Overview on gastroretentive drug delivery systems for improving drug bioavailability

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Abstract: During the last decades several efforts have been made in order to improve drug's bioavailability after oral administration. Gastroretentive drug delivery systems are a good example and they emerged to enhance the bioavailability and effectiveness of drugs with a narrow absorption window in the upper gastrointestinal tract and/or local activity in the stomach and duodenum. Several strategies were 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 the gastric retention time and the mechanism of action of gastroretentive systems, as well as their classification into single and multiple units systems.

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COVER LETTER

Oporto, 28th May 2014

To the Editor
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Dear Sir:

The topic of gastric retention is a very challenging, yet very interesting one, in the field of oral controlled drug delivery.

The past two years have shown an increased interest on publication of research in this specific area with the rise of new technologies and pharmaceutical systems that have proved to be effective mainly in increasing the bioavailability of the drugs that present a narrow upper GI tract window of absorption.

This paper aims to review the recent developments in this area, classifying the new systems into categories and evaluating their *in vitro* and *in vivo* performance. The authors are experienced either in the field of gastric retention and controlled drug delivery and have themselves developed gastroretentive systems that they include in this paper.

I also hereby declare that all authors have read and approved this version of the article, and no part of this paper has been published nor is it submitted for publication elsewhere and will not be submitted elsewhere.

Best regards

Pedro Barata, PhD, PharmD
Auxiliary Professor at Faculdade de Ciências da Saúde – Universidade Fernando Pessoa, Porto - Portugal

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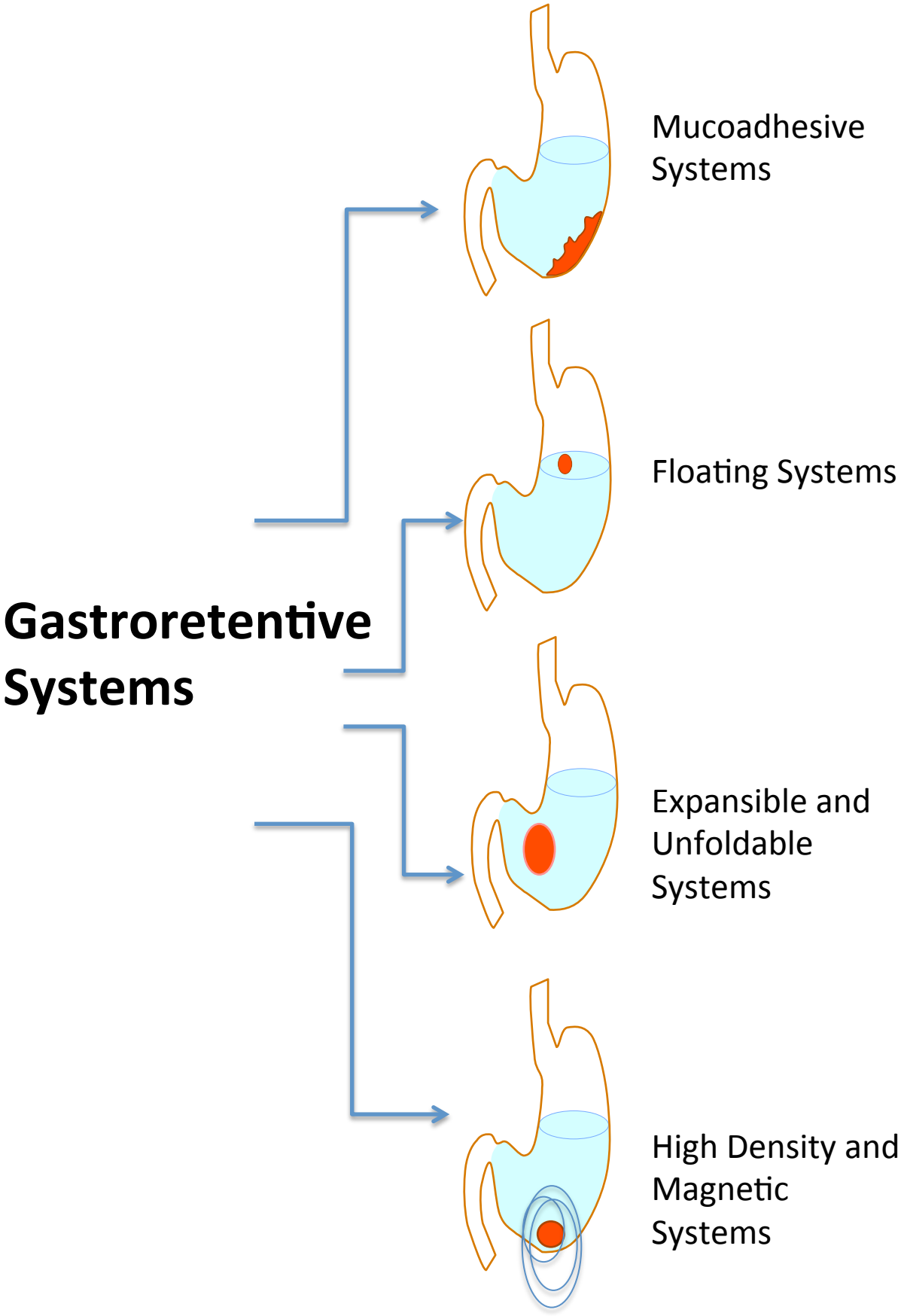

Recent overview on gastroretentive drug delivery systems for improving drugs bioavailability

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Abstract

During the last decades several efforts have been made in order to improve drug's bioavailability after oral administration. Gastroretentive drug delivery systems are a good example and they emerged to enhance the bioavailability and effectiveness of drugs with a narrow absorption window in the upper gastrointestinal tract and/or local activity in the stomach and duodenum. Several strategies were 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 the gastric retention time and the mechanism of action of gastroretentive systems, as well as their classification into single and multiple units systems.

Keywords: Narrow absorption window; Controlled drug release; Gastroretentive system; Gastric retention time; Multiple unit dosage form

1. Introduction

The oral administration route has always assumed a role of prominence in therapy due to the well established advantages. Several factors make this route the preferable by the patients. Less expensive, easy transport and storage, the flexibility of formulation, the readiness of administration are examples (Pinto, 2010).

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

In order to overcome these adversities, technological researchers have developed pharmaceutical systems that control drug release, which are already available in the market. However, conventional systems are not enough to overcome all the difficulties imposed by the GIT. 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 the gastric emptying; therefore, cannot be released at the colon level where they stay at the final period of their release time. Therefore, the incomplete release of drugs and the concomitant reduction of the dose effectiveness are a consequence of the incapacity of the conventional systems to be retained at the stomach level (Kagan and Hoffman, 2008).

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

Several strategies have been studied to formulate successful controlled drug delivery systems that increase the gastric residence time (GRT). These include: bioadhesive or

mucoadhesive systems; expandable systems; high-density systems; floating systems; superporous hydrogels and magnetic systems (Garg and Gupta, 2008). This review aims to evidence 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 into single and multiple units 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 of development GR systems such as an upper GI narrow absorption window, short drug half-life time, drug instability in the GIT environment, local activity at the upper part of the GIT, poor solubility at alkaline pH (Chavanpatil et al., 2006, Gröning et al., 2007, Jiménez-Martínez et al., 2008, Rajinikanth et al., 2007).

[Please insert Table 1 about here]

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

The drugs that can benefit from GR systems belong to different therapeutically groups and are effective in various pathologies, reflecting their therapeutic diversity. Some examples of drugs formulated in GR systems are: amoxicillin, antibiotic used in *Helicobacter pylori* eradication; furosemide for the treatment of congestive heart failure, chronic renal failure and liver cirrhosis; levodopa, beneficial in the treatment of Parkinson disease. A wide range of pathologies can, therefore, find in these systems a

key for a better therapeutic effectiveness with less side-effects and 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 affects drug absorption, particularly in the case of drugs with absorption window in the stomach. The absorption area is limited between the stomach and duodenum, and the residence time in this area limit the absorption of drugs. Therefore, the longer the drug stays in contact with the absorbing membrane, the rate and extent of absorption will improve. However, the time in the upper part of the GIT is short due to the fast gastric empting time that generally lasts about 2 to 3 hours (Hoffman et al., 2004, Singh and Kim, 2000).

The gastric retention time is, therefore, an important parameter in drug absorption. Several methods were used to determine the GRT, 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 in a specific site (Yuen, 2010).

Various factors influence the 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.

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 opposite 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 higher retention time and a decrease in the effect of the presence of food (Sauzet et al., 2009). Also an increase in the density of dosage form could be

responsible for a raise in GRT. In order to become this effect significant it is required a density of about 2.5 g/cm^3 (Clarke et al., 1993).

3.1.2. Size of dosage form

The size of the dosage form is a characteristic that can be changed in order to increase the GRT for non-floating systems. For non-disintegrating systems, it is logical that the 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, increasing therefore the GRT that will lasts 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 GRT include those that can be controlled by the patient, such as: nature, caloric content and frequency of food ingestion, concomitant ingestion of drugs that influence the 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 and they result from the presence or absence of food (Klausner et al., 2003b). Gastric motility in fasten condition is originated in the stomach and it is known as interdigestive myoelectric motor complex (IMMC) that presents a cyclic behavior of four phases according to the intensity and frequency between gastric contractile events. Food ingestion disrupts this cycle determining an 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, occurring an increase of drug absorption in the upper digestive system (Talukder and Fassihi, 2004).

The GRT is also affected by posture and it varies in opposite directions for floating and non-floating dosage forms (Garg and Gupta, 2008). 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 near to the pylorus. In the supine position, non-floating are the systems that have a raise on gastric retention time (Garg and Gupta, 2008). This issue is one of the most frequent criticisms to gastric retention in the studies performed in animals.

3.2.1. 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 determine significant changes in pharmacokinetics profile which may lead to different responses to drugs. For instance, differences in the GIT such as pH, gastric motility and gastric emptying time affect oral drug delivery (Freire et al., 2011, Firth and Prather, 2002).

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

Finally, the presence of illness is another factor to take into account since pathologic conditions such as *diabetes mellitus* and Parkinson's disease can also influence the GRT (Triantafyllou et al., 2007, Krygowska-Wajs et al., 2009). In the case of longstanding type I and type II diabetes, there is a decrease in gastric emptying around 30 to 50 % (Triantafyllou et al., 2007). As for 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 GR systems reported in the literature can be classified in two classes. The first class comprises tablets and capsules that are composed by a single unit, therefore known as single unit dosage forms (SUDFs), i.e. non-divided formulation. The second class refers to formulations composed of more than one unit and is known as multiple unit dosage forms (MUDFs), among which are included granules, pellets and mini-tablets (Ishida et al., 2008).

SUDFs are a uniform system, which comprises solid matrix systems and capsules. The former refer to a monolithic system in which the drug is dispersed or dissolved and the drug release is modulated through incorporation of suitable filler (matrix system), or by coating with polymer film(s) (reservoir or multi-layered matrix system). The use of capsules as SUDF controlled release systems requires the clever use of suitable excipients (Efentakis et al., 2000).

MUDFs consist of small single and individual units (e.g. pellets, granules and mini-tablets), that may or not be coated, combining into a unique final pharmaceutical form upon filling or compression. A single unit filling is generally accomplished through their encapsulation in hard gelatine 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). Besides, these systems have many additional advantages, such as lower toxicity risk (due to a lower risk of dose dumping), lower dependency on gastric emptying (which leads to a lesser degree of inter and intra-individual variability), avoidance of all-or-none effect (failure of some individual units doesn't compromise the entire system) and higher dispersion on the digestive tract (which lowers the risk of local high concentrations, minimizing local irritation and allowing for a greater drug protection) (De Brabander et al., 2000, Dey et al., 2008).

Among MUDFs, mini-tablets are those that best illustrate these advantages, due to their physical properties and production process. The tablet technique leads to solids with

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 (**Figure 1**). This means that it can induce an initially rapid release, which might work as a loading dose, followed by a sustained drug release, that allows for the maintenance of drug plasmatic levels that are needed to achieve therapeutic effect and 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 a fast drug release, and sustained or delayed single release units (Efentakis et al., 2000).

[Please insert Figure 1 about here]

Bandari and collaborators (2010) developed a floating biphasic gastroretentive system for fenoverine administration. The delivery system consisted of a loading-dose tablet and a 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 reflect its biphasic release behaviour.

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

5. Gastroretentive Delivery Forms (GRDFs)

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

5.1. Single unit systems

5.1.1. Expandable systems

As suggested by its own name, expandable system reaches a higher GRT through the increase in its volume and/or shape. Interestingly, these systems were initially designed for veterinary use and it was 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 swallow or patients won't be willing to take them. The second one is the size that the system acquires after reaching the stomach, which must be higher than that of the pyloric sphincter. Finally, it must be assured that, after the programmed drug release, the remaining structure decreased its size that allows for its elimination (**Figure 2**) (Klausner et al., 2003b).

[Please insert Figure 2 about here]

The expandable systems can stay in the gastric compartment by two strategies, which consist in swelling and unfolding systems that allow a volume and shape modification.

Swellable systems are retained in stomach due to their mechanical properties. The size increase observed in the swelling systems after contact with the gastric fluids usually occurs by osmosis. 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. The water absorption leads to numerous modifications in the polymer, which provides the drug release, including: polymer swelling and plasticization (lowering of the glass transition temperature), diffusion coefficient increase and erosion (due to polymer disentanglement) (Siepmann and Peppas, 2001). Both water absorption and the downstream modifications occur in a slow rate that allows drug release for some hours (Laity and Cameron, 2010). The events that take place highlight the importance of the hydrophilic polymer choice in these systems. According to Chen and collaborators (Chen et al., 2000), hydrogels must possess some important characteristics in order to assure gastric retention, such as: fast swelling; swelling to a large size; and high mechanical strength to hold out gastric movements. The polymers that combine these three characteristics are designated by superporous hydrogels (Chen et al., 2000) and, according to some authors, they are enough distinct from the conventional swelling systems to be classified separately (Chavda and Patel, 2010). Research of new hydrogels has been growing and it has already resulted in the development of novel polymers, which include the intelligent polymers and starch copolymers. In response to certain stimulus including temperature, pH, solvent composition and electric fields, intelligent polymers are able to change its swelling behavior and fluid release characteristics (Fu and Soboyejo, 2010). Starch copolymers, like tapioca graft copolymers, seem to behave as inert matrix that allows a controlled drug release by diffusion (Casas et al., 2010).

The unfoldable systems are commonly composed of biodegradable polymers that are folded and encapsulated in a carrier that is degraded at the stomach level. The carrier degradation allows the release of drug from pharmaceutical system that 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 and collaborators (2006) tested this system in humans and it shown gastric retention capacity, without the need of a caloric meal, and the ability to increase

the bioavailability of riboflavin (i.e. a narrow absorption window drug) by saturated transport. Other 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 mean absorption time significant higher for levodopa loaded in the 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 *in vitro* unfoldable system for cinnarizine, an antihistamine with a narrow absorption window. For this propose, they prepared drug loaded polymeric films containing different amount of stearic acid that were folded into hard gelatin capsules. Drug release studies revealed an immediate release of drug in the first hour, followed by a gradual release during a 12 hours period. The amount of stearic acid was crucial for this release pattern, acting as a sustained delivery agent. Evaluation of floating and mechanical properties showed the gastroretentive potential of the system, making it suitable for *in vivo* studies.

Dey and collaborators (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 delivered rapidly the dose of atorvastatin, a member of lipid-lowering agent, and sustained the atenolol release, demonstrating a faster absorption and an increased oral bioavailabilty of atorvastatin, as well an achievement of a sustained therapeutic blood levels of atenolol.

El Zahaby and colleagues (2014) developed a size increasing levofloxacin 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 tailor release control of levofloxacin, obtaining a promising system for eradication of *Helicobacter pylori*.

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

5.1.2. Superporous hydrogels

As previously mentioned, the superporous hydrogels are a type of expandable systems that are often classified as a group of its own (Nayak et al., 2010). Superporous hydrogels are composed of cross-linked hydrophilic polymers, with numerous pores connected together to form open channel structures. This structure allows superporous hydrogels to swell immediately upon contact with water – irrespective of their size – and to absorb considerable quantities of water reaching a large size (i.e. 10–1000 times of their original weight or volume). The water uptake is provided by capillarity (Omidian et al., 2005). The fast swelling, that occurs in less than 20 min, helps fight premature gastric emptying by housekeeper wave, increasing the gastric residence time (Klausner et al., 2003b). A certain amount of mechanical strength is also required to make these systems resistant to gastric contractions.

According to their properties, superporous hydrogels are classified in three different generations: (1) the first generation, also known as conventional hydrogels, characterized by fast swelling, high swelling ratio and weak mechanical properties; (2) the second generation, hydrogels composites, that features fast swelling, medium swelling ratio and improved mechanical properties and (3) the third generation, named hybrids, with a very high mechanical strength, which make them useful in the development of gastrointestinal devices (Omidian et al., 2005). Hybrids hydrogels are prepared by adding a hybrid agent (crosslinked hydrophilic polymers) after superporous hydrogels is formed. Omidian et al. (2006) prepared a hybrid superporous hydrogels of polyacrylamide and sodium alginate able stretched up to 2 to 3 times of its original length, after partial or complete swollen. This formulation was also capable of withstanding several cycles of stretching/unloading, suggesting its potential in pharmaceutical applications.

Recently, El-Said and collaborators (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 of baclofen bioavailability and effectiveness of the designed system for baclofen sustained release.

5.1.3 Bio/Mucoadhesive systems

Since first introduced by Park and Robinson in 1984, 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 GRT, mucoadhesive systems increase the intimacy and duration of drug contact with biological membranes. Bioadhesive polymers may be natural or synthetic and are defined by their ability to adhere to biological tissues. They can be divided into citoadhesive or mucoadhesive, depending on the binding established between the polymer and the epithelial surface. The citoadhesive 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 the cells (Vasir et al., 2003). Some polymers show both of these properties. Examples of polymers commonly used for bioahesion 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, summarize in **Table 2**, based in the type of molecular link that is established between the macromolecules (polymer) and the mucin proteins have been put forward to explain the mucoadhesion phenomena (Vasir et al., 2003).

[Please insert Table 2 about here]

The bioadhesion systems present some important advantages. The adhesion to the epithelial surface will not only lead to the proper location and mobilization of the drug but also favour a closest 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 to the stomach turnover, the constant renewal of the mucus layer, and to the high stomach hydration

that decreases the bioadhesion of the polymers (Bardonnet et al., 2006). Another factor to take into account is the risk of adhesion to the oesophagus that may lead to collateral lesions (Talukder and Fassihi, 2004).

Zate and colleagues (2011) developed a gastroretentive mucoadhesive tablet for sustained venlafaxine hydrochloride release using Carbopol 971P as mucoadhesive agent and Eudragit RS-PO and ethyl cellulose as controlled release agents. The authors concluded that an increase of Carbopol 971P concentration increases the adhesion time and higher ethyl cellulose levels decreased the 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 superior of 10 h in a 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 the systems, the bioavailability studies, performed in rabbits, demonstrated that drug release was controlled for over 12 h, enhancing the oral bioavailability.

5.1.4. Floating systems

From all the gastroretentive systems described in the literature, the floating systems are the most prominent (Choi et al., 2002). Such systems are characterized by the capacity of floating in and over the gastric content due to their low density, below 1.004 g/cm^3 (Whitehead et al., 1998). This characteristic allows for the slow and controlled release of the drug by the system during its GRT which affect the gastric content empting rate (Jiménez-Martínez et al., 2008). After the drug release, the residual system is emptied from the stomach.

These systems can remain buoyant in the stomach by two distinctly technologies, essentially differentiated by gas production, which divide them into: non gas-generating or non-effervescent systems and gas-generating or effervescent systems.

The non-effervescent approach relies in two ways by which the systems float. In a first one, high swelling and gelling capacity polymers are used, such as highly swellable cellulose type of hydrocolloid, polysaccharides, polycarbonate, polyacrylate, polymethacrylate and polystyrene (Singh and Kim, 2000). Upon reaching the gastric fluid, these systems swell by hydration forming a gelling layer at the device surface, which is partially responsible for the controlled drug release. The entrapped air in the polymer at its expansion (i.e. swollen matrix) provides its floating capacity (Singh and Kim, 2000). Another method is based on the formulation incorporating a gas chamber of specific gravity that allows the floating of the system (Harrigan, 1977).

In the slightly effervescent systems, CO_2 production may also occur by two distinct manners. In the first one, gas production is due to the reaction of carbonates and bicarbonates present in the formulation with the gastric acid or co-formulated acids (e.g. citric or tartaric). Gas formed 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, and the concomitant CO_2 production, 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 of the drug release rates. The same authors reported that in a second stage of the drug release process, the gas production could favor the drug delivery.

In the second mechanism, the gas production requires the presence of a volatile organic solvent, introduced in a chamber, which volatilizes at the body temperature allowing the system floating (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 a controlled release of the drug (Baki et al., 2011, Sriamornsak et al., 2007). The controlled drug release is again due to the formation of a viscous hydrated layer around the tablet that acts as a barrier for the 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. In fact, it is known that water soluble drugs are primarily released by diffusion contrarily to drugs with low aqueous solubility, in which the erosion mechanism is predominant (Hodsdon et al., 1995).

The exploitation of these systems is wide and allows the development of several floating systems that combine different variables such as: effervescence, geometric shape, size, area/volume ratio, coating and production technique. Different formulation strategies arise from this intersection either in MUDFs or in SUDFs.

The Hydrodynamically Balanced Systems (HBS^{TM}) were firstly developed by Seth and Tossounian (1984), and became a highly recognized floating system. They are composed by one or more gel-forming hydrophilic polymers in which the drug is embedded, and the resultant mixture is usually encapsulated in a gelatin capsule. The capsule degradation occurs in contact with the gastric fluid and it is followed by the polymer hydration with the formation of a surrounding layer that allows the controlled release by diffusion and erosion (Sheth and Tossounian, 1984). These systems display an increase in both the GRT and the amount of the drug that reaches the absorption site in a soluble form (Garg and Gupta, 2008).

Other experiments have been performed to highlight the GRT increase for the single floating systems. Tadros (2010) evaluated, *in vitro* and *in vivo*, the behavior of ciprofloxacin hydrochloride floating tablets. The optimized tablet was selected for determination of the GRT in humans, with residence time of 5.50 ± 0.77 h. Hu *et al.* (2011) have shown that floating tablets of dextromethorphan hydrobromide based on gas forming technique display an *in vivo* slower release profile, when compared with dextromethorphan hydrobromide sustained release tablets, without a decrease in the bioavailability or plasmatic variations of the drug. Therefore, these results demonstrated a sustained release for drugs with a narrow absorption window.

As previously mentioned, the technology used to develop floating systems also deeply influences their behavior and parameters such as the GRT and drug release profile. Sauzet and colleagues (2009) developed a new low density floating system obtained by

wet granulation. The tablets have shown a final porous structure with improved cohesion properties, offering a good alternative to produce sustained drug release, in which the floating capacity is mainly due to the high porosity of the system. Another strategy that can be used is the formulation of bi or multiple layer systems. This strategy 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 is responsible for the floating properties and the other, in which the drug is incorporated, guarantees the controlled release (Ozdemir et al., 2000, Wei et al., 2001). These systems permit, an independent formulation of the drug and excipients, the incorporation of the effervescent agent in any one of the layers and the matrix coating with a water-permeable and CO_2-impermeable polymer (Ozdemir et al., 2000; Wei et al., 2001). In order to improve metformin bioavailability, Oh et al. (2013) formulated floating gastroretentive tablets using camphor as sublimation material. This strategy consists in subjecting camphor, incorporated in the matrix, to a temperature above its sublimation temperature, resulting in the formation of pores in the matrix that allows the tablet to float. In a first approach, the authors studied the influence of the amount of polyethylene oxide and camphor in 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 have no floating lag time and floated for at least 24 h. Camphor did not affect significantly the metformin release profile. The pharmacokinetic studies, undertaken in mini pigs, showed an enhanced bioavailability of the floating gastroretentive tablet compared to the commercial product (glucophase XR).

In 2006, Losi et al. (2006) introduced a novel flexible drug delivery system platform, based on modular technology, which consists of assembled drug release modules. Each module consists in a cylindrical tablet with cupola-shape geometry, having one concave and one convex base. The modular technology, named Dome Matrix®, allows the assemblage of two or more modules in two different conformations: the "piled configuration", in which the convex base of a 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 float (Losi et al., 2006). Strusi et al. (2008) confirmed, by γ-scintigraphy study in

healthy human volunteers, that this system is capable of reach up to 5 h of GRT 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 given rise to a four module assembled delivery system for a multi-kinetics and site-specific release of artesunate and clindamycin for the treatment of malaria (Strusi et al., 2010). 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 possible reducing dose frequency.

An additional approach is the raft-forming systems (Prajapati et al., 2013). These systems consist of a gel-forming solution (e.g. sodium alginate solution) containing carbonates or bicarbonates that form a gel in contact with gastric fluids. This solution form a viscous and cohesive gel once swelled with entrapped CO_2 bubbles produced by the reaction of (bi)carbonates with stomach's acid (Bardonnet et al., 2006). Due to the incorporation of CO_2, raft-forming system have a very low bulk density that enables them to float on the surface of the gastric contents, forming a gel floating layer named raft. These systems can remain intact in the stomach for various hours promoting a sustained release of the drug (Lahoti et al., 2011). Due to the raft, such systems are used to delivery antacids drugs like aluminum hydroxide or calcium carbonate used in gastroesophageal reflux treatment (Hampson et al., 2010).

5.1.5. Magnetic systems

Magnetic systems represent a strategy that is very different from those of all GRDFs described previously, as they are based on the magnetic attraction between two magnets. 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.* (Fujimori et al., 1995) have shown an increase of GRT and bioavailability for acetaminophen, when administered in the form of magnetic tablets to beagle dogs with

a simultaneous use of an external magnet, when compared with magnetic tablets that were not under an external magnetic field. Gröning et al. (1998) made a similar study in humans, using acyclovir magnetic 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 being obtained in its presence. The area under curves obtained from plasma concentration values versus time were significantly different between both situations. One of the disadvantages of magnetic systems, when compared to the others, is the requirement of an external device. In order to allow for the 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 (MUDFs)

MUDFs, as already mentioned, have some advantages over SUDFs, 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).

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 just coated with it. Among their potentialities, controlled drug release and drug targeting stand out (Vasir et al., 2003).

The use of bioadhesive microspheres has been widely studied envisaging its applicability on *Helicobacter pylori* eradication therapy. As such, Liu et al. (2005) developed bioadhesive microspheres containing amoxicillin (Amo-ad-ms). The system has shown long permanence ability in the GIT, a good protection of the drug and a tendency to increase its effectiveness, which has shown it as a promising system to the treatment of *Helicobacter pylori* infection. Tao et al. (2009) shown, *in vivo*, an increase in acyclovir bioavailability, when formulated in mucoadhesive microspheres administered to rats. A recent study performed by Jha and collaborators (2011) has also

emphasized the promising features of this system. These authors developed mucoadhesive microspheres containing raloxifene hydrochloride complexated 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 rafampicin, 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 functionality of the bioadhesive system. This functionality was assessed *in vitro* by texture analysis and *in vivo* by gamma-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 muchoadhesive properties behaviour were ex-vivo verified in rats using confocal laser scanning microscopy. It was found that the formulations tended to penetrate in the mucosal part of the upper intestine combining enhanced gastric retention with mucopenetrations which makes these systems quite interesting for drug delivery.

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

Recently Jelvehgari and colleagues (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 GIT mucus remaining

retained at the site of action and improving the intimacy of contact of the system with the underlying absorptive membrane. This condition allows a better therapeutic performance of the release drug.

The use of preactivated thiomers was evaluated by Haupstein et al. (2013a), using a preactivated thiomer from pectine chemically modified with L-cysteine, for the preparation of gastroretentive minitablets. Rosuvastatin calcium was used as model drug and a 36 h sustained release was determined. Neither biodegradability nor Caco-2 cell viability was affected by the use of this polymer which makes it into a promising excipient for the gastric mucoadhesive area.

5.2.2. Floating systems

Similarly to what happens with single unit floating systems, multiple unit systems also offer a considerable number of different ways to obtain a higher GRT, such as air compartment multiple-unit systems (Iannuccelli et al., 1998a, Iannuccelli et al., 1998b), hollow microspheres (microballoons) (Sato et al., 2003), microparticles based on low-density foam powder (Streubel et al., 2002), beads (Malakar et al., 2011), mini-tablets (Goole et al., 2007), and the use of 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 excipients used and their proportion, lead to different formulations with distinct floating properties. Goole et al. (2007) demonstrated this by producing, through wet granulation followed by compression, levodopa minitablets with different compositions and/or produced with different production parameters. These different conditions have shown significant differences in the drug release profile, depending on their composition and diameter. In turn, Sungthongjeen and collaborators (2006) concluded the same by testing different compositions of a multiple-unit floating drug delivery system based on gas formation technique, composed 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 multiple floating system, developed by Kawashima et al. (1992), which are composed by 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, the drug pharmacokinetics was determined through analysis of its urinary excretion. These authors concluded that, in fed condition, riboflavin excretion was sustained when compared to the other pharmaceutical forms.

Similarly and more recently Dube et al. (2014) developed baclofen microballons using hydropropylmethylcellulose KM4 and ethylcellulose, to manufacture a floating oral controlled drug delivery system. X-rays showed that effective gastric retention was obtained with barium sulphate labelled floating microshperes for no less than 10 hours.

Streubel and collaborators (2002) developed a delivery system, using the solvent evaporation method, made of drug (verapamil HCl), highly porous carrier material (hydrophobic polypropylene foam powder), and polymer (Eudragit RS, ethylcellulose or polymethyl methacrylate). All the produced microparticles had 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 its release profile was dependent on the type and amount of polymer used in the formulation.

Another strategy to increase GRT refers to the formulation of floating, porous beads, in which polymers such as sodium alginate and sterculia gum are used (Singh et al., 2010). These are 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 that promote the extension of drug release. The *in vitro* assays showed

that this formulation needed some improvements in order to allow for a single daily intake (Stops et al., 2008). Recently, Malakar and colleagues (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 a sustained cloxacillin release, longer than 8h, in simulated gastric fluid. Moreover, the production method was shown to be simple, economic, reproducible, easily and controllable.

Another possible approach for multiple unit systems is the one that uses an air compartment that confers them the ability to float. These systems are appreciated in that 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 their production. They have obtained a system with floating properties in artificial gastric fluids, as well as in human gastric fluids.

Recently, Li and colleagues (2014) designed a multi-layered gastro-floating pellets of dipyridamole in order to obtain a 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 lag time and a sustained drug release for the same period of time. The pharmacokinetic study of the optimized GFP was performed in beagle dogs and revealed a sustained gastric retention and drug release, resulting in enhanced drug bioavailability. These results indicate the GFP as a promising approach for the gastroretentive drug delivery systems.

Recently the works of Hao et al. (2014), Arya and Pathak (2014) and Zhang et al. (2012) demonstrated the efficacy of this kind of systems for the delivery of metronidazole, with a gastric retention period superior to 8 hours, curcumin, with a 10 fold drug bioavailability increase, and ofloxacin, with a gastric retention in rabbits superior to 6h and 13% increase in drug relative bioavailability, respectively.

5.2.3. High-density systems

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

The first evidences for high-density systems arose from a study of Hoelzer who, in 1930, tested the effect of different material densities in the gastrointestinal transit time of several animal species including himself (Clarke et al., 1995). The densities tested ranged from 0.9 to 10.5g/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 (Clarke et al., 1995). 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 GRT, ranging 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 GIT time from 5.8 up to 25 h (and Gupta, 2008a). This GIT time extension depends greatly on pellet density, but not as much on pellet size. In spite of these advantages, these systems lack both animal and clinical studies, and it is technically difficult to produce high-density pellets with significant amounts of drug (Moës, 2003). Barium sulphate, zinc oxide, iron powder and titanium dioxide could be used as excipients due to high density (Devereux et al., 1990).

The work of Hao et al. (2014) focused in developing sinking magnetic microparticles using the electrospray method using Fe3O4 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 this period increased even further.

5.2. Combination strategies for gastroretention systems

In order to obtain a more significant GRT and different release profiles, several authors have associated 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 floatable properties will be compromised. This limitation may be overcome by using a combination of a floating system with other gastroretentive approaches. Arza et al. (2009) employed this strategy by formulating 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 GRT. In turn, *in vitro* studies performed by Chavanpatil and collaborators (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 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, with a volume swelling of 2 cm in diameter in a period of 3 h and a mean bioavailability of 164%, when compared to the commercial immediate release formulation (Cozaar®). Liu et al. (2011) developed microspheres in a synergic system that combined floatable and bioadhesive properties. This system has shown strong bioadhesion and good floatable abilities, both *in vitro* and *in vitro*. As far as pharmacokinetic studies are concerned, elimination half-life time was shown to be increased, while elimination rate was shown to be decreased (Liu et al., 2011).

Zou et al. (2007) developed and evaluated a multifunctional drug release system that combines floatable properties with a pulsatile release, known as floating-pulsatile system. It consists of a non-permeable polymeric capsule body with erodible plug filled with the drug tablet and the buoyant material filler. The i*n vitro* and *in vivo* results demonstrated immediate floating and a release profile comprising a lag phase, without drug release, followed by a pulsatile release. Guan and collaborators (2010) developed a novel high-density gastric-resident osmotic pump tablet by using iron powder. This excipient increases the system density and promotes gas formation by reacting with gastric fluids, which favours the drug release by osmotic pressure. The results demonstrated that the optimized formulation allowed for a zero-rate, complete drug

release and a GRT of 7 hours in beagle dogs, which are promising results that set the ground for studies in humans (Guan et al., 2010).

In the late times, the works of Sankar and Jain (2013) combined a mechanism of swelling and mucoadhesion for acyclovir sustained delivery using polymers such as carbomers, polyethylene oxide and sodium alginate. These formulations gave promising results once they has prolonged retention in the upper GIT, sustained in vitro drug release, prolonged in vivo absorption and enhance substantially the acyclovir relative bioavailability when compared to 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 acyclovir relative bioavailability and allowed to reduce frequency of administration.

Ngwuluka et al. (2013) designed a triple mechanism interpolyectrolyte 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 crossing of different strategies and technologies. Each type of GRDFs has distinct features which are reflected in advantages and disadvantages. The main disadvantages of each type of gastroretentive system are summarized in Table 3 (Pawar et al., 2012).

[Please insert Table 3 about here]

The floating and bioadhesive systems are the most developed by the pharmaceutical industry, therefore with biggest market share. In Table 4 we present the gastroretentive

GRDFs available in the market identified by its trade name, active ingredient(s), adopted technology and company (Pawar et al., 2012).

[Please insert Table 4 about here]

7. Conclusion

Gastroretentive dosage forms are systems that remain in the upper GIT for a prolonged period of time and allow for a 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 for a deep knowledge of the digestive apparatus anatomy and physiology, and the formulation of systems that remain effective in the stomach for a long time period in the fast state is still a challenge. In this field, floating systems seem to be the ones with better 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 higher GRT. GRDFs are promising drug delivery strategies with positive results in studies with humans for delivery drugs that present a narrow absorption window in the upper GIT and a short half-life.

CONFLICT OF INTEREST

The authors confirm that this review content has no conflict of interest.

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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)

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.

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/Mucoadhesive 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: Gastroretentive systems available on the market (adapted from Pawar et al., 2012).

Product	Drug	Technology	Pharmaceutical Company
Xifaxan	Rifaximin	Bioadhesive Tablets	Lupin, India
Zanocin OD	Ofloxacin	Effervescent floating system	Ranbaxy, India
Riomet OD	Metformine Hydrochloride		
Cifran OD®	Cifrofloaxacin		
Conviron	Ferrous Sulphate	Colloidal gel forming floating system	Ranbaxy, India
Iron Ace Tables	Siméthicone	Foam based floating system	Sato Pharma, Japan
Gabapentin GR	Gabapentin	Polymer Based Swelling technology: AcuForm™	Depomed, USA
proQuin XR	Ciprofloxacin		
Glumetza	Metformine Hydrochloride		
Metformin GR™	Metformine Hydrochloride		
Prazopress XL	Prazosin Hydrochloride	Effervescent and swelling based floating system	Sun Pharma, Japan
Metformin Hydrochloride	Metformine Hydrochloride	Minextab Floating ® system	Galanix, France
Cafeclor LP	Cefaclor		
Tramadol LP	Tramadol		
Cipro XR	Ciprofloxacin hydrochloride and betaine	Erodible matrix based system	Bayer, USA

Accordion Pill™	-----	Expandable system (unfolding)	Intec Pharma
Baclofen GRS	Baclofen	Coated multi-layer floating & swelling system	Sun Pharma, India
Coreg CR	Carvedilol	Gastro retention with osmotic system	Glaxosmithkline
Madopar HBS® Valrelease®	Levodopa and benserzide Diazepam	Floating system	Roche, UK
Liquid Gaviscon®	Alginic acid and sodium bicarbonate	Effervescent floating liquid alginate preparation	Reckitt Benckiser Healthcare, UK
Cytotec	Misoprostol	Bilayer floating capsule	Pfizer, UK
Topalkan®	Aluminum magnesium	Floating liquid alginate	Pierre Fabre Medicament, France

Figure(s)

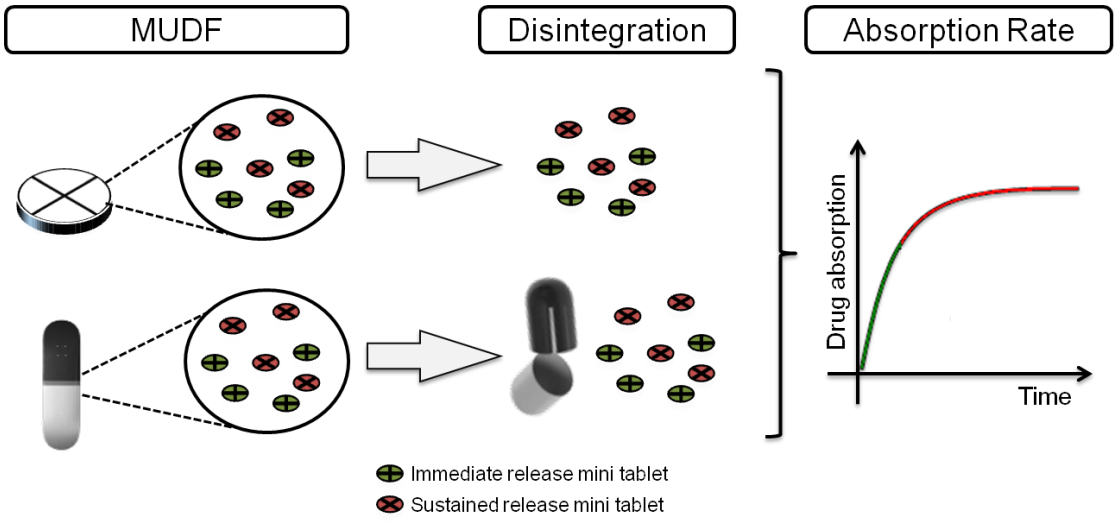

Figure 1

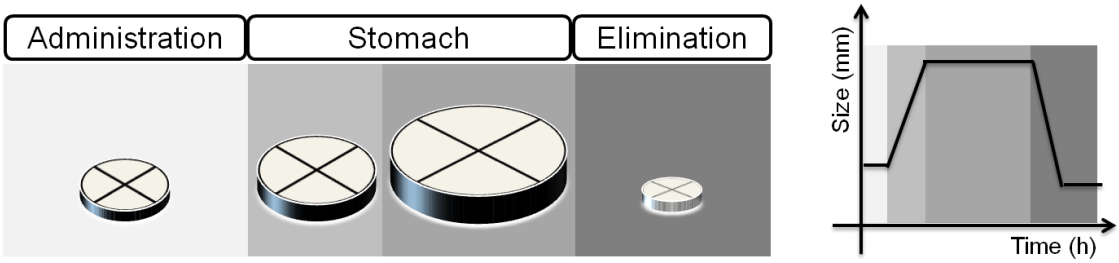

Figure 2

Figure Captions

Figure 1: Biphasic multi-unit dosage forms disintegration and absorption profile.

Figure 2: Three phases of an expanding system: before swallowing, swelling and elimination.