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Review

Enteric coating of oral solid dosage forms as a tool to improve drug bioavailability

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ABSTRACT

Enteric coating is a common procedure in the development of oral pharmaceutical dosage forms. The main advantage of enteric coating is that it protects the drug from acidic pH and enzymatic degradation in the stomach while protecting it from the undesirable effects of some drugs. There is certain controversy regarding the real influence of enteric coating on the bioavailability of many drugs. Various scientific articles have demonstrated an improvement in the extent of bioavailability of some drugs when enteric coating is used. In recent years, there have been many studies examining different formulation strategies for monolithic and multiparticulate systems, including different pharmaceutical oral dosage forms and delivery systems based on the combined use of enteric coating and other methods that improve the bioavailability of drugs administered orally. However, the real bioavailability, serum levels and therapeutic effect of these drugs may be influenced by gastrointestinal pH values, gastrointestinal environment, inter-individual or intra-individual variability in gastric emptying and gastrointestinal transit time, interpatient variability associated with the type of polymer used for enteric coating or other formulation variables. It deserves special attention to know the real influence of enteric coating on the bioavailability of new oral dosage forms.

1. Introduction

Enteric coating constitutes a strategy for the modified release of drugs incorporated in orally administered dosage forms whose traditional objective is to guarantee the stability of the drug in aggressive stomach conditions and guarantee its release in the digestive tract.

In theory, enteric coatings may improve absorption of a drug that is preferentially absorbed in distal portions of the gastrointestinal tract, but they can also alter the absorption process of a drug due to inter-individual variability in processes such as gastric emptying. This, in turn, can affect pharmacokinetic behavior and the emergence of drug response. In addition, delayed intestinal disintegration of enterically coated formulations may have undesirable clinical consequences, such as reduced bioavailability or delayed or ineffective therapeutic response (Varum et al., 2010).

Until the early 90's, there was thought to be considerable inter-individual and intra-individual variability in the onset of therapeutic action of drugs administered as enteric coated tablets (Aulton, 1988). In addition, some authors associate the use of enteric coating with an impaired bioavailability (Fine et al., 1991). However, different studies show an improvement in the oral bioavailability of various drugs administered as enteric coated oral formulations, such as salicylates, proton pump inhibitors or mycophenolic acid among other (Behrend and Braun, 2005; Nefesoglu et al., 1998; Wang-Smith et al., 2012). This lack of consensus makes it necessary to closely examine the different studies and strategies based on the use of enteric-coated formulations and their real influence on the oral bioavailability of drugs.

The aim of this work is to review formulation strategies for orally administered pharmaceutical dosage forms based on the use of enteric coating combined with other strategies that improve the bioavailability of drugs administered orally.

2. Physiological concepts of the gastrointestinal absorption

The digestive tube in humans, usually called the gastrointestinal (GI) tract, is a long tube of 10–12 m that begins in the mouth, extend to the anus, and can be divided into the mouth, the esophagus, the stomach, the small intestine and the large intestine. This, along with the salivary glands, liver and pancreas, forms part of the digestive system, whose function is the processing of food and the facilitation of nutrient incorporation to the rest of the body.

The GI tract consists of four concentric layers. Going from innermost

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to outermost, these are the mucous layer, where mucus and HCl secreting glands are located, a submucosal layer composed of connective tissue, an outer muscular layer and a serous layer.

The mouth is the beginning of the digestive tract and is followed by the esophagus, a tube of 20–30 cm in length that carries food to the stomach. Below this is a muscular, J-shaped cavity called the stomach, the widest part of the digestive tract, which acts as a temporary reservoir and facilitates the mixing and digestion of food *via* muscular contraction. The inside of the stomach contains glands that secrete gastric juice, which is composed of hydrochloric acid and enzymes that facilitate the digestion of starch, protein and triglycerides. The stomach also allows the absorption of water and some other substances.

The part of the GI tract most oriented towards the absorption of nutrients and other substances is the small intestine. This structure, 6–7 m in length (DeSesso and Jacobson, 2001; Snyder et al., 1975), can be divided into three different parts: the duodenum, the jejunum and the ileum. In the mucosal lining of the small intestine appear the villi, which are small, finger-shaped structures in the intestinal mucosa with a length of about 0.5 to > 1 mm. that increases the surface of the mucosa. These villi have many smaller structures called microvilli. The exterior of the villi consists of layers of cells while the interior consists of blood and lymphatic vessels that allow the absorption of nutrients, which are transported through the bloodstream and lymphatic system to the rest of the body. 90% of nutrients, are absorbed through the intestinal villi. The large intestine, measuring 1.5 to 1.8 m in length, is the final portion of the gastrointestinal tract and consists of the cecum, colon and rectum (DeSesso and Jacobson, 2001; Snyder et al., 1975). Its main function is to absorb and remove waste products from digestion.

The GI tract is essential for the absorption of nutrients incorporated in food and other substances, such as orally administered drugs. The majority of substances are absorbed in the GI tract through a passive diffusion mechanism that uses transcellular and paracellular absorption pathways, although some drugs are absorbed by carrier mediated transport (Ho, 2011).

A common way to assess the absorption of drugs administered *via* different routes of administration, is to evaluate their bioavailability. Bioavailability is a quantitative measure of the absorption of an active substance in the organism when incorporated in a particular dosage form (*e.g.*: tablet) and administered by a particular route of administration (*e.g.*: orally). It can be measured in terms of magnitude, percentage of drug incorporated in the dosage form that achieves systemic circulation, or rate. In addition, bioavailability in terms of magnitude can be assessed either as an absolute or relative value.

Numerous factors, many physiological, can influence the bioavailability of orally drugs.

Solubility of the drug and permeability of the membrane are considered the main factors that affect the bioavailability of oral drug absorption in amount and rate. In addition, oral bioavailability may be also influenced by different physiological factors, such as gastric emptying, gastrointestinal pH, food effects, small intestinal transit time, bile salt, liver metabolism, gut wall metabolism or absorption mechanism. Furthermore, formulation factors such as particle size, formulation excipients or type of coating may influence oral drug absorption (Martinez and Amidon, 2002; Song et al., 2004).

One of the factors that may affect the bioavailability of oral drugs is the nature and composition of the gastrointestinal fluids, particularly their pH. The gastrointestinal pH varies between different areas of the gastrointestinal tract and pH values show both inter-individual and intra-individual variability dependent on different factors (Abuhelwa et al., 2016; Abuhelwa et al., 2017). Fig. 1 shows a schematic representation of different gastrointestinal pH's and drug dissolution when the enteric coating is dissolved depending on the gastrointestinal pH (Lozoya-Agullo et al., 2018; Sosnik et al., 2014).

The intraluminal pH varies along the gastrointestinal tract, from very acidic in the stomach to about neutral in the large intestine. The pH progressively increases to 5.5 in the upper small intestine, reaching about pH 7.5 in the ileocolonic region, drops to 5.7 in the caecum, and increases again to pH about 6.7 in the rectum (Fallingborg, 1999; Maurer et al., 2015).

The gastrointestinal absorption of many drugs (mainly weak acids and bases) occurs *via* passive mechanisms in accordance with pH partition theory. According to this theory, only the unionized fraction of the drug has a lipid character and may pass through the membranes of the gastrointestinal tract *via* passive mechanisms given the lipidic nature of the membrane. The size of the unionized fraction depends on the relationship between the drug's medium pH and pKa according to the Henderson-Hasselbach equation (Tallarida and Murray, 1987). The pH of the stomach, usually being acidic, favors the absorption of weak acids, whereas the pH of the small bowel, being closer to neutrality, facilitates the absorption of weak bases. In addition, carrier mediated intestinal transport of some drugs, mainly hydrophilic molecules, may occur through specialized transporter proteins (Tsuji and Tamai, 1996).

The pH of the GI tract, especially the acid pH of the stomach, and the presence of enzyme systems can also affect the stability of many drugs (Abuhelwa et al., 2017). Gastrically secreted enzymes, may produce instability in many drugs containing peptides (Muheem et al., 2016).

One of the most commonly used technological resources for overcome adverse stomach conditions and avoiding instability in many drugs is the use of dosage forms provided with an enteric coating.

3. Enteric coating and its function

The enteric coating is an outer coating that can be used in oral pharmaceutical dosage forms, and is usually made up of synthetic polymers or natural products. There are numerous possible motivations for using enteric coating, including altering the odor or taste of the drug adding protection against environmental conditions (especially pH), the protection of gastric mucosa against the irritating action of some drugs or allowing for site or time specific drug release (Shokri and Adibkia, 2013).

The enteric coating prevents the delivery of a drug in the stomach but permits release of the drug in the small intestine. To achieve this, a polymer insoluble at acid pH but soluble at intestinal pH is used. When the drug reaches the upper small intestine, the coating dissolves allowing drug release.

The polymers commonly used to obtain enteric coatings are, among others, cellulose acetate phthalate, methacrylic acid copolymers and hydroxypropyl methylcellulose phthalate.

Technological procedures that can be used for these types of covers include film coating and sugar coating.

The weight of the enteric polymer should be sufficient to ensure that the intended effect is achieved. Usually, the amount of polymer used in enteric coating is double or triple that used for a normal coating. Enteric coatings are commonly used with two main objectives: 1. To preserve the drug from degradation of acidic pH and enzymes that can occur in the stomach. 2. To protect the stomach from the undesirable effects of a drug (Porrer, 1995).

4. Kinds of polymers for enteric coating

The usual polymers used in enteric coatings have carboxylic groups in their composition and their solubility depends on the number of carboxylic groups they contain. Enteric coating polymers may be grouped according to their chemical composition.

4.1. Polymethacrylates

These are synthetic polymers containing various types of methacrylates in different ratios and are produced using free radical addition polymerization (Gupta et al., 2015b; Holmes et al., 2008). Marketed as Eudragit®, they many applications for drug delivery such as enteric

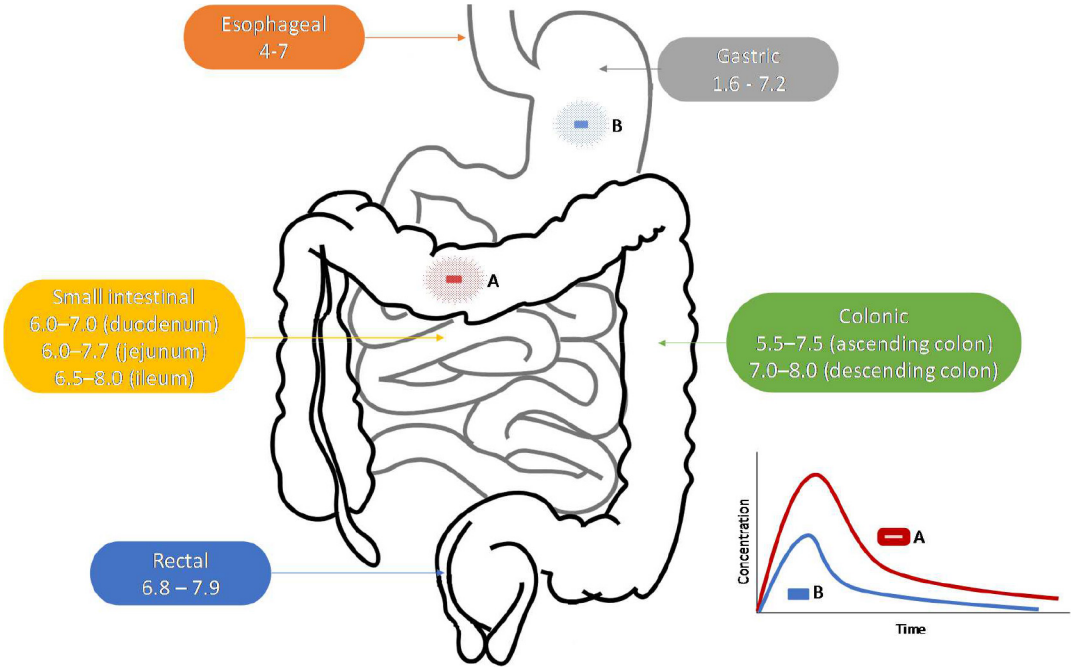

Fig. 1. Schematic representation of the different gastrointestinal pHs and the possible bioavailability impact of an enteric coated formulation (A) against non-enteric coated formulation (B) (Lozoya-Agullo et al., 2018; Sosnik et al., 2014).

coating or colon drug delivery (Thakral et al., 2013).

4.2. Cellulose derivatives

Esters derivatives of cellulose such as cellulose acetate phtalate (CAP), cellulose acetate trimellitate (CAT), or cellulose acetate succinate (CAS) have potential applications for enteric coating of pharmaceutical formulations. In addition, cellulose ether esters containing hydroxypropyl methylcellulose phthalate (HPMCP) or hydroxypropyl methylcellulose acetate succinate (HPMCAS) may be also used for enteric coating (Edgar, 2007).

4.3. Polyvinyl derivatives

Polyvinyl acetate phtalate (PVAP) is an enteric coating polymer that shows pH-dependent solubility and increases tablets' and capsules' resistance to alteration in the acidic pH of the stomach (Nesbitt et al., 1985).

4.4. Other materials

Other materials that may potentially be used for enteric coating are shellac (esters of aleuritic acid), zein, amylose starch, starch derivatives and dextrins (Dukić-Ott et al., 2008; Hussan et al., 2012; Pearnchob et al., 2003).

5. Coating process

There are four basic methods for coating solids for the purpose of control drug release: pan coating using solvent evaporation, fluidized-bed coating using solvent evaporation, compaction coating and hot melt coating (Mathiowitz, 1999). In addition to these, other coating methods include microencapsulation, electrostatic coating and 3D printing coating (Wang and Shmeis, 2005).

5.1. Pan coating

Pan coating using solvent evaporation is a classic technique used for sugar coating and film coating. The coating solution or dispersion is sprayed over the tablets while a drying system eliminates the aqueous or organic solvent. The coating material forms a layer on top of the formulation surface. Balance between the evaporation rate and the spraying rate is critical for achieving a smooth layer. Sugar coating consists of applying large quantities of syrup to the formulation after pre-coating with a water proofing layer. This pre-coating helps to prevent stability problems due to the aqueous nature of the sugar coatings. Sugar coating can result in a 30–50% increase in weight. Film coating consists of applying a polymeric solution or dispersion over the formulation in order to achieve a thin and smooth layer and can result in a 2–3% weight increase.

5.2. Fluidized coating

Fluidized-bed coating using solvent evaporation is a common technique that consists of spraying a coating solution or dispersion over a formulation as it is transformed into a fluidized bed by a column of hot air that moves upwards. The solvent evaporates and the polymer dissolved or dispersed in the solvent, forms the coating layer. Coating can be achieved using top spray, tangential spray or bottom spray (Wurster process) depending on the situation of the sprayer. Fluidized-bed coating occurs with minor defects in layers and minor variability than the coating pan process. Fluid bed coating equipment is mainly used for coating multiparticulate systems such as pellets.

5.3. Compaction coating

Compaction coating (tablet-in-tablet) consist of pressing a coating layer around a tablet core using a special compression machine with two feeding units, one of which transfers the core to the matrix and the other of which transfers the coating material. An initial compression forms a soft core that is placed on top of half of coating material. After that, the second half of the coating material is deposited on top of this core and the whole is compacted. This is a useful coating method in cases where it is not possible to use heat or solvents.

5.4. Hot melt coating

Hot-melt coating is a variant of film-coating process where traditional polymers are replaced with low melting point coating materials maintained at temperatures of about 40–60 °C. Thus, it is a solvent-free technique with advantages like faster processes, cheaper technology, the minor risk of drug dissolving during coating and minor risk of microbial growth (Bodmeier, 1997; Lopes et al., 2017). Generally, this coating technique uses lipid-based excipients like esters of long chain fatty acids, thermoplastic resins, or synthetic products like polyethylene glycol or polyethylene oxide. Only a few hydrophilic substances are used (*e.g.* polyethylene glycol) (Jannin and Cuppok, 2013; Lopes et al., 2017; Sauer et al., 2013).

5.5. Microencapsulation

Microencapsulation allows for the coating of particles (liquid, solid, semisolid or gases) with polymeric coating materials. They can be manufactured using several methods. The most common methodology is to induce coacervation or separation of macromolecules around the cores *via* a stimulus like temperature change or solvent change, *etc.* Particles that are able to form a coating are dispersed in a macromolecule solution and a stimulus is used to induce coacervation. The resulting coacervate droplets stay on the particle surface, forming the coating. Finally, this layer must be treated so that it becomes rigid.

5.6. Electrostatic coating

In order to coat without a solvent, electrostatic coating can be used with conductive substrates. The film formation is achieved by the attraction of opposite charges between the film forming particles and others to be coated. The deposited particles are then cured, usually by heat, to produce a film (Prasad et al., 2016).

5.7. 3D printing

3D printing is nowadays an innovative formulation technology. It is also a cheap and easy method for including a polymer for controlling the release of drugs without using classical coating technologies like coating pan or fluidized bed. An extruder device can be used to prepare polymer filaments loaded with one or more drugs adequate for fused-deposition 3D printing. 3D printer with more than one nozzle permits the manufacturing of different solid devices, such as multilayer or coated devices (Goyanes et al., 2015). Consequently, it may be possible to use hot melt extrusion to include coating polymers in filaments that can be used for printing around 3D printed cores (Goole and Amighi, 2016; Linares et al., 2019).

6. Entering coating and bioavailability

Enteric coating can be used in many orally administered pharmaceutical dosage forms, such as tablets, capsules, granules, pellets, microcapsules, micro and nanoparticles and drug delivery systems, and can have different impacts on the biopharmaceutical behavior of the active principle, particularly in terms of its bioavailability. What follows is a review of the impact of enteric coating on bioavailability for different types of oral dosage forms.

6.1. Monolithic dosage forms

6.1.1. Tablets

Omeprazole, a drug belonging to the proton pump inhibitors group, presents many formulation and stability problems: low aqueous solubility, rapid degradation at acidic pH, and sensitivity to moisture, temperature, solvents, acidic substances, UV light, and some metal ions (Davidson and McCallum, 1996; Hamdan, 2001; Qaisi et al., 2006; Tutunji et al., 2006). Coating omeprazole with enteric polymers and others proton-pump inhibitor formulations has been used as a method for improving its bioavailability. However, because of their acidic nature and the presence of carboxylic groups in them, stability problems may appear. Previous studies on the interaction of omeprazole with enterically coated salicylate tablets have shown an unchanged bioavailability of acetylsalicylic acid compared to uncoated tablets, although an increase in the absorption rate of salicylate from enterically coated salicylate tablets was demonstrated. This fact may be related to a gastric release of the drug due to the increase in the pH associated with omeprazole administration. In addition, a highly variable absorption of enterically coated tablets was reported (Nefesoglu et al., 1998). These findings are similar to the results obtained in a previous paper where antacid administration increased the release rate of enterically coated aspirin (Feldman and Carlstedt, 1974). However, another research about the influence of omeprazole on the pharmacokinetics of enterically coated ketoprofen tablets showed no differences in the pharmacokinetics of ketoprofen, possibly due to the dose of omeprazole used in this study (Qureshi et al., 1994).

Salicylates such as acetylsalicylic acid (ASA) show gastrointestinal side effects such as mucosa damage and bleeding. Low dose ASA is widely used as an antiplatelet agent in thromboembolism prophylaxis, in patients with cardiovascular disease. Enterically coated ASA has been developed to reduce gastrointestinal side effects. Some studies demonstrate reduced antiplatelet activity following the use of this kind of formulation in comparison with the same doses of plain aspirin. This reduced pharmacological effect may be related to a low bioavailability of ASA due to the pH of the small intestine (Cox et al., 2006; Haastrup et al., 2015). Also, in patients with rheumatoid arthritis, there was a reduction in the plasma salicylate concentration of enterically coated aspirin tablets compared to uncoated tablets. In addition, daily hemorrhages during treatment with uncoated aspirin tablets were greater than during treatment with enterically coated aspirin tablets (Howe et al., 1977). Another more recent research tried to correlate the oral bioavailability of enteric coating aspirin (EC aspirin) with the absence of pharmacological response in patients with diabetes mellitus. In this study, the bioavailability and antiplatelet activity of aspirin was comparatively evaluated using immediate release aspirin tablets, PL2200 (modified release aspirin) capsules and enterically coated aspirin tablets (Bhatt et al., 2017). As shown in Fig. 2A, when EC aspirin was administered, a reduction in both the extent and rate of bioavailability of aspirin was observed in comparison with the other formulations. The use of EC aspirin was related with a lack of response due to a lower bioavailability although with a high interindividual variability. In fact, 12 of the 35 patients treated with EC aspirin were responders and it was associated with higher serum levels of acetyl salicylic acid than non-responders, as shown in Fig. 2B (Bhatt et al., 2017).

A research about the bioavailability of prednisolone in healthy volunteers using enterically and non-enterically coated tables showed a higher intersubject variability in prednisolone plasma levels, and longer lag-times when enterically coated tablets were used. In addition, no changes in the bioavailability of prednisolone were observed between enterically and non-enterically coated tablets at equivalent doses (Morrison et al., 1977). Moreover, the joint administration of cimetidine did not modify the bioavailability of prednisolone from an enterically coated formulation (Morrison et al., 1980).

Mycophenolic acid (MPA) is an immunosuppressive agent characterized by its low oral bioavailability. One alternative used to improve its oral bioavailability is the administration of different prodrugs, namely chemically derived amino esters such as mycophenolate mofetil (MMF), a derivative of MPA that showed a better bioavailability of mycophenolic acid in monkeys (Lee et al., 1990) a result which was later confirmed in healthy volunteers (Bullingham et al., 1996).

Another strategy is to use enterically coated mycophenolate sodium salt tablets for oral administration (EC-MPS), which has been used as a substitute to mycophenolate mofetil (MMF) in patients suffering from

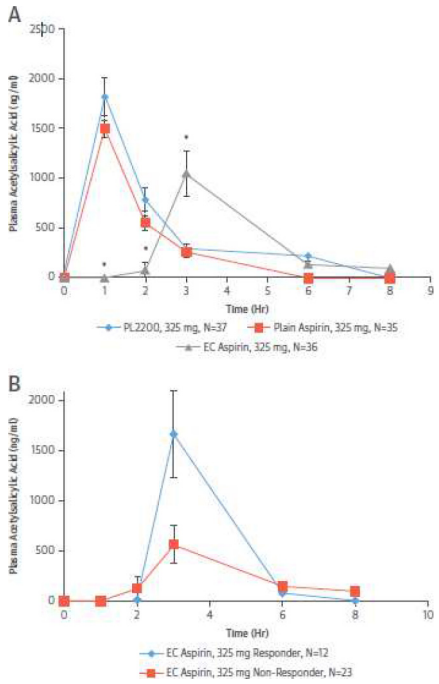

Fig. 2. (A) Plasma acetylsalicylic acid concentrations after administration of simple aspirin, PL2200 and enteric coated aspirin (EC aspirin). (B) Plasma acetylsalicylic acid concentrations after enteric coated aspirin administration for responders and nonresponders patients (Bhatt et al., 2017). Reproduced with permission.

severe gastrointestinal side effects. This type of drug combines two formulation strategies, namely the use of a salt and the enteric coating of the dosage form, to simultaneously achieve good tolerance and interesting bioavailability and stability characteristics (Ingle and Shah, 2005). Enterically coated MPS tablets are considered an advanced formulation that further reduces gastrointestinal side effects associated with MMF and allows selective absorption of this drug in the small intestine, where the mycophenolic acid is more soluble than in gastric fluids and results in an improvement in the pharmacokinetics. This improvement in bioavailability is achieved through a controlled release in the upper small intestine, resulting in a more homogeneous dissolution. This is achieved *via* the combined use of soluble drug salt and enteric coating. This can potentially lead to improved long-term results in solid organ transplantation, including kidney transplantation, with beneficial results in patients with renal transplantation. This type of pharmaceutical composition brought partial improvements in tolerance, improved pharmacokinetics and even clinical benefits (Bjarnason, 2001).

Two pivotal multicenter clinical trials in kidney transplant patients showed that, over a period of 180 days, there was a greater systemic MPA exposure when mycophenolate sodium was administered as an enterically coated formulation as compared when mycophenolate mofetil was administered as shown in Fig. 3 (Behrend and Braun, 2005; Granger, 2001).

Similar results with improved oral bioavailability of mycophenolic acid (MPA) by using EC_MPS tablets in beagle dogs have also been obtained (Haeberlin et al., 1996).

Also, this improvement in the bioavailability of the enterically coated MPA formulation is reflected in various studies that show improved bioavailability in the EC-MPS formulation in relation to MMF when both drugs are administered together with proton-pump inhibitors such as omeprazole or pantoprazole in healthy volunteers or in transplanted patients (Kees et al., 2012; Kofler et al., 2011; Rupprecht et al., 2009). This phenomenon is possibly related to the incomplete dissolution of MMF in the higher stomach pHs associated with the

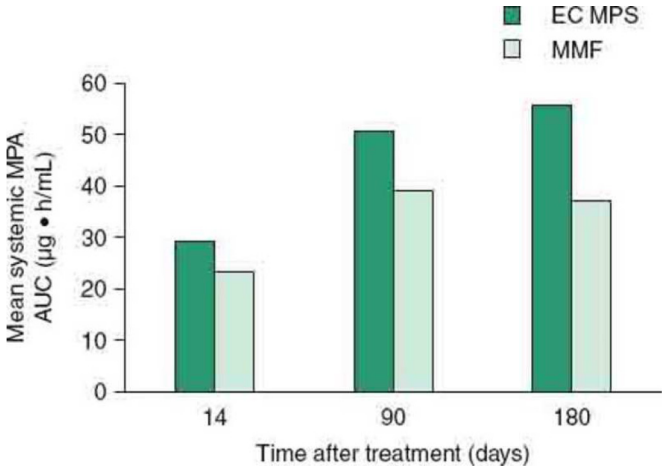

Fig. 3. Comparison of the area under the plasma levels curve of mycophenolic acid (MPA) after the administration of enteric coated mycophenolate sodium tablets (EC-MPS, 720 mg twice daily) and mycophenolate mofetil tablets (MMF, 1000 mg twice daily) in kidney transplant patients.
Adapted from Behrend and Braun (2005) (reproduced with permission).

administration of proton-pump inhibitors. It should be noted that drugs such as omeprazole and pantoprazole are inhibitors of gastric secretion of the stomach and are used as anti-ulcer drugs. Both drugs are often used in transplant patients undergoing treatment with immunosuppressive drugs. These results demonstrate that, when both drugs are administered in association with proton-pump inhibitors such as omeprazole or pantoprazole, the enterically coated MPS formulation showed better bioavailability with respect to the mycophenolate mofetil based formulation.

DX-9065a is a synthetic anticoagulant characterized by a low bioavailability (3%) in humans after oral administration of normal capsules (Fujii et al., 2011). Enterically coated DX-9065 tablets coated with hypromellose acetate succinate were designed to prevent interaction with bile acid and increase oral absorption. Bioavailability experiments performed on monkeys demonstrated that the area under the curve of DX- 9065 after administration of the enterically coated formulation was higher that of the aqueous solution as shown in the Fig. 4 (Fujii et al., 2011).

In addition, the gastrointestinal tract constitutes an adverse environment for macromolecular drugs such as peptides and other molecules. Oral administration of macromolecular drugs for local or systemic delivery should overcome some problems related to enzymatic barrier, mucus barrier and absorption barrier that may be responsible of erratic absorption and bioavailability of these kinds of compounds. Different solutions have been suggested to overcome these barriers (Bernkop-Schnürch, 2009). One of these strategies involves the use of colonic capsules or tablets with a combination of enteric coating and/or

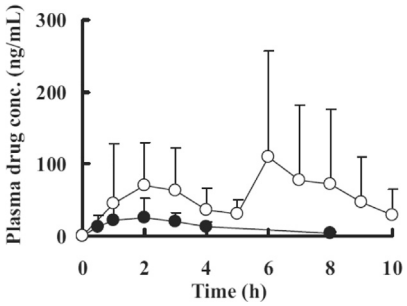

Fig. 4. Pharmacokinetic behavior of DX-9065a in fasted monkeys after the administration of enteric coated tablets (o) and the oral solution (●) at the dose of 5 mg (Fujii et al., 2011). Reproduced with permission.

protease inhibitors to avoid drug degradation and to incorporate permeation enhancers to facilitate the paracellular transport of molecules (Moroz et al., 2016).

Different approaches to the enhancement of the bioavailability of peptides administered orally to increase their physical stability and to reduce degradation by digestive enzymes, such as insulin, have been tested. These strategies are based on the use of carriers such as emulsions, nanoparticles, microspheres or liposomes. Another alternative is the use of enterically coated tablets (Wong et al., 2018; Wong et al., 2017; Wong et al., 2016). One strategy for enhancing the systemic bioavailability of insulin is uses a novel formulation of enterically coated insulin tablets that use cellulose acetate hydrogen phthalate as an enteric coating polymer to protect the tablets against acidic stomach pH, contain chitosan as an absorption enhancer and also contain sodium glycocholate as an enzyme inhibitor. An *in vitro* study of this type of formulation demonstrated minimal insulin release at acidic pH's and positive excipient effects on insulin-dependent Glut-4 translocation (Wong et al., 2017).

6.1.2. Capsules

Esomeprazole is a proton pump inhibitor whose stability is dependent on pH and which rapidly degrades in acidic media. The contact of esomeprazole with the acidic medium of the stomach produces a significant instability in the drug and a reduction of its bioavailability. For this reason, enteric coating formulations of esomeprazole have been proposed (Nair et al., 2010; Wang-Smith et al., 2012). In a pharmacokinetic study about the bioavailability of esomeprazole administered as enterically coated capsules, the bioavailability of enterically coated esomeprazole formulations was higher than that of non-enterically coated esomeprazole, possibly due to the acidic instability of the drug (Wang-Smith et al., 2012).

Oral administration of vanadyl sulfate has demonstrated a therapeutic effect in diabetic patients. Vanadyl sulfate is degraded in the stomach and is absorbed more efficiently in the ileum, compared to other parts of the gastrointestinal tract, and it has been suggested that enteric coating could facilitate absorption of the drug at that level (Fugono et al., 2001). In an experimental research in rats, the bioavailability of vanadyl sulfate administered in capsules enterically coated with HPMCP was almost double of the bioavailability obtained after the administration of gelatin capsules or solutions. This formulation strategy has been proposed as a means to improve vanadyl sulfate bioavailability (Fugono et al., 2002).

Several authors working on the same line of research designed chitosan and poly (γ-glutamic acid) freeze-dried nanoparticles incorporated in a enteric coated capsule for the oral administration of insulin. Studies about the distribution in rats showed that nanoparticles administered by oral route were retained in the stomach for a prolonged period, which could lead to their disintegration and the degradation of insulin, a problem they solved by enterically coating the capsule. After oral administration of the enteric coated capsule the nanoparticles were introduced into the small intestine, thereby improving intestinal insulin absorption and producing a reduction in blood glucose levels, suggesting that this type of formulation could be used as a promising approach for oral administration of that drug (Sonaje et al., 2010).

Enterically coated capsules have been used as a strategy for colon targeting and bioavailability control for different drugs. One study examined the behavior of paracetamol capsules enterically coated with hydroxypropyl methylcellulose (HPMC) as well as Eudragit® L 30 D-55 and Eudragit® FS 30 D, which are polymers specifically designed for colonic release. As shown in Fig. 5, HPMC coated capsules exhibited in healthy volunteers a delayed drug delivery in the middle and distal intestine (Cole et al., 2002).

Enterically coated hydroxypropyl methylcellulose capsules (ECHC) covered with 5-fluorouracil loaded microsponges and include 15% calcium pectinate beads for colon specific absorption have been developed. This delivery system provides a suitable carrier for colon targeting. In an experimental study in rabbits, significant modifications to the extent and rate of the bioavailability of 5-FU administered by the oral route in colonic delivery capsules were observed in comparison with aqueous 5-FU solution. A reduced release in the small intestine was observed in spite its high water solubility and a higher absorption in the colon (Gupta et al., 2015a).

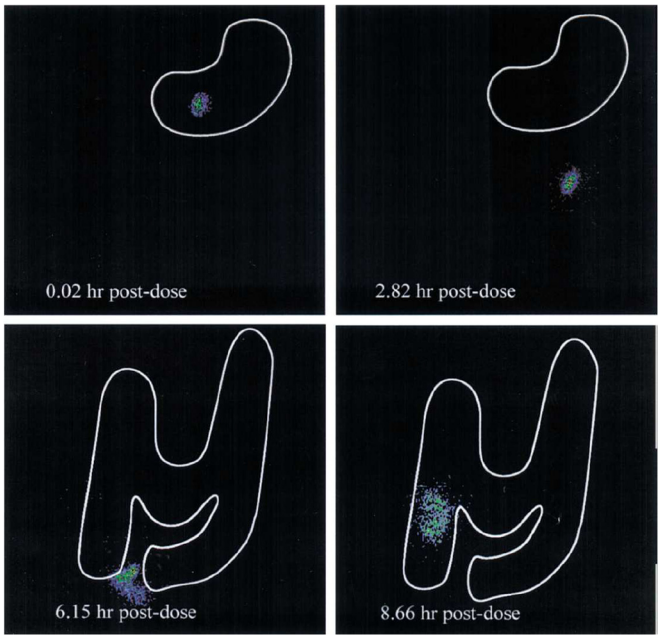

Fig. 5. Visualization of drug delivery using gamma scintigraphy from the Eudragit® FS 30 D HPMC capsules in a healthy volunteer (Cole et al., 2002). Reproduced with permission.

Probiotics are useful for the treatment of Irritable Bowel Syndrome (IBS). Joint therapy using probiotics and mosapride, which is a drug that stimulate gastrointestinal motility, appears to be effective for the relief of IBS symptoms and improvement of stool frequency and inconsistency in subjects with non-diarrheal-type IBS (Choi et al., 2015). Probiotics may be unstable in the stomach when they are administered orally. An enterically coated formulation has been proposed to protect them from degradation. This consists of enterically bi-coated probiotic and mosapride capsules, which combine a coating of HPMCP with an additional coating made up of hydrophilic polymer solutions containing mosapride. Polymer-mosapride coatings made with hydrophilic polymers such as HPMC, among others, increase the solubility of the drug and the enterically bi-coated mosapride and probiotics capsule shows improved drug solubility and enhanced oral bioavailability (Kim et al., 2015).

6.2. Multiparticulate dosage forms

6.2.1. Granules

Drug administration through enteral feeding tubes is a method that allow the administration of food and medicines for adult patients with swallowing difficulties. The administration of some drugs formulated as enterically coated granules *via* feeding tubes, such as esomeprazole, requires to prepare an aqueous suspension of the drug prior to administration. If the esomeprazole granules are not immediately delivered through the nasogastric tube, the suspension of enterically coated granules at different pH may produce alteration to the enteric coating and modify both the bioavailability and the therapeutic effect of the drug (Hoover et al., 2017).

Gastrozol is an enterically coated omeprazole granule formulation that serves as an alternative to GastroGard, used in the treatment of

esophageal gastroduodenal ulcer in horses. The relative bioavailability of omeprazole administered as Gastrozol was higher than for GastroGard, with a value of 1.25 (Birkmann et al., 2014).

Lansoprazole oral disintegrating tablets containing enterically coated granules show similar pharmacokinetics to standard capsule formulation (Horn and Howden, 2005).

Nateglinide stimulate the insulin secretion and is used for the treatment of type 2 diabetes. Controlled release tablets containing nateglinide have been designed that decrease blood glucose levels. This type of formulation combines both immediate release granules (60 mg) and compressible enterically coated granules (90 mg). In an experimental study in fasted beagle dogs, this kind of formulation was found to control glucose levels in both single and multiple oral administration studies (Makino et al., 2010). Oral insulin granules coated with HPMC and polymethacrylic polymers were shown their usefulness in enhancing the oral absorption of this drug in rats. Specifically, HPMC K100LV grade and E50LV grade had the best viscosity grades in terms of bioavailability results and the main conclusion was that the low viscosity HPMC enhanced the *in vivo* absorption properties of insulin (Singh et al., 2011).

6.2.2. Pellets

Formulation of coated pellets using different enteric polymers have been studied for the purpose of obtained specific release patterns. Table 1 shows different drugs formulated as pellets the consequences of this type of formulation in terms of bioavailability. Many of these studies were carried out when the drug presented a pH dependent solubility, particularly for drugs with high solubility in the stomach and poor solubility in the intestine (Cui et al., 2008; He et al., 2011). This can lead to fluctuations in blood levels and fluctuations in bioavailability. Thus, urapidil pellets with an enteric coating were developed, with the coating based on a methacrylic acid copolymer in order to improve the drug's bioavailability. The pH-dependent polymer used for coating pellets allowed to achieve increased relative bioavailability. The pellets obtained seem to achieve better *in vivo* sustained release pattern than the pH-independent pellets. Coatings with higher contents of Eudragit® L30D55, obtained systems with faster film coating dissolving. Consequently, the proportion of Eudragit® L30D55 exhibits a positive correlation with drug release in 6.8 phosphate buffer medium. (He et al., 2011).

Moreover, ofloxacin pellets with an enteric coating based on methacrylic acid copolymer were developed with the goal of controlling the amount of drug released in acidic media. When the dissolution medium tested was phosphate buffer at pH 4.5, higher proportions of Eudragit® L30D55 allowed to achieve more rapid drug release. The coating material in question was a combination of both Eudragit® L30D55 (pH dependent) and Eudragit® NE30D (pH independent). Sustained release ofloxacin pellets enhanced the *in vitro* release pattern in a 7.4 pH medium contrast with the reference formulation, gastroretentive tablets. As well as the enhanced bioavailability, these pellets improved the prolonged release pattern in contrast with the reference formulation in the multiple doses study (Cui et al., 2008).

Multiple-unit dosage forms, such as pellets (MUPS), are a good strategy for improving the biopharmaceutical behavior of many drugs. This may be due to the interindividual variability in gastric emptying and intestinal transit time in contrast with single-unit dosage forms. Additionally, less variability in drug release and minor risk of dose dumping may be obtained due to the multiple subunits of each dose of multiparticulate systems (Bodmeier, 1997; Zhang et al., 2005).

Using this approach, film-coated pellets containing clarithromycin were developed with the aim of improve the bioavailability of commercial immediate release formulations. Clarithromycin is a class II weak base and has a low, pH-dependent water solubility. Two formulations were obtained: F1, with three different pH-sensitive polymers to coated the pellets, and F2, with pellets coated with a pH-independent polymer alone. The dissolution profiles of F1 and F2 were similar at pH 5.0, but not at pH 6.0 and 6.8, where the F1 formulation had a higher release profile due to the higher pH. The relative bioavailability expressed as $AUC_{0-24\ h}$ for F1 and F2 was found to be 96.2% and 58.7% respectively, compared to immediate release (IR), while the Tmax was delayed, as can be seen in Fig. 6 (Zhang et al., 2005). Fig. 6 shows a sustained profile in plasma levels for formula F1 and a two hour lag time in the plasma concentration patterns of F2. The authors attribute the irregular bioavailability of F2 to the poor solubility values of clarithromycin at high gastrointestinal pH values. The GI side effects of aceclofenac and the solubility problems that limit its dissolution rate and, thus, its bioavailability can be overcome by combining several strategies: using an enteric polymer for coating (Eudragit® L100-55), formulation of pellets instead of any other solid dosage form because of the smaller size and larger surface area for dissolution (Ghebre-Sellassie, 1989; Kilor et al., 2010), using excipients like κ-carrageenan in the pellet to achieve immediate disintegration and decreasing the drug particle size.

Therefore, two types of multi-layer film formulations were proposed. One was omeprazole pellets coated with 3-layer films (salt, HPMC, Eudragit® L30D-55) while the other was a layered drug formulation with a multi-layer film coating (salt, HPMC, Eudragit® L30D-55). The HPMC-based layer must be of sufficient thickness to prevent both drug migration to the enteric coating, and interaction between the omeprazole and the acid polymer. The *in vivo* behavior of both

Table 1
Drugs formulated in enteric pellets and the bioavailability consequences.

Drug	Polymers	Bioavailability consequences	References
Urapidil	Eudragit® L30D55 (pH dependent) Eudragit® NE30D (pH independent)	↑	He et al. (2011)
Ofloxacin	Eudragit® L30D55 (pH dependent) Eudragit® NE30D (pH independent)	↑	Cui et al. (2008)
Clarithromycin	Eudragit® L30D-55 (pH dependent) Eudragit® L100 (pH dependent) Eudragit® S100 (pH dependent) Eudragit® RL30D (pH independent)	↑	Zhang et al. (2005)
Piroxicam	Eudragit® L30D55 (pH dependent)	↓	Dukić-Ott et al. (2008)
Theophylline anhydrous	Eudragit® L30D55 (pH dependent)	↓	Dukić-Ott et al. (2008)
Aceclofenac	Eudragit® L100-55 (pH dependent)	↑	Kilor et al. (2010)
Omeprazole	Eudragit® L30D55 (pH dependent)	↑	He et al. (2009)
Esomeprazole	Eudragit® L30D55 (pH dependent)	↑	Kan et al. (2016)
Duloxetine hydrochloride	Aqoat® AS-LF (pH dependent) Eudragit® L30D55 (pH dependent) HPMCP-HP55 (pH dependent)	↑	Kuang et al. (2017)
Protocatechualdehyde	Eudragit® NE 30D (pH independent)	↑	Zhang et al. (2016)
Ibuprofen	Aqoat® AS-MF and Aqoat® AS-HF (pH dependent)	↑	Marvola et al. (1999)

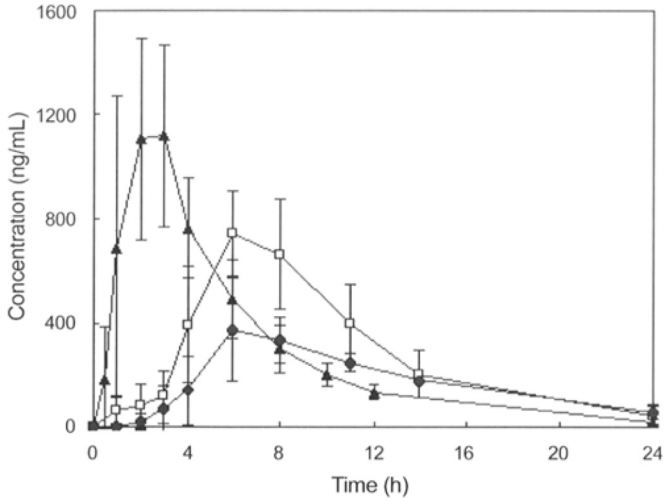

Fig. 6. Mean plasma concentration after administration of 250 mg clarithromycin different dosage. Each value represents mean (n = 3), and error bars indicate S.D. Symbols: Triangle = IR; square = F1 and circle = F2 (Zhang et al., 2005). Reproduced with permission.

formulations was compared in rats and dogs. Better bioavailability results were obtained for omeprazole when it was included in the multilayer films, than when was included in the pellet core (He et al., 2009).

Another multilayer pellet formulation was recently developed with the purpose of improve the bioavailability of esomeprazole magnesium. The formulation was designed to reduce the drug degradation in the stomach and to achieve minor drug plasma concentration variations. Inert core pellets were loaded by spraying a drug suspension. Once the drug layer was sprayed four more layers were sprayed: an initial isolated coating film to protect from possible reaction, an Eudragit® RS30D/RL30D layer to achieve sustained-release characteristics, a second isolated coating film to protect from possible reaction and finally a Eudragit® L30D-55 to grant enteric properties. Compared to the old commercial formulations (Nexium), the *in vivo* study showed that the novel formulation shows lower maximum plasma concentration (Cmax), higher maximum concentration time (Tmax) and mean residence time (MRT). In addition, the novel formulation achieved similar AUC values. The authors declared that the enteric formulation exhibited quite good sustained-release profile, a proper pharmacokinetic behavior, enhanced *in vivo* retention and minor plasma concentration variation of the drug. (Kan et al., 2016).

A proliposomal drug delivery system based on protocatechualdehyde (PD) (a salvia miltiorrhiza component) was developed in order to enhance bioavailability by reducing hepatic first-pass metabolism (Zhang et al., 2016). In addition, chronotherapeutic drug delivery system was chosen because of its better characteristics of safety, efficacy and patient compliance than approaches using synchronization of the circadian rhythm of variant angina with drug plasma concentrations (Krishna et al., 2012; Ohdo, 2010). With this in mind, PD proliposomes were used as pellet cores and Eudragit® NE 30D was the film forming polymer. With these strategies, a sustained-release effect was achieved in the enteric pellets and the destruction of the proliposomal preparation by the gastric environment was avoided. Moreover, the efficacy of the formulation proposed in drug delivery chronotherapeutic approach for angina treatment was demonstrated by the pharmacokinetic results obtained. The proliposomes showed higher Cmax and its AUC was about 200% that of the pure drug. However, the proliposomes had a short Mean Residence Time value (2.23 h). The enteric pellets have higher AUC_0 and longer MRT values (15.16 h). Moreover, the enteric pellets reduced the blood drug concentration variations, lowering the secondary effects compared to the immediate release formulation (Zhang et al., 2016). A study was undertaken in which two anti-inflammatory model drugs, ibuprofen and furosemide, were formulated as enteric polymer coated pellets with the aim of causing targeted drug release in the colon such that they could be used in the treatment of inflammatory colon diseases (Marvola et al., 1999). Both ibuprofen and furosemide are weak acids with low solubility in the stomach, but ibuprofen has good absorption throughout the GI tract while furosemide is mainly absorbed in the upper part of the GI tract. After testing different enteric polymers, it was concluded that the most suitable for targeted drug release was hydroxypropyl methylcellulose acetate succinate, which dissolves at pH's above 6.5. Ibuprofen reaches its target with a 20% coating, with a lag-time of 2 h and Tmax values of 4–5 h. This did not happen for furosemide, as it does not have good absorption properties in the colon, reducing its bioavailability, especially in feed-conditions.

Some authors highlight the *in vivo-in vitro* correlation (IVIVC) problems that may arise in the design of a sustained release formulation. In order to address these concerns, a formulation was arrived at that is bioequivalent to Voltaren despite having differences in the *in vitro* dissolution profiles with very low percentages of carbomer (4%) (Fu et al., 2011). Three main problematic scenarios that can lead to non-correlation were exposed: drugs with low solubility formulated with a high lag time, drugs with a specific absorption window may be affected by rapid gastric emptying in fasting conditions such that absorption remains incompleted, and formulations containing excipients with a low wetting capacity may condition the *in vivo* release of the drugs.

An interesting technology based on the use of enteric polymers combined with polysaccharides was tested. It was a multiparticulate system of budesonide coated with pectin and different acrylic polymers for the treatment of ulcerative colitis (Varshosaz et al., 2012). In this case, the technological strategy did not aim to enhance the drug bioavailability, but the opposite. The aim was to cause the release of the drug in the colon considerably reducing the plasma levels and therefore the toxic effects.

Some authors have substantially improved the bioavailability of novel designs already in the market. With this in mind, a formulation of naproxen/esomeprazole magnesium was developed with the purpose of improving the problems of the Vimovo® formulation (Astrazeneca) using the properties of enteric polymers (Lu et al., 2016). The commercial formulation consists of a core loaded with naproxen which is film coated with an enteric layer and an immediate release outer layer loaded with esomeprazole magnesium. Two different types of pellet were developed: one type was loaded with naproxen and given several layers of coating to target the drug specifically to the colon, while the other type was loaded with esomeprazole magnesium and given several layers of coating in order to control the release, thereby preventing the esomeprazole from being released into the stomach where it would otherwise degrade. This degradation would prevent the effect of the proton pump inhibitor and contributes to the appearance of side effects exacerbated by its degradation products.

6.2.3. Microcapsules

Recently, much emphasis has been placed on the development of enteric coated multiparticulate systems rather than single unit systems considering their potential advantages, such as improved bioavailability, decreased systemic toxicity and local irritation and retention in the intestine over a relatively long time. Additionally, their reduced particle size enables these systems to pass through the gastrointestinal tract easily, which leads to less interindividual variability.

Based on previous studies of enteric coating of acetylsalicylic acid that showed that the use of enteric coated granules decreases gastric bleeding and prolonged absorption time without reducing the amount of drug absorbed, sodium salicylate microcapsules coated with cellolate and castor oil were formulated (Bogentoft et al., 1978). *In vivo* study in dogs revealed a similar bioavailability between the enteric microcapsules and a conventional dosage form, but with the microcapsules

increasing the time needed to reach the maximum plasma concentration, causing less damage and producing only a slight loss of fecal blood during toxicity acute gastrointestinal bleeding test (O'Connell and Deasy, 1985).

Enteric microencapsulation has also been used as a means to minimize acid hydrolysis and enhancing oral drug delivery (Al-Ghananeem et al., 2010). The administration in Rhesus Macaques of TRAM-34 microparticles (potential immunosuppressant), coated with Eudragit® L100, illustrates six times the improvement in oral bioavailability compared to the powder form, due to bypassing the gastric acid conditions. Similar results have been obtained with preparations containing pancreatic enzymes in the enteric coated preparation (Vantini et al., 1993) where the enzymes are well protected against inactivation of the acid and which show that the enteric coating is a good alternative for lipophilic compounds and labile acids.

Despite the mentioned advantages of enteric coating, in some cases, it has produced a decrease in bioavailability. Roth et al., based on the WHO recommendation to administer prenatal calcium for the prevention of preeclampsia and iron and folic acid supplements in low-income settings, conducted a study to compare the bioavailability of microencapsulated calcium and iron to modulate a differentiated release in the GI tract, iron in the stomach and calcium in the middle/distal duodenum (Roth et al., 2014). Two formulations were compared, one of uncoated $CaCO_3$ (no EC) and one of $CaCO_3$ coated (EC) with a triple-layer pH-sensitive enteric coating to achieve calcium delivery at pH 5. The $CaCO_3$ granules, both EC and non-EC, were mixed with ferrous fumarate granules which were encapsulated to direct the release of gastric iron. Despite the promising results of the *in vitro* dissolution study, the *in vivo* study, conducted in women in the third trimester of pregnancy, showed that the enteric coating caused a substantial decrease in the bioavailability of calcium, with the fraction of the drug absorbed at 48 h, 85% lower in the enteric coated formulation with respect to the same uncoated formulation, together with greater adverse effects, such as vomiting. This decrease in bioavailability may be due to delayed or incomplete disintegration of the enteric coating due to a duodenal or jejunal pH of 5.5 (Khatik et al., 2015), or to poor absorption of calcium released into the small intestine, which is related in part on its solubility, which in turn, is a function of the kind of salt, the dose and the pH. Despite these results, a line of research has been opened to address the implementation and expansion of the WHO's recommendations for prenatal calcium.

6.2.4. Microparticles

The enteric coating has also been a resource to improve the administration of digoxin (Bergdahl et al., 1980). Most of the available digoxin preparations have been developed to facilitate absorption and avoid bioavailability problems related to pH, which generate a high concentration of glycosides in the plasma associated with secondary effects, such as nausea and arrhythmia. As a solution to these problems, capsules of a formulation loaded with digoxin microparticles protected by an enteric thin layer prepared to dissolve at a pH close to neutral have been formulated. The digoxin absorbed from the enteric formulation was equivalent to that of an immediate-release reference tablet, but with a decrease in plasma peaks and a significant delay in Tmax, which reduced some of the side effects of the treatment with digoxin. Similar results have been obtained by other authors by preparing microspheres with enteric coating of diclofenac sodium, using Eudragit® L100 as pH-dependent release-controlling polymer (Hosny et al., 1998).

The administration of coated microparticles of pantoprazole to dogs along with a single oral dose of pantoprazole (40 mg) as a reference tablet showing that the relative bioavailability of pantoprazole from both formulations after oral dosing was similar, with a significantly lower lag time after administration of the microparticles. The gastroresistant pantoprazole loaded microparticles were equivalent in the extent of absorption to the reference tablets but not in the absorption rate, showing that this system is an alternative to tablet and has the advantage of reducing time to response (Raffin et al., 2010).

Based on the same principle that enterically coating microparticles prevents stomach degradation and improves the bioavailability of poorly soluble drugs, the pharmacological potential of enterically coated biocin A microparticles (ECMP) in hypertensive ovariectomized rats (Ovx-HT) has been studied. The *in vitro* studies showed that the enteric coating prevents the delivery of the drug in the stomach and therefore the degradation of the biocide. The study was completed with the administration of deoxycorticosterone acetate to ovariectomized rats to induce Ovx-HT, and the formulation showed a delayed release of the drug, a significant increase in oral bioavailability, a significant reduction in mean arterial pressure, systolic and diastolic blood pressure, reduced lipid peroxidation and tumor necrosis factor-alpha (TNF-α) level, a significant increase in serum nitrite and reduced glutathione (GSH) level (Sachdeva et al., 2016).

An important subject in the field of enteric coating has been the search for new strategies for the formulation of protein drugs for oral administration. To resolve the problems of low bioavailability and the absorption capacity of allergens during oral immunotherapy, some stabilization strategies have been described lately, one of them being the enteric coating of particles (Polovic and Velickovic, 2008). Thus, the coating of ambrosia pollen with polymethacrylic acid makes the formulation resistant to acidic pH for at least 6 h and allows rapid dissociation at a pH higher than 6.0, where the proteins are released in their native form. Clinical studies showed that treated patients developed high titers of inmunoglobulin antibodies specific for ragweed without other side effects apart from mild gastrointestinal (Litwin et al., 1997; Litwin et al., 1996). A subsequent study showed that coencapsulation of ambrosia and ovalbumin proteins produces a greater immune response than encapsulation of ambrosia without ovalbumin (Michael, 1997). In the same way, different studies have formulated insulin for oral administration (Brange, 1997; Sood and Panchagnula, 2001). The encapsulation of insulin in Poly(lactic-*co*-glycolic acid) PLGA microparticles coated with Eudragit® L-30D combines the stability of the protein in polymeric particles, acid resistant capacity and rapid release of the protein at the alkaline medium, requirements for the development of the polymer formulation for the oral delivery of proteins. PLGA polymer particles are biodegradable and show a controlled release profile while the Eudragit® coating helps to protect insulin trapped in the polymer particles from acid denaturation, so that a single daily oral dose of microparticles loaded with insulin and coated with Eudragit® L30D allows for the maintenance of blood sugar levels in rats with induced diabetes (Naha et al., 2008).

The enteric coating of microparticles, combined with potentially mucoadhesive polymers, has been used for oral administration of ginsenoside saponins due to the limited stability of ginsenosides in acidic pH and the low permeability of saponins. The enteric polymer used was Eugragit® L-100-55, together with other excipients of the polymer type, such as ethylcellulose, chito-oligosaccharide and chitosan in order to increase mucoadhesivity. *In vitro* studies showed drug release mostly at neutral pH and mucoadhesive capacity at neutral pH, constituting a promising strategy to improve the bioavailability of saponins when administered orally (Baek et al., 2015).

6.2.5. Nanoparticles

Different studies have demonstrated the utility of enteric coating nanoparticles to modify bioavailability. The Val-Leu-Pro Arg peptide (VLPVPR) effectively decreases the blood pressure of spontaneously hypertensive rats, however, this effect is limited due to its low oral absorption. To solve this problem, enteric-coated nanoparticles were prepared and characterized. *In vivo* studies showed that orally administered VLPVPR nanoparticles reduced blood pressure, demonstrating that these nanoparticles have prolonged antihypertensive effects in hypertensive rats (Sun et al., 2014).

The enteric coated formulations may produce intestinal damage by

the rapid release of the drug in the small intestine. To solve these problems, enterically coated sustained release nanoparticles were developed, preparing the core-shell nanoparticles using acetylsalicylic acid (ASP) as a drug, the pH-sensitive polymer Eudragit® L100-55 as external coating and the polymer Eudragit® RS as the inner core (Hao et al., 2014; Hao et al., 2013). This system, can protect the stomach, to control the steady-state levels of the drug and reduce side effects. These results, together with the mild *in vitro* cytotoxicity and the fact that the nanoparticles are captured by the Caco-2 cells in the first hour of the cellular uptake study, indicate that the enterically coated sustained released nanoparticles preparation would be a safer and more effective for the oral administration of drugs, reducing secondary effects and improving the therapeutic effect, in diseases like epilepsy and depressive disorder, who must adhere to long-term treatment. The same results, with a sustained effect over time, have been shown with the use of enteric coated microparticles of metronidazole (Reddy et al., 2009).

Studies carried out with pH sensitive polymeric nanoparticles show also promise for the oral administration of peptidic drugs and poorly soluble drugs (Wang and Zhang, 2012). pH-sensitive nanoparticles can improve drug stability and mucoadhesion, increase residence time in GI tract, improve permeability and increase solubility for drugs with poor absorption. Thymopentin (TP5), a potent immunomodulating drug, was incorporated into chitosan nanoparticles coated with Eudragit® S100. The chitosan nanoparticles were able to protect TP5 from enzymatic degradation and increase the degradation half-time of TP5. The administration in suppressed rats, showed the lowered T-lymphocyte subsets values significantly increased and the CD4+/CD8+ ratio reduced, indicating these results that this kind of nanoparticles may be used as a delivery system for TP5 (Zheng et al., 2006).

Subsequently, the use of enteric-coated polymeric chitosan nanoparticles was proposed as a way to avoid the side effects of 5-FU, a drug used, together with oxaliplatin, in the treatment of colorectal cancer (Tummala et al., 2015). The *in vitro* release study showed that the 5-FU nanoparticles release the drug after some hours in contact with the intestinal fluid, which prevents release in the stomach and improves their release in the colonic region. These results show that the enteric nanoparticles thus formulated are candidates to improve the location of the drug in the area of the colon and achieve a sustained release over an extended period of time. This confirms the theory previously proposed by authors such as Kivilcim and colleagues, which revealed the future of 5-FU nanoparticles as a promise of a drug delivery system that could be improved, including enteric coating to overcome degradation (Öztürk et al., 2017).

6.3. Drug delivery systems

Enteric coating, as already mentioned above, allows the delivery of a drug in a specific part of the gastrointestinal tract or after a predetermined time after its administration. This is a very interesting challenge and has been widely studied, in particular in the design of colonic formulations. Some of these, already mentioned above, are formulations based on pellets that, in some cases, create an improvement in bioavailability with respect to formulations already on the market (Lu et al., 2016). Sometimes, the enteric coating has allowed for delivery of the drug to the colon, not in order to increase its absorption but to increase its local effect in that area, which significantly reduces its toxic effects (Gao et al., 2006).

The multiple variables involved in the behavior of pharmaceutical dosage forms during their passage through the GI tract make it necessary to look for systems that allow their behavior to be standardized in order to avoid high *in vivo* variability after the administration of the drugs. One of these variables is, for example, the gastrointestinal transit (Amidon et al., 2015; McConnell et al., 2008; Varum et al., 2010). Several authors have used the combination of enteric coatings with the mucoadhesive property of different polymers to reduce this variability (Varum et al., 2011). As a result, carbomer-based pellets (mucoadhesive) were formulated and coated with two layers of Eudragit® S in order to adjust the rate at which they dissolve. In this way, adhesion to the mucosa is achieved once the coat is dissolved. This led to longer residence time in the colon and an improvement in bioavailability.

Some authors combined the use of enteric polymers with the formulation of small systems, such as micro and nanosystems, based on the discovery that small size particulate delivery systems could be phagocytosed by the macrophages involved in the immune response generated in inflammatory bowel disease (Nakase et al., 2000). In this way, it is possible to deliver the drug in the biophase based on the targeting of immune cells. It has been found that the accumulation of these delivery systems based on this approach is dependent on the particle size of the system, being greater the smaller the particle size (Lamprecht et al., 2001; Stein et al., 1998). In light of this, a formulation was created consisting of pH sensitive nanospheres obtained by spontaneous emulsification and a combination of the enteric polymers Eudragit® S100 and PLGA to deliver the drug to the colon (Makhlof et al., 2009). This system prevents the release of the drug in the stomach and at the same time allows it to be released in a controlled manner to avoid significant losses before reaching the biophase, which is a frequent problem in formulations based only on the pH-sensitive formulation approach (Yang et al., 2002). Moreover, this combined strategies approach allows for an increase in the bioavailability of the drugs used for colonic diseases and a reduction in their common adverse effects.

Another way to target the drug to the colon is combining enteric coating and time-dependent systems as a way of addressing the disadvantages that both systems have when used separately. Consequently, there are several formulations on the market based on this approach, such as Pulsincap®, Chronotopic®, Eudracol® (Kotla et al., 2018; Park et al., 2017; Patel, 2011; Yang et al., 2002). This dual strategy, combined in turn with small-size formulations has been used by some authors, such as Naeem et al., who designed budesonide nanoparticles with coatings of Eudragit® RS100 (time-dependent polymer) and FS30D (pH-dependent polymer) to reduce the drug release in the upper part of the GI tract and target the colon (Kotla et al., 2018; Naeem et al., 2015). Conventional oral drug delivery with pH dependent polymers is conditioned by multiple factors involved in the GI environment, such as irregular pH changes, variability in transit time and inter-patient variability (Kotla et al., 2018). Instead of, microbiota-activated delivery systems are an interesting approach. Different authors, such as R. Dubey et al., have combined this strategy with enteric coating to target the system at the particular pH of the GI tract. These authors designed a multiparticulate delivery system based on chitosan and coated with an acrylic polymer such as Eudragit® S100. With this site-specific drug delivery system, the authors managed to reduce the absorption in the small intestine and consequently the side effects and the leak of drug from the distal part of the GI tract (Dubey et al., 2010).

The combination of enteric polymers in the coating and swelling polymers in the core has also been an interesting strategy for modifying the kinetics of drugs while maintaining or improving their bioavailability. Consequently, matrices of diltiazem were designed with cross-linked PVP in the core and an enteric layer based on ethylcellulose and Eudragit® L. This enteric layer was intended to achieve a pulsatile release kinetic while preventing the release of the drug in the stomach and allowing for its rapid release after a specific period of time (Fan et al., 2001). The thickness of the coating allowed the lag time to be adjusted and the Tmax to be delayed *in vivo* without losing bioavailability with respect to the commercial sustained release reference formulation and a good *in vivo-in vitro* correlation was also obtained.

Furthermore, nanoemulsions and self-nanoemulsifying drug delivery systems (SNEDDS) in particular are very interesting methods for improving the bioavailability of many drugs, including proteins that are inactivated in the stomach or that present permeability problems (AboulFotouh et al., 2018; Singh et al., 2016). This is the case with insulin. The oral bioavailability of insulin is negligible, mainly due to its

inactivation at acid pH, its proteolytic degradation by different enzymes of the GI tract and its low permeability through the GI membranes (Grabovac et al., 2008; Li et al., 2014). Consequently, the formulation of insulin for oral administration is an important challenge (Li et al., 2012). Several systems have been tested to get over these difficulties, such as liposomes or nanoparticles (Mathiowitz et al., 1997; Takeuchi et al., 1996). An insulin SNEDDS was developed and then later introduced into a capsule before being coated with Eudragit® L100 with the purpose to avoid the release of the drug at pH < 6 (Li et al., 2014). This system allowed the insulin to be targeted to the small intestine, with the enterically coated SNEDDS capsules obtaining an enhancement in insulin transport as well as a prolonged hypoglycemic effect in contrast with plain insulin solution. An oral formulation of insulin, in this case a patch system, was also designed. This is constituted by three layers: a mucoadhesive layer, a water-insoluble layer and a final layer based on an enteric polymer. This system provides improvement of intestinal absorption thanks to the combined use of an enteric polymer that avoid the drug release in the stomach and a mucoadhesive excipient that guarantees prolonged residence time in the intestine. An increase of insulin in blood was achieved around 4 h after administration, which corresponded with a reduction of blood glucose levels after the insulin administration. The oral formulation based in a patch system has a relative bioavailability of 2.2% with the subcutaneous formulation (Grabovac et al., 2008).

Another possible strategy for delivering drugs in a controlled manner is OROS systems, which are based on the constant release of a drug by an osmotic pressure gradient created within the system. The factors involved in the physiological conditions of the GI tract, such as water/fluid availability, are a challenge for the development of osmotic drug delivery systems. A microporous bilayer osmotic pump tablet was developed using a coating of pectin and Eudragit L-100-55 in different proportions for the treatment of irritable bowel syndrome (Chaudhary et al., 2011).

6.4. Coated formulation types review

The improvement of bioavailability of enteric coated monolithic systems such as tablets, capsules or delivery systems is based on the controlled release in a specific site of the small intestine producing a more homogeneous dissolution and a more efficient absorption. Also, enteric coated monolithic systems have been used as a strategy for colon targeting and absorption control for different drugs.

Enteric coated multiparticulate systems such as pellets or microcapsules may achieve better *in vivo* sustained release behavior and are a good strategy for improving the bioavailability of many drugs. In addition, a greater stability, reduced toxicity and local irritation, increased transit time in the intestine and a lower interindividual variability in the absorption is obtained with this kind of systems.

As disadvantages, enteric coating may produce in some cases a decrease in the bioavailability due to formulation problems, incomplete or delayed disintegration of the enteric coating due to the variability in the intestinal pH or problems related to the low solubility of the drug.

Some of these coated formulations have been marketed. Table 2 summarizes the marketed products cited in this review based on enteric coating.

6.5. Enteric formulations using alternative strategies to coating

An alternative to the use of enteric coating formulations for drugs that are instable to the acidic pH of the stomach is the use of solid dispersions containing alkalizers. MgO-containing solid dispersions with HPMC 6 cps grade were a promising system for stabilizing esomeprozole magnesium dihydrate without using enteric coating while still maintaining bioavailability: Its gastric stability was confirmed in *in vivo* studies in Beagle dogs where this system showed a similar drug bioavailability to the enteric reference tablet (Van Nguyen et al., 2017). The mechanism of the drug's protective effect is not clear, though the formation of intermolecular complex and the microenvironmental (pHM) modulation appear to be involved (Park et al., 2015).

Similar results were obtained previously through the control of the environmental pH in a crystalline solid dispersion of clarithromycin. In this study, the solid dispersions were obtained using HPMC and Polyvinylpyrrolidone (PVP) as polymers and MgO and NaHCO3 as alkalizes (Park et al., 2015).

Another alternative to enteric coated formulations is to use buffered immediate release formulations that, through the use of buffering substances increase the stability of acid-labile drugs with good absorption capacity into the stomach. These formulations are called *in situ* buffer formulations and can be prepared as different types of monolithic or multiparticulate systems such as buffer tablets, buffer capsules or buffer microspheres. In enteric-coated formulations, a delay in the absorption of the drug and in the onset of action can occur depending on the gastric emptying however in buffered formulations the acid-labile substances may be absorbed in the stomach (Khulbe et al., 2017).

7. *In vitro* evaluation of enteric coated dosage forms

Usually, *in vitro* evaluation of enterically coated dosage forms involves the use of classical pharmacopeia disintegration tests or dissolution testing using phosphate buffer medium at pH's of 1.2 or 6.8. The phosphate buffers used have a high buffer capacity in comparison with the small intestine and appreciable differences between disintegration *in vitro* and *in vivo* are observed. There is a fairly oversimplifying concept that the disintegration and dissolution of enterically coated dosage forms begins immediately after gastric emptying. This is assumed by some pharmacokinetic software, such as Gastroplus, which assumes that the release starts immediately after arriving in the small intestine, or Simcyp, which consider that the release starts at an intestinal segment where the pH is similar to the pH of dissolution of the cover (Al-Gousous et al., 2017).

A modified Hanks buffer was developed to evaluate dissolution profiles of enterically coated dosage forms. Prednisolone tablets coated with different kinds of enteric polymers showed delayed drug release similar to the delayed disintegration times cited in previous research for enterically coated formulations (Liu et al., 2011). Bicarbonate buffer systems are quantitatively the most important buffer of the extracellular fluid and may be used to simulate the intestinal buffer system. These kinds of buffers have been proposed to predict the behavior of enterically coated dosage forms after gastric emptying (Shibata et al., 2016). A device called Auto-pH system™ allow a pH dissolution media to be controlled using a physiological bicarbonate buffer. With this system, dissolution testing under dynamic mode (pH 5.6–6.8) provides a more realistic *in-vitro* assessment for enteric-coated dosage forms (Garbacz et al., 2014; Merchant et al., 2014; Varum et al., 2014).

Differences in the dissolution profiles of enteric coated formulations have been observed between physiological bicarbonate buffers and compendial buffers. A study demonstrate that dissolution testing of enteric coated tablets of proton pump inhibitors allows to establish the differences in the dissolution profiles of different types of enteric coated formulations using bicarbonate buffers compared to mHanks buffer. Dissolution profiles in bicarbonate buffer are slower than in mHanks buffer although the clinical implications of these differences are still unknown (Shibata et al., 2016).

Moreover, an *in vitro* evaluation method with specific predictivity for enteric dosage forms has been proposed (Al-Gousous et al., 2016; Al-Gousous et al., 2017). In addition to *in vitro* studies, the use of mathematical tools such numerical convolution contribute to the prediction of the *in vivo* behavior, bioavailability and the IVIVC of enteric dosage forms (Al-Gousous et al., 2016; Al-Gousous et al., 2017).

Table 2
Marketed products commented in this review based on enteric coating as a tool to enhance the bioavailability.

Drug	Marketed products	Dosage form	Manufacturer
Acetylsaliciylic acid	Premaspin®	Enteric-coated tablets	Lääke
	Aspirin Enteric Coated®		Chain Drug Consortium
Acetylsaliciylic acid	Reumyl®	Enteric-coated granules (in hard gelatin capsules)	Hässle
Diclofenac sodium	Voltaren®	Enteric-coated tablets	Novartis Pharma
	Dicloas®		Astra Life Care Pvt.
	Dicloran®		Unique Pharmaceutical Labs
	Diclo-denk®		Denk pharma Gmbh & Co
Ketoprofen	Forenol®	Enteric-coated tablets	PHARMA INVESTI
	Profenid®		Sanofi-Aventis
Esomeprazole magnesium	Nexium Mups®	Multiple Unit Pellet System with enteric coated pellets	AstraZeneca AB
Esomeprazole magnesium	Nexium®	Enteric-coated granules (in hard gelatin capsules)	AstraZeneca AB
Mycophenolic acid	Myfortic®	Enteric-coated tablets	Novartis Pharma
Omeprazole	Losec Mups®	Multiple Unit Pellet System with enteric coated pellets	AstraZeneca AB
Omeprazole	Losec®	Enteric-coated granules (in hard gelatin capsules)	AstraZeneca AB
	Omeprazol EDG®		GERMED FARMACÉUTICA
Naproxen/esomeprazole magnesium	Vimovo®	Enteric-Coated Pellet Formulations	AstraZeneca AB

8. Conclusions

In recent years, different formulation strategies based on the use of enteric coating combined with other methods that improve the bioavailability of orally administered drugs have been tested. Among the strategies used, the following can be highlighted. For molithic systems such as tablets or capsules, the combined use of enteric coating and soluble salts of the drug resulting in a more homogeneous dissolution and improved bioavailability. In addition, when there is an absorption window the enteric coating facilitates the dissolution of the drug in specific parts of the gastrointestinal tract such as the ileum improving the absorption.

In the case of multiparticulate systems, such as granules, pellets, microcapsules, micro and nanoparticles, the strategies to improve bioavailability based on the enteric coating are, among others, the controlled release of the drug in a pH–dependent way, to reduce the drug degradation in the stomach and to reduce the variability in plasma concentrations, the combination of enteric coating and multi-layer formulation to control drug release and bioavailability and the combination of the enteric coating of microparticles with potentially mucoadhesive polymers specially for drugs with poor absorption.

In spite of many strategies associated with enteric coating achieving improvements in both rate and magnitude of bioavailability, the problems which may influence serum levels and the onset of the drug's therapeutic action are gastrointestinal pH values, gastrointestinal environment, inter-individual or intra-individual variability in gastric emptying and gastrointestinal transit time, interpatient variability associated with the type of polymer used for enteric coating or other formulation variables may influence the changes in bioavailability associated with the enteric coating.

Interindividual variability in gastric emptying and transit time may alter the absorption in the distal portions of GI specially in drugs with low solubility or with a specific absorption window. Enteric coated multiparticulate systems may contribute to improve the biopharmaceutical behavior and drug absorption and to reduce the inter-individual variability in comparison with monolithic dosage forms.

In summary, the enteric coating of oral pharmaceutical dosage forms should be considered as a formulation factor with potential implications for the bioavailability of drugs and must be taken into account in the initial stages of drug development and evaluation.

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