestinal tract environment, local activity in the upper part of the gastrointestinal tract, or poor solubility at alkaline pH (Chavanpatil et al., 2006; Gröning et al., 2007; Jiménez-Martínez et al., 2008; Rajinikanth et al., 2007).

Gastroretentive systems can increase the therapeutic effectiveness of a drug through the removal and/or the reduction of more than one physiological constraint. For example, studies in dogs have shown long-term absorption and sustained blood levels of levodopa when it was delivery in a sustained profile from a gastroretentive system, in opposition to non-gastroretentive controlled release system and to an oral solution providing immediate release (Klausner et al., 2003a). The results demonstrated that the gastroretentive system was able to circumvent limitations such as the short half-life and narrow absorption window that limit both drug release and complete drug absorption.

The drugs that can benefit from gastroretentive systems belong to different therapeutic classes and are effective in various pathologies, reflecting their therapeutic diversity. Examples of drugs formulated for gastroretentive systems are: amoxicillin, an antibiotic used in *Helicobacter pylori* eradication; furosemide for the treatment of congestive heart failure, chronic renal failure and liver cirrhosis; and levodopa, which is beneficial in the treatment of Parkinson's disease. A wide range of pathologies can, therefore, find in these systems the key to better therapeutic effectiveness with fewer side-effects and a lower frequency of administration (Rajinikanth et al., 2007; Klausner et al., 2003a; Klausner et al., 2003c).

3. Factors affecting gastric retention time

The gastric retention time can affect drug absorption. Absorption is often limited to areas between the stomach and duodenum, and the residence time in this area limits the absorption of drugs. Therefore, the longer the drug stays in contact with the absorbing membrane, more is the rate and extent of absorption. However, the time in the upper part of the gastrointestinal tract is short due to the fast gastric empting time and generally lasts about 2–3 h (Hoffman et al., 2004; Singh and Kim, 2000).

The gastric retention time is, therefore, an important parameter in drug absorption. Several methods have been used to determine the gastric residence time, which include direct methods (e.g. X-ray imaging, radiotelemetry, magnetic moment imaging, gamma-scintigraphy) and indirect methods that comprise the hydrogen breath test and the use of markers that are absorbed at a specific site (Yuen, 2010).

The mechanisms that control the gastric emptying process are complex and considerable variations should be taken into account. Therefore, various factors influence gastric empting, and consequently the gastric retention time of the dosage forms. They can be classified in two groups: (i) pharmaceutical technology factors and (ii) factors that depend on individual parameters linked to intrinsic (biologic) factors.

Table 1
The most relevant drug candidates suitable for GR systems.

Bioavailability hurdles	Therapeutics	Drug(s) (References)
Local activity	Eradication of *Helicobacter pylori*	Amoxicillin (Rajinikanth et al., 2007; Badhan et al., 2009)
Local activity	Eradication of *Helicobacter pylori* adjunct	Metronidazole (Ishak et al., 2007)
Plasma fluctuations Short half-live	Eradication of *Helicobacter pylori* Upper respiratory tract infections	Clarithromycin (Nama et al., 2008; Jain and Jangdey, 2008)
Narrow absorption window in upper GIT	Prophylaxis/treatment of bacterial urinary infections	Nitrofurantoin (Gröning et al., 2007)
Narrow absorption window in upper GIT	*Herpes simplex* infections	Acyclovir (Gröning et al., 2007; Ruiz-Caro et al., 2012)
Narrow absorption window in upper GIT	Treatment of congestive heart failure, chronic renal failure and hepatic cirrhosis	Furosemide (Klausner et al., 2003c; Meka et al., 2009)
Unstable in the colonic environment Short half-live	Treatment of hypertension and congestive heart failure	Captopril (Gröning et al., 2007; Jiménez-Martínez et al., 2008)
Short half-live Narrow absorption window in upper GIT	Treatment of Parkinson	Levodopa (Klausner et al., 2003a; Ngwuluka et al., 2013)
Short half-live Narrow absorption window in upper GIT	Treatment of hypertension, congestive heart failure, angina and arrhythmias	Metoprolol succinate (Boldhane and Kuchekar, 2010)
Short half-live Narrow absorption window in upper GIT	Treatment of type II diabetes	Metformin (Ali et al., 2007; Ige and Gattani, 2012)
Short half-live Local activity	Treatment of peptic ulcer and reflux oesophagitis	Ranitidine (Rohith et al., 2009)
Low solubility at alkaline pH	Treatment of bacterial genitourinary and respiratory infections	Ofloxacin (Chavanpatil et al., 2006; Patil et al., 2013)
Low solubility at alkaline pH	Treatment of hypertension and tachycardic disturbances	Verapamil (Sawicki, 2002)
Poor absorption from lower GIT	Treatment of hypertension	Atenolol (Pawar et al., 2013; Dey et al., 2014)
Short elimination half-life Limited absorption by a saturable L-amino acid transport system	Management of postherpetic neuralgia	Gabapentin (Irving, 2012; Rauck et al., 2013; Gupta and Li, 2013)

3.1. Pharmaceutical technology factors

3.1.1. Density of the dosage form

The density of the dosage form is a physical parameter that influences the gastric retention time by two opposing behaviors: floatation and sinking. In the former, the dosage form displays a lower apparent density than that of the gastric fluid, i.e., below 1.004 g/cm^3 (Chauhan et al., 2012). Increasing the floating capacity will enhance the probability of a longer retention time and a decrease in the effect of the presence of food (Sauzet et al., 2009). Also, an increase in the density of the dosage form could be responsible for an increase in gastric residence time. To become this effect significant, a density of about 2.5 g/cm^3 is required (Clarke et al., 1993).

3.1.2. Size of the dosage form

The size of the dosage form is a characteristic that can be changed in order to increase the gastric residence time for non-floating systems. For non-disintegrating systems, it is logical that an increase in the size of the dosage form for values higher than the pyloric sphincter diameter (mean 12.8 ± 7 mm in humans) (Salessiotis, 1972) prevents its passage to the duodenum, therefore increasing the gastric residence time; this will last as long as the digestive phase (Talukder and Fassihi, 2004).

3.2. Physiological factors

3.2.1. Extrinsic factors

The extrinsic factors that affect the gastric residence time include those that can be controlled by the patient, such as the nature, caloric content and frequency of food ingestion, concomitant ingestion of drugs that influence gastrointestinal motility (e.g. anticholinergic drugs, opiates and prokinetic agents), posture, physical activity, sleep, and body mass index (Streubel et al., 2006; Klausner et al., 2003b; Talukder and Fassihi, 2004).

The stomach is a dynamic organ of the body. Two main profiles of gastric motility can be identified; they result from the presence or absence of food (Klausner et al., 2003b). Gastric motility under fasting conditions originates in the stomach a cyclic patter. It is known as the interdigestive myoelectric motor complex (IMMC) and presents cyclic behavior of four phases according to the intensity and frequency between gastric contractile events. Food ingestion disrupts this cycle, leading to irregular contractile activity. Its length depends on the quantity and nature of the meal (Klausner et al., 2003b).

The presence of food increases the dosage form residence time since it decreases the rate of gastric emptying, resulting in an increase of drug absorption in the upper digestive system (Talukder and Fassihi, 2004).

The gastric residence time is also affected by posture and varies according to this parameter in opposite directions for floating and non-floating dosage forms (Garg and Gupta, 2008; Nguyen et al., 2015). For the first, the upright position favors gastric retention since the system floats on top of the gastric contents, while the non-floating systems tend to settle close to the pylorus. In the supine position, non-floating systems have an increased gastric retention time (Garg and Gupta, 2008). This issue is one of the most frequent criticisms of gastric retention measurements in the studies performed on animals.

The viscosity of semi-solid food may also influence the gastric emptying rate. Despite some studies reported that increasing food viscosity could result in delay gastric emptying rate (Juvonen et al., 2009; Zhu et al., 2013); Shimoyama et al. (2007) obtained contradictory results. Therefore, a challenge for future research is to understand the influence of rheological properties of food in drug absorption.

The ingested beverages, i.e. the volume of fluid, the composition, the energy density, and eventually the osmolality and temperature, is also a relevant parameter that could control the stomach emptying and small intestinal absorption rates (Leiper, 2015). Teramoto et al. (2014) studied the effects of a liquid meal with monosodium glutamate on the gastric emptying and duodenal motility in healthy volunteers. The results of this study suggest that monosodium glutamate accelerates gastric emptying by facilitating duodenal motility. Brun et al. (2012) demonstrated that in children with cerebral palsy using gatrostomy, gastric

emptying rate is influenced by the protein composition in the liquid meals.

However, more research is required to study the influence of composition liquid meal in the GIT parameters and consequently in the absorption process.

3.2.2. Biological factors

Biological factors are intrinsic to the patient and include gender, age, illness and emotional state (Garg and Gupta, 2008; Talukder and Fassihi, 2004).

Physiological differences (e.g. gender and age) can have significant effects on the pharmacokinetic and pharmacodynamic profiles, which may lead to different responses to drugs. For instance, differences in the GIT physiology such as luminal pH, gastric motility, mucosal features and gastric emptying time affect the absorption process of oral drug delivery (Freire et al., 2011; Firth and Prather, 2002). Much of the current knowledge about inter-gender and age GIT differences is based on old studies and in many instances no information is available as reported by Freire et al. (2011). Despite gender-differences in absorption process of some molecules is well established, e.g. copper (Johnsen et al., 1992), iron (Woodhead et al., 1991) and ranitidine in the presence of polyethylene glycol 400 which enhance the bioavailability of ranitidine in males (Ashiru et al., 2008), it is essential further research to understand and clarified the true mechanisms that justify these differences. In a recent study, Wang et al. (2015) reported a robust evidence that gender and age influence regional gastrointestinal transit times and also intra-luminal pH. The authors demonstrated that females had longer gastric emptying time and whole gut transit time. Increasing age was related with shorter small bowel transit time. Camilleri et al. (2012) conducted a study with healthy humans despite gender was significantly associated with gastric emptying rate (i.e. slower in female than in men), age (in the range 18–65 years) and body mass index were not. Hormonal influences could explain the slower GIT transit in women than in men. Gastric acid output and consequently pH of the stomach differs by gender, i.e. men present more acidic conditions (Feldman and Barnett, 1991; Prewett et al., 1991). The basal secretion of mucosal bicarbonate is hormone dependence (Tuo et al., 2008). Bouras et al. (2002) reported postprandial changes in gastric volumes by gender which was higher in men than in women. Gender-differences in absorption process could also be related with mucosal enzymes and transporters, for example differences in postprandial gastric emptying of alcohol which was longer in women than in man due to significant sex-related differences in the expression of alcohol dehydrogenase (ADH) (i.e. a gastric mucosal enzyme) (Baraona et al., 2001). The gastric ADH activity is also age-dependence (Parlesak et al., 2002).

The emotional state of the patient also seems to play a role in determining the gastric residence time, since it has been observed that there is a decrease in the gastric emptying rate when the patient is in a depressed emotional state, whereas the opposite is observed in individuals experiencing anxiety (Talukder and Fassihi, 2004).

Finally, the presence of illness is also a factor to take into account since pathological conditions such as diabetes mellitus and Parkinson's disease can also influence the gastric residence time (Triantafyllou et al., 2007; Krygowska-Wajs et al., 2009). In the case of longstanding type I and type II diabetes, there is around a 30–50% decrease in gastric emptying (Triantafyllou et al., 2007). In cases of Parkinson's disease, all patients present a delay in gastric emptying that can be frequently accompanied by constipation (Krygowska-Wajs et al., 2009).

4. Single and multiple unit dosage forms

The gastroretentive systems reported in the literature can be classified into two classes. The first class comprises tablets and capsules that are composed of a single unit, and therefore known as single unit dosage forms, i.e. non-divided formulations. The second class refers to formulations composed of more than one unit, known as multiple unit dosage forms, among which are included granules, pellets and mini-tablets (Ishida et al., 2008).

The single unit dosage form is a uniform system, including solid matrix systems and capsules. The solid matrix system refers to a monolithic system in which the drug is dispersed or dissolved and drug release is generally modulated through the incorporation of suitable polymeric agent(s). The use of capsules as single controlled release systems requires the selection of appropriate excipients (Efentakis et al., 2000).

Multiple unit dosage forms consist of small single and individual units (e.g. pellets, granules and mini-tablets), that may or not be coated, then combined into a unique final pharmaceutical form upon filling or compression. Single unit filling is generally accomplished through their encapsulation in hard gelatin capsules, while compression leads to tablets that contain both single units and excipients (Varum et al., 2010).

These systems are valuable because the patient, by taking one capsule or tablet, is administering multiple single units of a pharmaceutical form that could contain different drugs, dosages and release profiles (Lopes et al., 2006; Bandari et al., 2010). Moreover, these systems have many additional advantages, such as lower toxicity risk (due to a lower risk of dose dumping), reduced dependency on gastric emptying (which leads to a lesser degree of inter and intra-individual variability), avoidance of the all-or-none effect (the failure of individual units does not compromise the entire system), and greater dispersion throughout the digestive tract (which lowers the risk of local high concentrations, minimizing local irritation and allowing for greater drug protection) (De Brabander et al., 2000; Dey et al., 2008).

Among the multiple unit dosage forms, mini-tablets are an attractive system due to their physical properties and production process. Their production can be accomplished using common industrial tableting machines, providing additional advantages over other delivery systems, as the presence of liquids can be avoided and high production yields can be obtained. Additionally, the tablet technique leads to solids with a uniform size, regular shape, smooth surface, low porosity and high strength, which allow for more reproducible results (Lingam et al., 2008).

The concept of mini-tablets can be used to reproduce a biphasic release system (Fig. 1). This means that it can induce an initially rapid release, which might work as a loading dose, followed by sustained drug release, allowing for the maintenance of drug plasma levels that are needed to achieve the therapeutic effect;

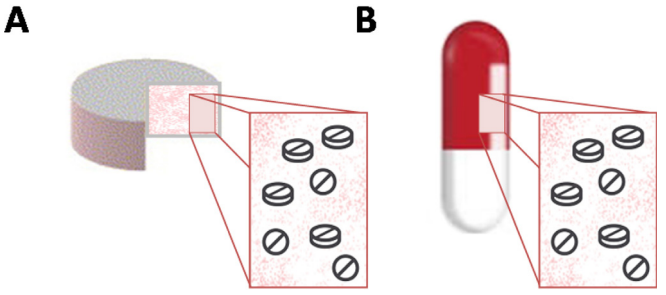

Fig. 1. Biphasic Release Systems. A: Compressed mini-tablets. B: Encapsulated mini-tablets.

this also provides for a reduction in the number of drug intakes (Lopes et al., 2006; Lingam et al., 2008). These systems are made by incorporating, in the same capsule or tablet, single and individual units as mini-tablets or pellets with distinct release profiles, i.e. single immediate release units that allow for fast drug release, and sustained or delayed single release units (Efentakis et al., 2000).

Bandari et al. (2010) developed a floating biphasic gastroretentive system for fenoverine administration. The delivery system consisted of a loading-dose tablet and floating multiple matrix tablets. The authors reported an initial peak of release, followed by a zero-order release profile with buoyant properties of the floating mini-tablets, which reflects its biphasic release behavior.

Rajput et al. (2014) developed a bifunctional capsular dosage form composed by a gastroretentive funicular cylindrical system (FCS) for controlled release of clarithromycin and granules for immediate release of ranitidine HCl. A 2^3 full-factorial design was used to optimize the funicular cylindrical formulation using detachment stress, floating time and cumulative drug release percentage (8 h) as the dependent variables. The optimized funicular cylindrical system was combined with immediate release granules of ranitidine HCl and fitted into a capsule. The formulation presented a biphasic release pattern with 98.80% ranitidine HCl release in 60 min and 97.72% clarithromycin release in a period of 8 h. The authors concluded that this bifunctional dosage form is potentially useful for *Helicobacter pylori* eradication.

5. Gastroretentive delivery forms

As stated before, gastroretentive delivery forms are an attractive approach by which the pharmaceutical industry has tried to cope with some of the limitations presented by conventional oral dosage forms. Therefore, in the last decades, a number of strategies have been proposed by academics and industries aiming to increase the gastric residence time. Some gastroretentive products are available on the market (Garg and Gupta, 2008). In this section, we will describe the main outcomes of each group of gastroretentive system, i.e. expandable systems, bioadhesive or mucoadhesive systems, high-density systems, floating systems, superporous hydrogels, and magnetic systems. Raft-forming systems have been explained in detail elsewhere (Prajapati et al., 2013) and represent another interesting approach to gastric retention.

5.1. Single unit systems

5.1.1. Expandable systems

As suggested by its name, an expandable system achieves a longer gastric residence time through an increase in its volume and/or shape. Interestingly, these systems were initially designed for veterinary use and were rapidly explored for human applications (Garg and Gupta, 2008).

Three common aspects must be always present for the proper function of these systems, irrespective of the expansive system. The first one is that they should be easily swallowed, since the pharmaceutical dosage form must have the proper size for swallowing or patients will not be willing to take them. The second one is the size that the system acquires after reaching the stomach, which must be greater than that of the pyloric sphincter. Finally, it must be assured that, after programmed drug release, the remaining structure decreases to a size that allows for its elimination (Fig. 2) (Klausner et al., 2003b).

Expandable systems stay in the gastric compartment using two strategies, which consist of swelling and unfolding systems that allow for volume and shape modification.

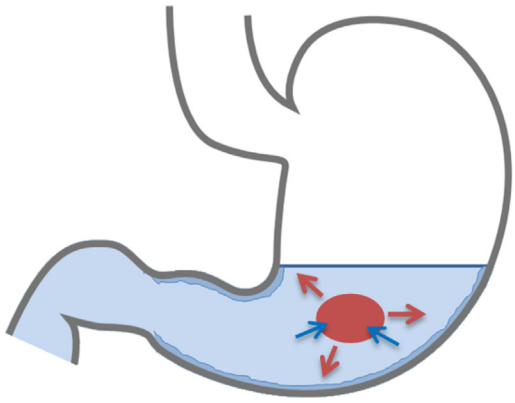

Fig. 2. Mechanism of drug release in stomach content through expandable release systems.

Swellable systems are retained in stomach due to their mechanical properties. These systems increase in size after coming into contact with gastric fluids, i.e. after hydration. This process is only possible due to the use of hydrophilic polymers (e.g. hydroxypropylmethylcellulose, polyethylene oxide and carbopol) which absorb water from the gastric fluids. Water absorption leads to numerous modifications to the polymer, which allows for drug release, including polymer swelling and plasticization (lowering of the glass transition temperature), an increased diffusion coefficient, and erosion (due to polymer disentanglement) (Siepmann and Peppas, 2001). Both water absorption and the downstream modifications occur at a slow rate that allows for drug release to continue for several hours (Laity and Cameron, 2010). The events that take place highlight the importance of the hydrophilic polymer choice in these systems. Research into new expandable systems has been growing and has already resulted in the development of novel polymers, which include intelligent polymers and starch copolymers. In response to certain stimuli including temperature, pH, and solvent composition, intelligent polymers are able to change their swelling behavior and release characteristics (Fu and Soboyejo, 2010). Starch copolymers, like tapioca graft copolymers, seem to behave as an inert matrix that allows for controlled drug release by diffusion (Casas et al., 2010).

Unfoldable systems are commonly composed of biodegradable polymers that are folded and encapsulated in a carrier that is degraded in the stomach. Carrier degradation allows the drug release from the pharmaceutical system as it unfolds and reacquires its initial geometrical form (Klausner et al., 2003a). The literature describes numerous geometrical forms for this system, such as the "accordion pill" (Kagan et al., 2006). Kagan et al. (2006) tested this system in humans and showed that it increased gastric retention capacity, without the need of a caloric meal, and provided increased bioavailability of riboflavin (i.e. a narrow absorption window drug) by saturated transport. Another example that illustrates the potential of these systems to become an adequate route for sustained drug absorption is a study performed by Klausner et al. (2003b). These authors observed a significantly longer mean absorption time for levodopa loaded in an unfolding system in comparison to an oral solution and non-gastroretentive controlled release particles (Klausner et al., 2003a). Verma et al. (2014) developed and characterized an unfoldable system containing cinnarizine, an antihistamine with a narrow absorption window. These authors prepared drug-loaded polymeric films containing different amounts of stearic acid that were folded into hard gelatin capsules. *In vitro* drug release studies revealed immediate release of the drug in the first hour, followed by gradual release during a 12 h period. The amount of stearic acid was crucial to this release pattern, acting as a sustained delivery

agent. Evaluation of the floating and mechanical properties showed the gastroretentive potential of the system, making it suitable for *in vivo* studies.

Dey et al. (2014) developed a biphasic delivery system based on the use of β-cyclodextrin, employed in the fast-release layer, and xantham and guar gum, both used in the sustained-release layer. This system rapidly delivered a dose of atorvastatin, a lipid-lowering agent, and provided sustained atenolol release, demonstrating faster absorption and increased oral bioavailabilty of atorvastatin, as well the achievement of sustained therapeutic blood levels of atenolol.

El-Zahaby et al. (2014) developed size increasing tablets using *in situ* gel forming polymers, such as gellan gum, sodium alginate, pectin and xantham gum, and cross linkers (e.g. calcium and aluminum chloride) in order to control the release of levofloxacin, obtaining a promising system to be use in the *Helicobacter pylori* eradication.

In summary, it is possible to state that expandable systems allow for sustained release in the absorption window and provide some advantages, including reduced plasma level variability of the drug and a reduction in both side effects and dosage.

5.1.2. Superporous hydrogels

Superporous hydrogels are composed of cross-linked hydrophilic polymers, which absorb a significant amount of water or aqueous fluid very rapidly (i.e. in a shorter period of time) and swell to equilibrium size, creating a structure with numerous large pores connected together to form open channel structures (Omidian et al., 2005; Chavda et al., 2012) (Fig. 3). Water uptake into the dried system is provided by capillary action (Omidian et al., 2005). The fast swelling that occurs in less than 20 min helps fight premature gastric emptying by housekeeper waves, thereby increasing the gastric residence time (Klausner et al., 2003b). However, a certain mechanical strength is also required to make these systems resistant to gastric contractions, since the fully swollen superporous hydrogels are mechanically very fragile (Omidian et al., 2005). Chen et al. (2010) used different superdisintegrant agents (e.g. Ac-Di-Sol®, Explotab®, Primojel® – i.e. sodium starch glycolate – and Crospovidone® – crosslinked polyvinylpyrrolidone) in the composition of superporous hydrogels in order to main mechanical strength. Ac-Di-Sol® demonstrated the best improvement. In contact with aqueous media, it absorbed water and expanded and, consequently, opened up the closed capillary channels in the superporous hydrogel that allowed it to swell quickly.

According to their swelling and mechanical properties, superporous hydrogels are classified into three different generations (Omidian et al., 2005): the first generation, also known as conventional superporous hydrogels, characterized by rapid swelling, a high swelling ratio and mechanical fragility; the second generation, superporous hydrogel composites, that feature quick swelling, a moderate swelling ratio and superior mechanical properties; and the third generation, hybrid superporous hydrogels, that present very high mechanical strength (i.e. elastic properties) which make them promising systems for gastroretention. Hybrids superporous hydrogels are prepared by adding a hybrid agent after the superporous hydrogel is formed. Omidian et al. (2006) prepared a hybrid superporous hydrogel of polyacrylamide and sodium alginate able to stretch up to 2–3 times its original length, after partial or complete swelling. This formulation was also capable of withstanding several cycles of stretching/unloading, suggesting its potential in pharmaceutical applications.

El-Said et al. (2014) studied an extended release superporous hydrogel hybrid system using different polymers, namely gellan gum, guar gum, polyvinyl alcohol and gelatin. Animal studies performed in dogs demonstrated an increase in baclofen bioavailability and the effectiveness of the designed system for sustained drug release.

5.1.3. Bio/mucoadhesive systems

Since first introduced by Park and Robinson in 1984 as a new approach for drug delivery purposes, the concept of bioadhesion has been thoroughly exploited in order to create more efficient and controlled drug delivery systems. This interest is clearly visible in the enormous effort to develop new bioadhesive polymers for different routes of administration, namely oral, nasal, ocular, and vaginal (Thirawong et al., 2007; Vasir et al., 2003).

In order to extend gastric residence time, mucoadhesive systems increase the intimacy and duration of drug contact with biological membranes (Fig. 4). Bioadhesive polymers may be natural or synthetic and are defined by their ability to adhere to biological tissues. They can be divided into cytoadhesive or mucoadhesive, depending on the binding established between the polymer and the epithelial surface. The cytoadhesive property corresponds to the ability of the polymer to bind to the epithelial cell layer, a connection that is made by interactions with cell-specific receptors, while the mucoadhesion property refers to the capacity to bind to the mucus layer and not to cells (Vasir et al., 2003). Some polymers show both of these properties. Examples of polymers commonly used for bioadhesion include poly(acrylic acid), chitosan, cholestyramide, tragacanth, sodium alginate, carbopol, hydroxypropylmethylcellulose, Sephadex, sucralfate, polyethylene glycol, dextran, poly(alkyl cyanoacrylate), and polylactic acid (Bardonnet et al., 2006). Five theories, summarized in Table 2, based on the type of molecular link that is established

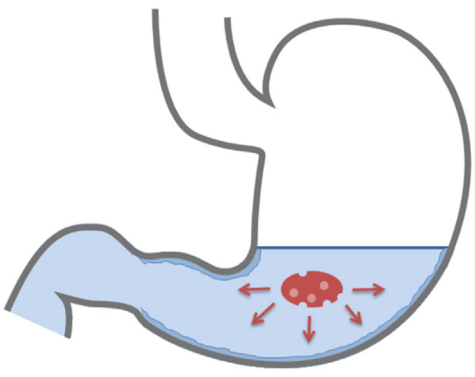

Fig. 3. Mechanism of drug release in stomach content through superporous hydrogels.

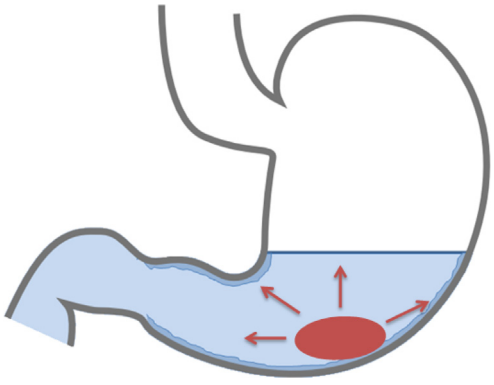

Fig. 4. Mechanism of drug release in stomach content through bio/mucoadhesive systems.

Table 2
Theories for bioadhesive mechanism (adapted from Andrews et al., 2009).

Theory	Bioadhesive mechanism
Wettability theory	• applicable to liquids and low viscosity systems; • the polymer penetrates in the irregularities of the biological surface and anchorages there; • it is defined in terms of spreadability.
Electronic theory	• electron transfer between the polymeric system and the mucus; • formation of a double layer of electrical charges at the interface mucus-polymer with attractive forces.
Fracture theory	• is based on the force that is needed to separate the two surfaces: mucus and polymer; • the detachment force reflects the force of the adhesive binding.
Adsorption theory	• results from the primary forces (ionic, covalent and metallic) and secondary forces (van der Waals, hydrophobic and hydrogen bonds) between surfaces.
Diffusion-interlocking theory	• the diffusion process that occurs between mucus and polymers, is bidirectional and depends of the diffusion coefficient of them both; • it is influenced by: molecular weight, cross-linking density, chain mobility/flexibility and expansion capacity of both networks.

between macromolecules (polymer) and mucin proteins have been put forward to explain the mucoadhesion phenomena (Vasir et al., 2003).

The bioadhesion systems present some important advantages. Adhesion to the epithelial surface will not only lead to the proper location and mobilization of the drug but also favor a closer and more lasting association between the drug and the local microenvironment. These characteristics lead to an increase in the residence time of the drug in the target area and to its controlled and predictable release, thereby diminishing the amount of the drug required (Huang et al., 2000).

The main drawback of such systems is that they are unable to resist stomach turnover, the constant renewal of the mucus layer, and the high stomach hydration that decreases the bioadhesion of polymers (Bardonnet et al., 2006). Another factor to take into account is the risk of adhesion to the esophagus which may lead to collateral lesions (Talukder and Fassihi, 2004).

Zate et al. (2011) developed a gastroretentive mucoadhesive tablet for sustained venlafaxine hydrochloride release using Carbopol 971 P as the mucoadhesive agent and Eudragit RS-PO and ethyl cellulose as controlled release agents. The authors concluded that an increase in the Carbopol 971 P concentration increases the adhesion time and higher ethyl cellulose levels decrease drug release. Three formulations showed an adhesion time of 12 h.

Patil and Talele (2014) developed a mucoadhesive controlled release tablet of lafutidine, a new histamine H2 receptor antagonist, using polymers like sodium alginate, xantham and karaya gum. Radiological studies suggested that the formulation adhered for a period longer 10 h in the rabbit stomach while providing an adequate drug release rate.

Pandey et al. (2013) prepared a bilayered mucoadhesive patch for a stomach-specific drug delivery of lercanidipine HCl. The patch system consisted of a drug release rate controlling film, using a combination of Eudragit RSPO and RLPO, and a muchoadhesion film, combining various hydrophilic polymers. Besides the mucoadhesive effectiveness of these systems, bioavailability studies performed in rabbits demonstrated that drug release was controlled for over 12 h, thus enhancing the oral bioavailability.

5.1.4. Floating systems

Of all the gastroretentive systems described in the literature, floating systems are the most prominent (Abduljabbar, 2016; Choi et al., 2002; Pandey 2016; Zhang et al., 2016). Such systems are characterized by the capacity of the formulation to float in and over the gastric contents due to its low density, which must be below 1.004 g/cm^3 (Whitehead et al., 1998), without affecting the gastric emptying rate (Fig. 5). This characteristic allows the system to remain buoyant in the stomach for a prolonged period of time while the drug is released at the desired rate from the system during its gastric residence time (Jiménez-Martínez et al., 2008; Rossi et al., 2015). The residual system is emptied from the stomach depending on the gastric contents and the level of floating force (Mayavanshi and Gajjar, 2008).

These systems can remain buoyant in the stomach via two distinct mechanisms, differentiated by gas production, i.e. non-effervescent systems and effervescent systems.

The non-effervescent approach relies in two ways by which the systems float. In the first one, a combination of high swelling and gelling capacity polymers, such as cellulose type of hydrocolloid, polysaccharides, and matrix-forming polymers, like hydroxypropylmethylcellulose, polycarbonate, polyacrylate, polymethacrylate, sodium alginate, agar polystyrene, are used (Singh and Kim, 2000). Upon reaching the gastric fluid, these systems swell by hydration, forming a gel layer with entrapped air around the system core, which controls drug release. The entrapped air provides the floating capacity of the system (Singh and Kim, 2000). A different method is based on the formulation incorporating a gas-filled chamber of specific gravity into a microporous component that allows the system to float (Harrigan, 1977).

Hydrodynamically Balanced Systems (HBS^{TM}) are a sub-type of the non-effervescent systems. They were first developed by Sheth and Tossounian (1984), and became a highly recognized floating system. They are composed of one or more gel-forming hydrophilic polymers in which the drug is embedded. The mixture is usually

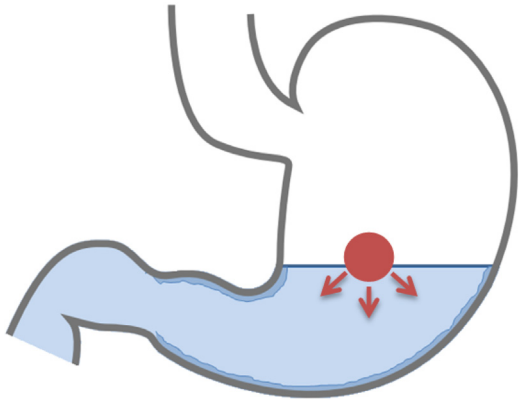

Fig. 5. Mechanism of drug release in stomach content through floating systems.

administrated in a gelatin capsule. Capsule degradation occurs when it comes into contact with the gastric fluid; the polymer swells to form a surrounding layer that allows controlled release by diffusion and erosion (Sheth and Tossounian, 1984). These systems display an increase in both the gastric residence time and the amount of the drug that reaches the absorption site in a soluble form (Garg and Gupta, 2008).

The effervescent systems can include gas-generating systems and volatile liquid containing system. In the gas generating systems, gas production is due to the reaction of carbonates and bicarbonates present in the formulation with gastric acid or co-formulated acids (e.g. citric or tartaric acid). The gas that forms is retained in the gel hydrocolloid matrix (Baumgartner et al., 2000), and its presence influences the drug release profile. In a comparative study, using a hydroxypropylmethylcellulose matrix, the addition of bicarbonate sodium, and the concomitant production of CO_2, increased the hydration volume of the dosage form and thus the superficial area for drug diffusion (Jiménez-Martínez et al., 2008). However, in contrast, the carbon dioxide bubbles obstructed the diffusion path, leading to a decrease in the drug release rate. The same authors reported that in the second stage of the drug release process, gas production could favor drug delivery. Using this strategy, Tadros (2010) evaluated the *in vitro* and *in vivo* behavior of ciprofloxacin hydrochloride effervescent floating tablets. The optimized tablet was selected regarding it gastric residence time in humans, i.e. 5.50 ± 0.77 h. Hu et al. (2011) showed that floating tablets of dextromethorphan hydrobromide based on a gas forming technique display an slower *in vivo* release profile when compared with dextromethorphan hydrobromide sustained release tablets, without a decrease in the bioavailability or plasma level variations of the drug. Therefore, these results demonstrate sustained release for drugs with a narrow absorption window.

The raft-forming systems consist of a gel-forming solution (e.g. sodium alginate solution) containing carbonates or bicarbonates that form a gel upon contact with gastric fluids (Prajapati et al., 2013). This solution forms a viscous and cohesive gel once swelled with entrapped CO_2 bubbles produced by the reaction of (bi) carbonates with stomach acid (Bardonnet et al., 2006). Due to the incorporation of CO_2, raft-forming systems have a very low bulk density that enables them to float on the surface of the gastric contents, forming a gel floating layer, i.e. a raft. These systems can remain intact in the stomach for several hours, promoting the sustained release of the drug (Lahoti et al., 2011). Due to the raft, such systems are used to deliver antacid drugs like aluminum hydroxide or calcium carbonate used in the treatment of gastroesophageal reflux (Hampson et al., 2010). In 2015, Abou Youssef demonstrated the feasibility of prolonging gastric residence time and the release rate of metronidazole by preparing a floating raft system (FRS) using ion-sensitive *in situ* gel forming polymers (Abou Youssef, 2015).

Volatile liquid systems contain a volatile liquid such as ether or cyclopentane, introduced in an inflatable chamber, which volatilizes at body temperature allowing for inflation of the chamber in the stomach (Talukder and Fassihi, 2004). As in the non-effervescent systems, hydrophilic polymers, such as alginate and different types of hydroxypropylmethylcellulose, are often used as matrices since these polymers allow the control of drug release (Baki et al., 2011; Sriamornsak et al., 2007). Controlled drug release is again due to the formation of a viscous hydrated layer around the tablet that acts as a barrier to water intake and the free movement of solutes to the outside of the matrix (Sriamornsak et al., 2007). The nature of the matrix determines the degree of swelling and erosion as well as the degree of drug diffusion, which determines the mechanism and kinetics of drug release (Jiménez-Martínez et al., 2008). However, the drug release mechanism from the matrix does not only depend on the nature of the barrier but also on the drug solubility in water.

The exploitation of these systems has allowed for the development of several floating systems that combine different variables such as effervescence, geometric shape, size, area/volume ratio, coating, and production techniques. Different formulation strategies arise from this intersection in single unit dosage forms.

As previously mentioned, the technology used to develop floating systems also influences their behavior and parameters, such as the gastric residence time and drug release profile. Sauzet et al. (2009) developed a non-effervescent floating system obtained by wet granulation. The tablets have a final porous structure with improved cohesion properties, offering a good alternative to sustained drug release, in which the floating capacity was mainly due to the high porosity of the system.

One more strategy that can be used is the formulation of bi or multiple layer systems that was employed by Ozdemir et al. (2000) and Wei et al. (2001) to maximize the absorption and bioavailability of furosemide and cisapride, respectively. The authors formulated bilayer tablets in which one of the layers was responsible for the floating properties and the other promoted controlled drug release. These systems permit the incorporation of the effervescent agent in any one of the layers and a matrix coating with a water-permeable and CO_2-impermeable polymer.

In order to improve metformin bioavailability, Oh et al. (2013) formulated floating gastroretentive tablets using camphor as the sublimation material. This strategy consists of subjecting camphor, incorporated into the matrix, to a temperature above its sublimation temperature, resulting in the formation of pores in the matrix that allows floating. The authors studied the influence of the polyethylene oxide and camphor amount in the formulation, concluding that polyethylene oxide influences the time of the extended release, as well as the swelling and eroding properties. Formulations with over 40 mg of camphor had no floating lag time and floated for at least 24 h. Camphor did not significantly affect the metformin release profile. The pharmacokinetic studies, undertaken in mini pigs, showed enhanced bioavailability with the floating gastroretentive tablet compared to the commercial product (glucophase XR).

In 2006, Losi et al. introduced a novel flexible drug delivery system platform, based on modular technology, which consists of assembled drug release modules. It is a non-effervescent floating system (Losi et al. 2006). Each module consists of a cylindrical tablet with a cupola-like geometry, having one concave and one convex base. The modular technology, called Dome Matrix®, allows the assemblage of two or more modules in two different conformations: the "piled configuration", in which the convex base of one module is stacked in to the concave base of another module, and the "void configuration", obtained by interlocking the concave bases of two modules. This latter configuration is characterized by the presence of an empty chamber between the modules that confers to the assembled system the capacity of floatation. Strusi et al. (2008) confirmed, in a γ-scintigraphy study in healthy human volunteers that this system is capable of reaching up to 5 h of gastric residence time in humans. The assembled system is very flexible; moreover, the shape of the module and its position in the assembled system can affect the floating behavior and the drug release rate (Hascicek et al., 2011).

The Dome Matrix® system was also formulated with four units that combine both "void" and "piled" configurations, giving rise to a four module assembled delivery system for a multi-kinetic and site-specific release of artesunate and clindamycin for the treatment of malaria (Strusi et al., 2010). A bioavailability study, performed in dogs, showed that the clindamycin prolonged release modules could maintain a significant plasma level up to 8 h,

increasing the extent of bioavailability and possibly reducing the dose frequency.

A combination of floating and bioadhesive properties is also commonly used. Abduljabbar (2016) developed ranitidine HCl gastroretentive floating-bioadhesive tablets using polymers such as HPMC and carbomer and demonstrated its adequate *in vivo* performance. Similarly, Yusif et al. (2016) used simple direct compression, combining floating and bioadhesive mechanisms, employing hydroxypropylmethylcellulose, sodium carboxymethylcellulose, pectin, and/or carbopol as bioadhesive polymers and sodium bicarbonate as the gas former with quite interesting results.

5.1.5. Magnetic systems

Magnetic systems represent a strategy that is very different from those of all other gastroretentive delivery forms described previously, as they are based on the attraction between two magnets (Fig. 6). These systems are made of two components: the pharmaceutical dosage form itself, which contains a small internal magnet, and an external magnet, a device which is placed under the abdomen, near the stomach (Murphy et al., 2009). Fujimori et al. (1995) have shown an increase in the gastric residence time and bioavailability of acetaminophen when administered in the form of magnetic tablets to beagle dogs with the simultaneous use of an external magnet when compared with magnetic tablets that were not under an external magnetic field. Gröning et al. (1998) performed a similar study in humans, using magnetic acyclovir tablets. Upon peroral administration of the magnetic tablets, the drug plasma concentration was measured in the presence and in the absence of an external magnet located under the stomach, with higher concentrations obtained in its presence. The area under the curve obtained from the plasma concentration values versus time was significantly different between both situations. One of the disadvantages of magnetic systems, when compared to the others, is the requirement for an external device. In order to allow drug release in the appropriate place and to avoid discomfort for the patient, it must be carefully used and precisely located (Dubernet, 2004).

5.2. Multiple unit dosage forms

Multiple unit dosage forms, as already mentioned, have some advantages over single unit dosage forms, namely their ability to avoid the all-or-none effect. This property is particularly important when sustained release systems are concerned, because a system flaw can lead to a toxic dose (Abdul et al., 2010).

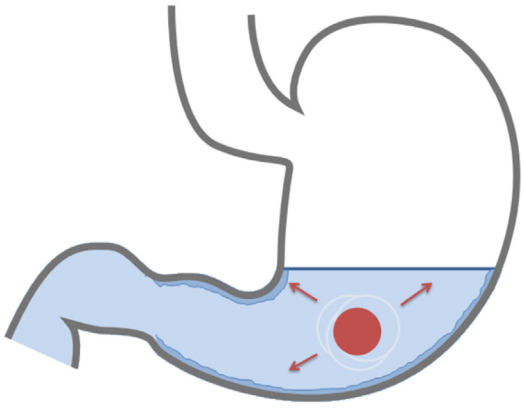

Fig. 6. Mechanism of drug release in stomach content through magnetic systems.

5.2.1. Bioadhesive systems

Bioadhesive microspheres constitute an efficient and relevant drug release system, since they combine the advantages of conventional microspheres with those of mucoadhesive systems. Microparticles and microcapsules are comprised within this group, being either composed entirely of a bioadhesive polymer or simply coated with it. Among their potential uses, controlled drug release and drug targeting stand out (Vasir et al., 2003).

The use of bioadhesive microspheres has been widely studied envisaging its applicability to *Helicobacter pylori* eradication therapy. As such, Liu et al. (2005) developed bioadhesive microspheres containing amoxicillin (Amo-ad-ms). The system has long permanence ability in the gastrointestinal tract, good protection of the drug and a tendency to increase its effectiveness, i.e. desirable properties to consider it a promising system for the treatment of *Helicobacter pylori* infection. Tao et al. (2009) showed an increase in *in vivo* acyclovir bioavailability, when formulated in mucoadhesive microspheres administered to rats. A study performed by Jha et al. (2011) also emphasized the promising features of this system. These authors developed mucoadhesive microspheres containing raloxifene hydrochloride complexed with cyclodextrins. The results demonstrated an increase in the absorption, bioavailability and sustained release of the drug.

Pund et al. (2011) developed a gastrointestinal biphasic system for rifampicin, a first line anti-tubercular drug. The formulation consisted of drug pellets for immediate release, containing the loading dose, and a bio/mucoadhesive drug tablet for prolonged release, containing the maintenance dose. Both phases of the biphasic system were analysed, namely for their mechanical and micrometrical properties of the pellets and the functionality of the bioadhesive system. This functionality was assessed *in vitro* by texture analysis and *in vivo* by γ-scintigraphy. Both assays gave positive results and the formulation was considered promising and worthy of further bioavailability studies in humans.

Sugihara et al. (2012) investigated submicron-sized chitosan-coated liposomes, whose mucoadhesive properties were verified *ex vivo* in rats using confocal laser scanning microscopy. It was found that the formulations tended to penetrate into the mucosal part of the upper intestine, combining enhanced gastric retention with mucopenetration which made these systems quite interesting for drug delivery.

Hauptstein et al. (2013) developed a mini-tablet mucoadhesive system for rosuvastatin calcium, a drug with approximately 20% oral bioavailability. The aim of the study was to evaluate the potential use of preactivated thiolatedpectin derivative (Pec–Cys–MNA) as a mucoadhesive excipient. For this, the authors compared mini-tablets prepared with the preactivated thiomer, the thiolated intermediate and unmodified pectin in accordance with their mucoadhesive properties, hardness, disintegration behavior, swelling characteristics, and drug release. The results showed improved mucoadhesion, increased water uptake capacity, and sustained release of rosuvastatin calcium over 36 h for the Pec–Cys–MNA system, indicating the great potential of this excipient in the formulation of an effective mucoadhesive delivery system.

Jelvehgari et al. (2014) developed metformin multiple unit bilayered discs using Carbopol 934 P as a mucoadhesive polymer and ethylcelullose as a release control polymer. It was found that this system interacts with the gastrointestinal tract mucus and is retained at the site of action, thereby improving the intimacy of contact of the system with the underlying absorptive membrane. This condition allows for better therapeutic performance of the drug released.

The use of preactivated thiomers was evaluated by Hauptstein et al. (2013), using a preactivated thiomer from pectin chemically modified with L-cysteine for the preparation of gastroretentive mini-tablets. Rosuvastatin calcium was used as the model drug and

a 36 h of sustained release was observed. Neither biodegradability nor Caco-2 cell viability were affected by the use of this polymer, which makes it a promising excipient for the gastric mucoadhesive area.

5.2.2. Floating systems

Multiple unit systems also offer different ways to obtain a longer gastric residence time based on floating mechanisms, such as the use of different swellable polymers and effervescent compounds (Sungthongjeen et al., 2006; Amrutkar et al., 2012).

As expected, in multiple unit systems, different production variables such as the production method, the type, and the ratio of excipients lead to different floating properties. Goole et al. (2007) demonstrated that the composition and manufacturing parameters (e.g. compression force and diameter) of mini-tablets affect the floating and levodopa release properties. Sungthongjeen et al. (2006) reached the same conclusion by testing different compositions of a multiple-unit floating delivery system based on the gas formation technique. This system consisted of a drug-containing core pellet, coated with a primary effervescent layer and with a second gas-entrapped polymeric membrane. Only systems in which the polymer membrane was composed of Eudragit® RL 30D had the ability to float, and their floatation was dependent on the amount of effervescent agent and polymer membrane. A similar study was conducted by Amrutkar et al. (2012) using zolpidem tartarate-containing core pellets. The system floated completely within 5 min, maintaining its floating ability for at least 10 h.

Hollow microspheres, also known as microballoons, are a floating multiple system developed by Kawashima et al. (1992), composed of a hollow center and an external polymer layer in which the drug is loaded. This system is most frequently obtained by solvent evaporation or solvent evaporation/diffusion methods (Kawashima et al., 1992). Sato et al. (2003) used the solvent diffusion/evaporation technique to prepare microballoons containing riboflavin, in order to evaluate its usefulness in sustained release, when compared to riboflavin powder and non-floating microspheres. Upon administration to three healthy volunteers, drug pharmacokinetic was assessed through the analysis of urinary excretion. These authors concluded that, under fed conditions, riboflavin excretion was sustained with the microballoons when compared to others pharmaceutical forms.

Similarly Dube et al. (2014) developed baclofen microballoons using hydropropylmethylcellulose K4M and ethylcellulose to manufacture a floating oral controlled drug delivery system. X-rays showed that effective gastric retention was obtained with barium sulfate labeled floating microspheres for no less than 10 h.

Streubel et al. (2002) developed a delivery system, using the solvent evaporation method, made of the drug (verapamil HCl), a highly porous carrier material (hydrophobic polypropylene foam powder), and a polymer (Eudragit RS, ethylcellulose or polymethyl methacrylate). All the produced microparticles had an irregular shape and were highly porous, showing good encapsulation efficiency and good *in vitro* floating properties. These authors observed that the drug was distributed into microparticles in the dissolved and amorphous state and the release profile was dependent on the type and amount of polymer used in the formulation.

An additional strategy to increase gastric residence time refers to the formulation of floating porous beads in which polymers, such as sodium alginate or sterculia gum, are used (Singh et al., 2010). These are the polymers of choice given their biocompatibility and inotropic gelation ability under normal conditions. Stops et al. (2008) developed calcium alginate beads by extruding a sodium alginate solution drop wise into a calcium chloride solution. The obtained beads were then freeze-dried and filled with riboflavin as the active substance and citric acid to promote the extension of drug release. *In vitro* assays showed that this formulation needed some improvements in order to allow for a single daily intake (Stops et al., 2008). Malakar et al. (2011) developed a paraffin-entrapped multiple-unit alginate-based floating system containing cloxacillin, prepared through emulsification-gelation. The optimized system showed good encapsulation efficiency and floating ability with a reduced lag phase, allowing for sustained cloxacillin release, i.e. longer than 8 h, in simulated gastric fluid. Moreover, the production method was shown to be simple, economic, reproducible, easy, and controllable.

Another possible approach for multiple unit systems is the use of an air compartment that confers the ability to float. These systems are appreciated since they provide immediate floatation; however, their production is difficult. Iannuccelli et al. (1998a, 1998b) have worked in this field by developing a simple technology for the production of these systems. They have obtained a system with floating properties in artificial gastric fluids, as well as in human gastric fluids.

Li et al. (2014) designed multi-layered gastro-floating pellets of dipyridamole in order to obtain sustained drug release in the stomach. The gastro-floating pellets consisted of a porous matrix core, a drug loaded layer (dipyridamole and hydroxypropylmethylcellulose), a sub-coating layer (hydroxypropylmethylcellulose), and a retarding layer (Eudragit® NE 30D). The buoyancy was due to the air entrapped in the matrix cores. The gastro-floating pellets were optimized by orthogonal array design after an evaluation of the porous matrix cores. Optimized gastro-floating pellets exhibited floating proprieties for at least 12 h without a lag time and sustained drug release for the same period of time. A pharmacokinetic study of the optimized gastro-floating pellet was performed in beagle dogs and revealed a sustained gastric retention and drug release, resulting in enhanced drug bioavailability. These results indicate that gastro-floating pellets are a promising approach for gastroretentive systems.

The works of Hao et al. (2014), Arya and Pathak (2014), and Zhang et al. (2012) demonstrated the efficacy of this kind of system for the delivery of metronidazole, with a gastric retention period greater than to 8 h for curcumin and a 10-fold increase in drug bioavailability, while ofloxacin demonstrated gastric retention in rabbits for longer than 6 h and a 13% increase in drug relative bioavailability.

5.2.3. High-density systems

High-density systems use density as a strategy to produce a retention mechanism. Such systems have a higher density than that of gastric fluids (i.e. ~1.004 g/cm^3) (Bardonnet et al., 2006) that allows the system to settle down to the bottom of the stomach, where they remain located.

The first evidence for high-density systems arose from a study by Hoelzer who, in 1930, that tested the effect of different material densities in the gastrointestinal transit time of several animal species (Clarke et al., 1995). The densities tested ranged from 0.9 to 10.5 g/cm^3. The resulting data pointed towards a relatively proportional relation between density and gastrointestinal transit time. Denser materials showed a slower transit time through the gastrointestinal tract. Since then, several studies were conducted in order to understand this relation and to determine the most appropriate density values for these systems. Clarke et al. (1995) showed that critical density values, required for an increase in gastric residence time, range from 2.4 to 2.8 g/cm^3.

It has been reported that small high-density pellets are able to resist gastric peristaltic movements due to their retention in the antrum rugae or folds, increasing the gastrointestinal tract time from 5.8 up to 25 h (Garg and Gupta, 2008). This gastrointestinal tract time extension depends greatly on pellet density, but not as much on pellet size. In spite of the advantages, these systems lack

both animal and clinical studies, and it is technically difficult to produce high-density pellets containing significant amounts of drug (Moës, 2003). Barium sulfate, zinc oxide, iron powder and titanium dioxide could be used as excipients due to their high density (Devereux et al., 1990).

The work of Hao et al. (2014) focused on developing sinking magnetic microparticles using the electrospray method and Fe_3O_4 nanoparticles. The prepared particles displayed strong magnetism and a density of 3.52 g/cm^3 and were retained in the stomach for over 8 h without the use of an external magnet. When this device was externally applied, the period increased even further.

5.3. Combination strategies for gastroretention systems

In order to obtain a more significant gastric residence time and different release profiles, several authors have combined distinct gastroretention strategies, as well as gastroretentive systems and modified release strategies such as osmotic pumps.

To be actually effective, floating systems require the presence of a minimum amount of gastric fluid in the stomach; otherwise, their floatation properties will be compromised. This limitation may be overcome by using a combination of a floating system with other gastroretentive approaches. For example, Arza et al. (2009) formulated tablets with both swellable and floatable properties. Their work aimed to improve ciprofloxacin HCl release in the stomach and duodenum. The *in vivo* results showed that there was, in fact, an increase in ciprofloxacin HCl mean gastric residence time. In turn, *in vitro* studies performed by Chavanpatil et al. (2006) showed a possible association between floatable, swellable and bioadhesive properties in a single formulation, using ofloxacin as a model drug. Chen et al. (2010), aiming to develop an optimal gastroretentive system for losartan administration, formulated also tablets with swellable and floatable properties. Upon optimization, clinical assays showed that the formulation was floatable for more than 16 h in an artificial gastric fluid and swelled to 2 cm in diameter in a period of 3 h. The authors reported a mean bioavailability of 164%, when compared to the commercial immediate release formulation (Cozaar®). Liu et al. (2011) developed microspheres in a synergistic system that combined floatable and bioadhesive properties. This system showed strong bioadhesion and good floatable abilities for both *in vitro* and *in vitro* studies. As far as pharmacokinetic studies are concerned, elimination half-life time was shown to be increased, while the elimination rate was found to be decreased (Liu et al., 2011).

Zou et al. (2007) developed and evaluated a multifunctional drug release system that combines floatable properties with pulsatile release, known as a floating-pulsatile system. It consists of a non-permeable polymeric capsule body with erodible plugs filled with drug tablets and a buoyant filler material. The *in vitro* and *in vivo* results demonstrated immediate floating and a release profile comprising a lag phase without drug release, followed by pulsatile release. Guan et al. (2010) developed a novel high-density gastric-resident osmotic pump tablet using iron powder. This excipient increases the density of the system and promotes gas formation by reacting with gastric fluids, which favors drug release by osmotic pressure. The results demonstrated that the optimized formulation allowed for a zero-order drug release rate and a gastric residence time of 7 h in beagle dogs, which are promising results that set the ground for studies in humans.

Sankar and Jain (2013) combined mechanisms of swelling and mucoadhesion for acyclovir sustained delivery using polymers such as carbomers, polyethylene oxide, and sodium alginate. The authors suggested that this formulation would improve both patient compliance and the efficacy of therapy based on prolonged retention in the upper gastrointestinal tract, sustained *in vitro* drug release, prolonged *in vivo* absorption and superior relative acyclovir bioavailability when compared to the immediate release formulation.

The same drug was studied by Svirskis et al. (2014) while preparing mucoadhesive floating hollow chitosan beads using a solvent-free ionotropic gelation method. This system also enhanced the relative acyclovir bioavailability and allowed for a reduced frequency of administration.

Ngwuluka et al. (2013) designed a triple mechanism inter-polyectrolyte complex matrix for levodopa site-specific zero order delivery, comprising high density, swelling, and bioadhesiveness strategies. The results showed that this system has the potential to improve the absorption and bioavailability of narrow absorption window drugs with constant and sustained drug delivery rates.

6. Gastroretentive dosage forms – the current options

As shown in this review, there are different types and subtypes of gastroretentive dosage forms. This variety is due to the combination of different strategies and technologies. Each type of gastroretentive delivery form has distinct features which are reflected in its advantages and disadvantages. The main disadvantages of each type of gastroretentive system are summarized in Table 3 (Pawar et al., 2012).

The floating and bioadhesive systems are the most gastroretentive approaches explored by the pharmaceutical industry, and therefore have the biggest market share. In Table 4, we compile the

Table 3
Main drawbacks of the five types of gastroretentive systems (adapted from Pawar et al., 2012).

Gastroretentive System	Drawbacks
Expandable systems	• Maintenance problems due to the use of hydrolyzable and biodegradable polymers; • Difficult to hold mechanical shape; • Difficult to manufacture with high costs.
High density systems	• Not allow the incorporation of large amounts of drug due to technical limitations; • To date, none is commercially available.
Magnetic systems	• May be uncomfortable, compromising patient compliance.
Bio/Mucoadhesiv systems	• Efficiency can be reduced by constant turnover of the mucus; • Ability to link to other epithelial mucosa as the esophagus.
Floating systems	• Highly dependent on the presence of food and gastric contents; • Need for high levels of gastric fluid in the stomach; • Lag time until reaching fluctuation.

Table 4
Some gastroretentive systems available on the market (adapted from Pawar et al., 2012).

Trade Made	Active ingrediente(s)	Gastroretentive technology	Pharmaceutical Company
Xifaxan®	Rifaximin	Bioadhesive Tablets	Lupin, India
Cytotec®	Misoprostol	Bilayer floating capsule	Pfizer, UK
Baclofen GRS®	Baclofen	Coated multi-layer floating and swelling system	Sun Pharma, India
Conviron®	Ferrous Sulphate	Colloidal gel forming floating system	Ranbaxy, India
Zanocin OD®	Ofloxacin	Effervescent floating system	Ranbaxy, India
Riomet OD®	Metformine Hydrochloride	Effervescent floating system	Ranbaxy, India
Cifran OD®	Cifrofloxacin	Effervescent floating system	Ranbaxy, India
Liquid Gaviscon®	Alginic acid and sodium bicarbonate	Effervescent floating liquid alginate preparation	Reckitt Benckiser Healthcare, UK
Prazopress XL	Prazosin hydrochloride	Effervescent and swelling based floating system	Sun Pharma, Japan
Cipro XR	Ciprofloxacin hydrochloride and betaine	Erodible matrix based system	Bayer, USA
Accordion Pill™	–	Expandable system (unfolding)	Intec Pharma
Topalkan®	Aluminum magnesium	Floating liquid alginate	Pierre Fabre Medicament, France
Almagate FlatCoat®	Aluminium-magnesium antacid	Floating liquid form	Pierre Fabre Medicament, France
Madopar HBS®	Levodopa and benserzide	Floating system – controlled release capsule	Roche, UK
Prolopa HBS®	Levodopa and benserzide hydrochloride	Floating system – controlled release capsule	Roche, UK
Valrelease®	Diazepam	Floating system – controlled release capsule	Roche, UK
Inon Ace Tables®	Siméthicone	Foam based floating system	Sato Pharma, Japan
Coreg CR®	Carvedilol	Gastroretention with osmotic system	GlaxoSmithKline, UK
Metformin Hydrochloride	Metformine hydrochloride	Minextab Floating® – floating and swelling system	Galanix, France
Cafeclor LP	Cefaclor	Minextab Floating® – floating and swelling system	Galanix, France
Tramadol LP	Tramadol	Minextab Floating® – floating and swelling system	Galanix, France
Gabapentin GR	Gabapentin	Polymer based swelling technology: AcuForm™	Depomed, USA
proQuin XR	Ciprofloxacin	Polymer based swelling technology: AcuForm™	Depomed, USA
Glumetza	Metformine hydrochloride	Polymer based swelling technology: AcuForm™	Depomed, USA
Metformin GR™	Metformine hydrochloride	Polymer based swelling technology: AcuForm™	Depomed, USA

gastroretentive delivery forms available on the market identified by its trade name, active ingredient(s), adopted gastroretentive technology, and company of manufacture (Pawar et al., 2012).

7. Conclusion

Gastroretentive dosage forms are systems that remain in the upper gastrointestinal tract for a prolonged period of time and allow for continuous and sustained drug release in the stomach and upper small intestine. Thus, they are valuable for narrow absorption window drug targeting or when drugs have a local effect in these organs. The development of such systems demands deep knowledge of the anatomy and physiology of the digestive apparatus, and the formulation of systems that remain effective in the stomach for a long period of time in the fasting state is still a challenge. In this field, floating systems seem to be those with the best perspectives, and there are an increasing number of studies that combine them with other gastroretentive strategies in order to overcome their limitations and to allow for an even longer gastric residence time. Gastroretentive delivery forms are promising drug delivery strategies with positive results in studies with humans for the delivery of drugs that present a narrow absorption window in the upper gastrointestinal tract and a short half-life.

Conflict of interest

The authors confirm that the contents of this review have generated no conflicts of interest.

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