PPIs' Drug Dosage Forms Development - Formulation Challenges

Subjects: Pharmacology & Pharmacy

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Proton Pump Inhibitors, also known as PPIs, belong to a group of antisecretory drugs. Since their introduction to pharmacotherapy, PPIs have been widely used in the treatment of numerous diseases manifested by excessive secretion of gastric acid. There are still unmet needs regarding their availability for patients of all age groups. Their poor stability hinders the development of formulations in which dose can be easily adjusted.

Keywords: proton pump inhibitors ; delayed-release tablets ; enteric coating ; stability ; PPIs ; formulation development ; drug dosage form ; modified release

1. Introduction

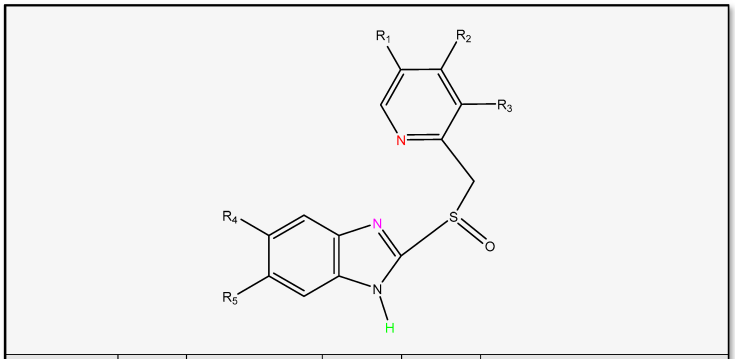
Proton pump inhibitors have been found to be very effective in suppressing gastric acid secretion. They share the same mechanism of action, although there are slight differences in their chemical structure [1]. PPIs inhibit the activity of the enzyme H+/K+-ATPase, also named gastric proton pump, located in the parietal cells of the stomach. Proton pump inhibitors are inactive compounds (often simply but incorrectly called ‘prodrugs’), which require activation in the low pH of parietal cells, to suppress the activity of the proton pump. Therefore, to avoid premature activation in the stomach after oral administration, they must be protected from gastric acid, e.g., with enteric coating [2].

2. The Most Important Issues to Be Considered in the Formulation of Medicinal Products with PPIs

The formulation of medicinal products containing proton pump inhibitors is a challenging process, mainly due to their low water solubility and stability problems [3].

2.1. Physicochemical Properties of PPIs

The molecular structure of all proton pump inhibitors (beside tenatoprazole) is based on the 2-pyridylmethylsulfinylbenzimidazole moiety (**Figure 1**). It can exist in several states of protonation depending on the pH of the solution. Therefore, they can be characterized by two or even three pKa values. The first value of pKa ranging from 3.55 to 4.77 is associated with the acceptance of protons in the nitrogen atom of pyridine (marked red in **Figure 1**) in an acidic environment and the second results from the dissociation of a proton from the benzimidazole ring (marked green in **Figure 1**) in presence of alkalis [4]. The pKa_2 values reported in the literature range from 9.15 for pantoprazole to 10.10 for ilaprazole [5].



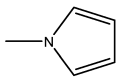
PPIs	R1	R2	R3	R4	R5
Omeprazole	$-CH_3$	$-O-CH_3$	$-CH_3$	-H	$-O-CH_3$
Pantoprazole	-H	$-O-CH_3$	$-O-CH_3$	-H	$-O-CHF_2$
Lansoprazole	-H	$-O-CF_3$	$-CH_3$	-H	-H
Rabeprazole	-H	$-O-(CH_2)_3-O-CH_3$	$-CH_3$	-H	-H
Ilaprazole	-H	$-O-CH_3$	$-CH_3$	-H	

Figure 1. Chemical structure of proton pump inhibitors.

Another important aspect of the chemical structure of proton pump inhibitors is their chirality. PPIs possess the asymmetric sulfur molecule in the sulfinyl moiety, which binds pyridine with the benzimidazole group or, in the case of tenatoprazole, with the imidazopyridine core. Therefore, all PPIs may exist in the forms of S- or R-enantiomers as well as racemates [6][7].

PPIs are very slightly soluble in water but dissolve easily in alkali solutions or ethanol. In the form of sodium or magnesium salts (e.g., omeprazole sodium) are freely soluble in water and ethanol and therefore are used in intravenous administration. Proton pump inhibitors are lipophilic drugs with logP values in the range of 1.6 to 2.8 [5]. Omeprazole and lansoprazole, as well as their stereoisomers, belong to class II of the Biopharmaceutical Classification System, due to their poor solubility in water and high permeability through cell membranes [8][9][10][11]. On the other hand, pantoprazole and rabeprazole were classified as provisional BCS class III [12][13].

2.2. Stability of Proton Pump Inhibitors

Proton pump inhibitors are sensitive to the acidic environment, light, temperature, oxidative conditions, and the presence of other salts. They are relatively stable at pH = 7.0, but quickly decompose in acidic solutions. The degradation of omeprazole at low pH occurs within 24 h while it is most stable at pH = 11.0. It was found that in solutions with pH above 7.8 the degradation of this PPI followed the first-order kinetics [14].

2.2.1. Stability in Solutions

DellaGreca et al. [15] investigated the degradation products of omeprazole and lansoprazole in aqueous solutions using NMR spectroscopy. Hydrolysis reaction was observed in water solutions and solutions adjusted to a pH of 4.0. At pH of 7.0 and 9.0 lansoprazole and omeprazole remained unchanged for 43 and 72 h, respectively. For both drugs, the main hydrolysis products were benzimidazolones, sulfides, and the red residue identified as a very labile mixture of degradation products, impossible to separate. Exposition of the water solution and solutions adjusted to a pH = 7.0 to solar light accelerated the degradation of the PPIs. In this case, dianilines, pyridines, and benzimidazoles were found among the degradation products [15].

Studies on the stability of rabeprazole revealed that it was highly unstable in 0.1 M hydrochloric acid solution, as well as in a 30% solution of hydrogen peroxide, in which it decomposed within 60 min [16].

Mahadik et al. [17] studied the stability of tenatoprazole under various stress conditions. Hydrolytic decomposition of the drug substance was measured in 0.1 M hydrochloric acid. After 30 min of study, 40% of tenatoprazole remained unchanged. At a lower concentration of the acid solution (0.01 M), complete degradation of the substance occurred after 4 h. In a basic environment of 1 M sodium hydroxide at 80 °C, approximately 20% of tenatoprazole decomposed after 4 h of incubation. The drug substance was also unstable under oxidative conditions of 30% hydrogen peroxide solution, in which 60% of the drug degraded in 1 h. After exposure to solar light for 1 h, more than 20% of tenatoprazole has been decomposed. Despite that, the substance in its solid form remained stable for 2 months exposed to dry heat (50 °C) [17].

In another research, it was found that omeprazole solutions in the presence of acids change their color to yellow, dark red, brown or purple, whereas pharmaceutical formulations containing PPIs were unstable under heat and moisture conditions, changing their color from brown to dark brown [18].

2.2.2 Influence of Temperature

Several research studies evaluated the effect of storage temperature on the stability of omeprazole, which has a significant impact on extemporary compounded medicines, which are usually prepared for pediatric patients. In one of them, the 2 mg/mL omeprazole solution in 8.4% sodium bicarbonate was kept at −20 °C, 5 °C, and 24 °C for 30 days. The liquid stored at room temperature gradually changed color to brown, indicating the appearance of degradation products. At the end of the study, the omeprazole content in the sample was 84.2% of the initial concentration. The solutions stored at low temperatures remained stable for the research period [19]. It was found in another study that the half-life of omeprazole in the solution at pH 7.5 at a temperature of 4 °C was 125 days, while at a temperature of 40 °C it was only 42 h [20].

2.2.3 Influence of Salts

The stability may be affected not only by the pH value but also by the presence of other ions in the solution. In one of the studies on the stability of omeprazole, pantoprazole and lansoprazole, it was found, that the most stable compound in the pH range of 4.0 to 7.0 was pantoprazole, whereas the least stable was lansoprazole. The degradation of PPIs was related to the increasing concentration of hydrogen ions and salts in the solutions. The lowest stability of the investigated PPIs was observed in the 0.5 M citric, phosphate, and acetate buffer solutions (at pH = 6), as well as in the trisodium citrate solution (0.025 M and 0.25 M). The highest stability was achieved in the water and sodium chloride solutions (0.05 M and 0.5 M) in the entire range of measured pH values [21]. The half-life of pantoprazole sodium in phosphate-buffered solution maintained at pH = 7.4 was found to be approximately 124 h [22].

2.2.4 Influence of Light

Dhurke et al. [23] investigated the effect of UVA, UVC, and solar light on the degradation of pure and microencapsulated pantoprazole. After seven days of exposure to pure pantoprazole to UVC radiation (254 nm), its degradation rate was 38.09%, while in UVA radiation conditions (366 nm) 35.11%. What is more, the half-life of pure pantoprazole affected by solar light was found to be 8.6 days. The process of microencapsulation with the Eudragit S significantly improved the stability of pantoprazole during exposure to all types of radiation investigated, because the physical barrier for light was formed [23].

The impact of UVC radiation on pantoprazole was also measured by Raffin et al. [24]. Pantoprazole methanolic solutions were exposed to radiation at 254 nm. It has been reported that 98.8% of API degraded within 120 min of the study. The stability of pantoprazole powder was higher than that of the methanolic solution, i.e., 27% of the drug remained stable after 10 days of exposure to UVC radiation. Similarly to the previously mentioned study of Dhurke, microencapsulation with Eudragit S100 increased the stability of pantoprazole. After 10 days of exposure to UVC radiation, 55% of the API remained unchanged [24].

Garcia et al. [16] investigated the stability of rabeprazole methanolic solutions (800 µL/mL) exposed to UVC radiation. It was observed that 88% of the substance decomposed in 30 min, characterized by zero-order kinetics. It was found that the two main photodegradation products of rabeprazole were benzimidazole and benzimidazolone. The same experimental conditions were applied to the crushed and solid tablets containing rabeprazole—the degradation products of API could be observed after 10 and 50 days, respectively. The higher stability of rabeprazole in solid form than in solution was explained by the presence of excipients and the smaller surface area exposed to radiation in the case of tablets. Furthermore, tablets containing rabeprazole were found to remain unchanged for 4 days at a temperature of 80 °C [16].

2.3 Interaction of Enteric Polymers with PPIs and Its Effect on the Stability

One of the most challenging aspects of the PPIs' pharmaceutical development is their instability under acidic conditions. To avoid premature release and degradation of API in the stomach, enteric-coating polymers are used. The gastro-resistant coating provides delayed, site-specific, and pH-dependent release of the drug substance in the small intestine. Enteric polymers are composed of long chains of organic monomers with free carboxylic residues. Their pKa values range between 4 and 6. Acidic moieties of enteric polymers undergo ionization and dissolve rapidly in the small intestine, but remain unionized in an acidic environment [3][18][25]. Examples of polymers commonly used for enteric coating are polymethacrylates (Eudragit® L, Eudragit® S), cellulose derivatives (cellulose acetate phthalate, CAP), polyvinyl

derivatives (Opadry® Enteric), resins (AquaGold® shellac), and starch derivatives (Aqua-Zein®) [3]. Unfortunately, the presence of free acidic moieties in the tablet coat or in tablet mass can affect the stability of PPIs. A series of experiments conducted by Riedel et al. [26][27] provided data on the molecular interactions between omeprazole and enteric coating polymers [26][27].

To avoid the risk of interaction between the enteric coating layer and the drug substance, an inert polymer can be applied to create a separating layer on the tablet or granule core. For this purpose, cellulose derivatives (HPC, HPMC), sucrose, polyethylene glycol, and povidone are generally used. A separating coat can also be formed with alkaline substances, such as sodium salts of weak inorganic or organic acids. Moreover, it was described that a pH buffering coat can be created in situ. In this case, a separation layer is formed in the reaction of the alkaline base material with an acidic enteric coating material [18].

3. PPIs' Pharmaceutical Formulations Available on the Market

PPIs are administered by two different routes: oral or intravenous. Currently manufactured dosage forms for oral administration include enteric-coated capsules, enteric coated tablets, multiple-unit pellet system (MUPS), and suspensions with microparticulates. For intravenous administration, PPIs are available as lyophilized powders for reconstitution [25]. There are a large number of manufactured brand and generic products, among which are:

- Delayed-Release Tablets, including MUPS and ODT formulations,
- Delayed-Release Capsules,
- Oral Suspensions,
- Powders for Injections or Infusions,
- Fixed-Dose Combinations.

It is worth mentioning, that proton pump inhibitors can be administered to adult and pediatric patients who require enteral nutrition via a feeding tube. However, factors such as the risk of clogging the tube or adhering the drug to the walls of the tube or the possibility of drug degradation should be carefully considered before administration . The most convenient dosage forms for application via feeding tube are those composed of pellets or granules that can be easily dispersed in water or other vehicles. These include tablets or capsules containing delayed-release pellets, as well as granules for oral suspensions [28]. PPIs should be administered via feeding tube only in accordance with the manufacturer's recommendations.

4. Development of New Formulations with PPIs

Proton pump inhibitors have been marketed worldwide for more than 30 years [29][30]. At this time, many pharmaceutical solutions have been proposed to improve their acceptability, stability, safety, and efficacy. The most popular route of administration of PPIs is oral, which is the most common for all medicinal products. Formulations with PPIs include numerous dosage forms, starting from simple enteric-coated tablets or pellets encapsulated in hard gelatine capsules, through the other novel form of tablets, and ending with many different forms of micro- or nanoparticulates. There have also been some approaches to the administration of PPIs through alternative routes of administration, such as transdermal or rectal.

The detailed information on PPIs' formulations described in the literature have been collected in table 1.

Table 1. PPIs' formulations described in the literature.

Formulation	PPI	Development Stage	Description
Nanoparticles			
		In vitro **In vivo antiulcer activity (rats)**	• Enteric-coated nanocapsules, • Functional polymers: HPMCP, PVAP, • Obtained by emulsification method
	Omeprazole		
		In vitro **In vivo antiulcer activity (rats)**	• Enteric-coated nanoparticles, • Functional polymers: Eudragit L 100–55, chitosan, • Obtained by complex coacervation method
		In vitro	• pH-sensitive polymeric nanoparticles, • Functional polymers: Eudragit S 100, HPMCP (HP–55), • Obtained by nanoprecipitation method
	Pantoprazole		
		In vitro	• Sustained-release solid lipid nanoparticles (SLNs), • Functional polymers: ethylcellulose, chitosan, HPMC K100, PVA, • Obtained by nanoprecipitation method
	Pantoprazole + Aceclofenac	**In vitro** **In vivo (rats)**	• Sustained-release nanofibers, • Functional polymers: zein, Eudragit S 100, • Obtained by single nozzle electrospinning

Formulation	PPI	Development Stage	Description
		In vitro	• Sustained-release nanoparticles, • Functional polymers: Eudragit RS 100, • Obtained by oil-in-water emulsion-solvent evaporation method
	Lansoprazole	**In vitro**	• Controlled-release nanosponges, • Functional polymers: ethylcellulose, PVA, • Obtained by emulsion solvent diffusion method
		In vitro	• Immediate-release niosomes, • Obtained by reverse phase evaporation method
		In vitro	• Nanosuspensions composed of β-cyclodextrin-API complexes or β -cyclodextrin-API nanosponges, • Obtained by physical method or polymer condensation method respectively
	Lansoprazole + curcumin	**In vitro**	• Bioactive solid self-nanoemulsifying drug delivery systems (Bio-SSNEDDS), • Functional excipients: black seed oil, Zanthoxylum rhetsa oil, • Obtained by emulsification method
	Esomeprazole	**In vitro** **Ex vivo permeability study** **In vivo PK and PD studies (rats)**	• Proniosomes, • Functional excipients: maltodextrin (carrier), cholesterol, • Obtained by slurry method

Formulation	PPI	Development Stage	Description
Microparticles			
		In vitro **In vivo PK study (rabbits)**	• β-cyclodextrin-API complexes encapsulated with antacids in gelatine capsule, • Functional excipients: $NaHCO_3$, Na_2CO_3, MgO, $Mg(OH)_2$, • Obtained by saturated aqueous solution method
		In vitro	• Microcapsules composed of Lactobacillus acidophilus surface layer protein, • Functional excipients: ATCC 4356 S-layer protein
	Omeprazole	**In vitro**	• Complexes of latex particles with API, • Functional polymers: Aquateric (cellulose acetophthalate latex), • Obtained by adsorption method
		In vitro	• Immediate-release microparticles, • Functional polymers: Kollicoat IR, hydroxypropyl-β-cyclodextrin, • Obtained by spray-drying or freeze-drying
		In vitro	• Gastro-resistant microparticles, • Functional polymers: Eudragit S 100, hydroxypropyl-β-cyclodextrin (carrier), • Obtained by spray-drying or emulsification method
	Omeprazole + piperine	**In vivo PK and bioavailability studies (rabbits)**	• Gastroretentive microspheres, • Functional polymers: ethylcellulose, HPMC • Obtained by emulsification-solvent evaporation method
	Omeprazole + clarithromycin	**In vitro**	• Sustained-release mucoadhesive microspheres, • Functional polymers: HPMC K4M/K100M, Carbopol 971p • Obtained by non-aqueous emulsification-solvent evaporation method

Formulation	PPI	Development Stage	Description
	Pantoprazole	**In vitro**	• Gastro-resistant microparticles with improved photostability, • Functional polymers: Eudragit S 100, • Obtained by solvent evaporation method
		In vitro	• Microparticles with improved photostability, • Functional polymers: Eudragit S 100, poly(e-caprolactone), HPMC, • Obtained by emulsification- solvent evaporation method or spray-drying
		In vitro	• Gastro-resistant microparticles, • Functional polymers: Eudragit S 100, HPMCP (HP–55), • Obtained by emulsion-solvent evaporation method
		In vitro	• Sustained-release floating microspheres, • Functional polymers: Eudragit S 100, HPMC K100M, • Obtained by non-aqueous solvent evaporation method
		In vitro	• Double-walled sustained-release microspheres, • Functional polymers: HPMC, sodium alginate (1st layer), Eudragit RS 100 (2nd layer), • Obtained by emulsification- solvent evaporation method
		In vitro	• Sustained-release microsponges, • Functional polymers: Eudragit RS 100, • Obtained by quasi-emulsion solvent diffusion method
		In vitro **In vivo antiulcer activity (rats)**	• Enteric-coated, controlled-release microparticles, • Functional polymers: Eudragit S 100, poly(ε-caprolactone), • Obtained by solvent evaporation method

Formulation	PPI	Development Stage	Description
		In vitro **In vivo antiulcer activity (rats)**	• Gastro-resistant microparticles, • Functional polymers: Eudragit S 100, • Obtained by O/O emulsification- solvent evaporation method
		In vitro **In vivo antiulcer activity (rats)**	• Floating microballons, • Functional polymers: Eudragit L 100, Eudragit RS 100, • Obtained by emulsion solvent diffusion method
		In vitro **In vivo antiulcer activity (rats)**	• Gastro-resistant, controlled-release microparticles, • Functional polymers: Eudragit S 100, Methocel F4M • Obtained by spray-drying
		In vitro	• Gastro-resistant microparticles (agglomerates), • Functional polymers: Eudragit S 100, Methocel F4M, • Obtained by spray-drying
		In vitro	• Gastro-resistant microparticles, • Functional polymers: Eudragit S 100, • Obtained by spray-drying (performed in various conditions)
		In vivo bioavailability study (dogs)	• Gastro-resistant microparticles (soft agglomerates), • Functional polymers: Eudragit S 100, • Obtained by spray-drying
		In vitro **In vivo antiulcer activity (rats)**	• Gastro-resistant microparticles, • Functional polymers: Eudragit S 100, Eudragit RS 100, • Obtained by spray-drying

Formulation	PPI	Development Stage	Description
		In vitro	• Gastro-resistant microspheres, • Functional polymers: ethylcellulose, HPC (1st layer), Eudragit L-100, sodium alginate (2nd layer), • Obtained by emulsification-solvent evaporation method

Formulation	PPI	Development Stage	Description
	Lansoprazole		
		In vitro **In vivo PK and antiulcer activity studies (rats)**	• Enteric-coated, sustained-release microparticles, • Functional polymers: Eudragit RS 100, Eudragit S 100, HPMCP (HP–55), • Obtained by solvent evaporation method, coated in fluidized bed
		In vitro	• Enteric-coated microspheres, • Functional polymers: cellulose acetate phthalate (CAP), • Obtained by solvent evaporation method
		In vitro	• Sustained-release, floating microspheres, • Functional polymers: ethylcellulose, HPMC, • Obtained by solvent evaporation method
		In vitro	• Enteric-coated micropellets, • Functional polymers: HPMC E5 (sublayer), Acrycoat L-30D • Obtained by fluid bed coating
		In vitro	• Sustained-release, floating micropellets, • Functional polymers: HPMC, MC, chitosan, • Obtained by emulsion- solvent diffusion method
		In vitro	• Gastro-resistant microparticles, • Functional polymers: Eudragit S 100, Eudragit L 100, Eudragit L100-55, • Obtained by spray-drying
		In vitro	• Enteric-coated, sustained-release microspheres, • Functional polymers: Eudragit RS 100 (1st layer), HPMCP (HP-55) (2nd layer), • Obtained by solvent evaporation method and spray-drying

Formulation	PPI	Development Stage	Description
		In vitro	• Cyclodextrin metal-organic frameworks (CD-MOFs) microparticles with improved thermostability, • Functional excipients: γ-CDs, KOH, cetyltrimethyl ammonium bromide (CTAB) (stabilizer)
		In vitro **In vivo antiulcer activity (rats)**	• Gastro-resistant, sustained-release mucoadhesive microspheres, • Functional polymers: ethylcellulose, Eudragit L 100, HPMC, CMC sodium, HEC, HPC, • Obtained by solvent evaporation method and dip coating technique
	Rabeprazole	**In vitro**	• Sustained-release floating microspheres, • Functional polymers: ethylcellulose, HPMC K15M, • Obtained by emulsification- solvent evaporation method
		In vitro **In vivo floating study (rabbits)**	• Controlled-release floating microbeads, • Functional polymers: sodium alginate, HPMC, $BaCl_2$/ $CaCl_2$ (crosslinking agents), • Obtained by ionotropic gelation method
	Rabeprazole + amoxicillin	**In vitro** **In vivo antiulcer activity and radiographic study (rats)**	• Sustained-release microballoons, • Functional polymers: Eudragit S 100, HPMC, • Obtained by emulsion solvent diffusion method
	Esomeprazole	**In vitro**	• Sustained-release floating microspheres, • Functional polymers: HPMC, MC, chitosan, • Obtained by solvent evaporation method

Formulation	PPI	Development Stage	Description
Minitablets	**Omeprazole**	**In vitro**	• Enteric-coated minitablets, • Functional coating: HPMC (sublayer), Eudragit L 30D-55, • Obtained by direct compression, coated in fluidized bed
	Pantoprazole	**In vitro**	• Enteric-coated minitablets, • Functional coating: Eudragit L 30D-55, Acryl-Eze II • Obtained by direct compression, coated in fluidized bed

Formulation	PPI	Development Stage	Description
Pellets			
		In vitro **In vivo PK and gastro-resistance studies (dogs/rats)**	• Enteric-coated pellets, • Functional polymers: HPMC (sublayer), Eudragit L 30D-55, • Core pellets coated in fluidized bed
		In vitro **In vivo PK and bioequivalence studies (rabbits)**	• Delayed-release pellets, • Functional excipients: MMC, lactose, PVP K30, • Obtained by sieving-spheronization and extrusion-spheronization methods
	Omeprazole	**In vitro** **In silico (ANN, modelling tablet properties)**	• Enteric-coated pellets, • Functional polymers: HPMC (sublayer), Eudragit L 30D-55, • Core pellets coated in fluidized bed
		In vitro	• Gastro-resistant, alginate beads, • Functional polymers: sodium alginate, SBA-15 mesoporous matrix
		In vitro	• Multiparticulate pulsatile drug delivery system, • Functional excipients: HPMC, ethylcellulose, Eudragit RS 30D, Eudragit RL 30D, NaCl (osmogent), • Obtained by film casting/extrusion-spheronization method or fluid bed coating
	Pantoprazole	**In vitro**	• Enteric-coated pellets, • Functional polymers: Eudragit L100-55 (organic/aqueous dispersion), Eudragit L 30D-55, • Obtained by film casting and extrusion-spheronization method

Formulation	PPI	Development Stage	Description
		In vitro	• Gastro-resistant multilayer pellets, • Functional excipients: Na_2CO_3 (alkaline layer), HPMC (sublayer), Eudragit L 30D-55 (outerlayer), • Core pellets coated in fluidized bed
		In vitro	• Enteric-coated pellets, • Functional polymers: HPMC (sublayer), Eudragit L100-55, • Coated in fluidized bed
		In vitro	• Gastro-resistant pellets, • Functional excipients: carboxymethyl tamarind kernel powder (CMTKP), croscarmellose sodium, MCC, • Obtained by extrusion-spheronization method
	Lansoprazole	**In vitro** **In vivo PK study (dogs)**	• Gastro-resistant pellets, • Functional polymers: HPMC, aqueous enteric coating, • Obtained by fluid-bed granulation, coated in fluidized bed
		In vitro	• Enteric-coated pellets, • Functional polymers: HPMC (sublayer), methacrylic copolymer, • Coated in fluidized bed
		In vitro **In vivo bioavailability study (dogs)**	• Enteric-coated pellets, • Functional polymers: HPMC (sublayer), Eudragit L dispersion, HPMCAS, • Coated in fluidized bed

Formulation	PPI	Development Stage	Description
		In vitro	• Enteric-coated pellets, • Functional coating: HPMC (sublayer), Eudragit L 30D-55, • Coated in fluidized bed
	Rabeprazole	**In vitro**	• Enteric-coated pellets, • Functional coating: HPMC (sublayer), Eudragit L 30D-55, • Coated in fluidized bed
		In vitro	• Enteric-coated pellets, • Functional coating: Eudragit L 30D-55 or HPMCP (HP–55), • Coated in fluidized bed
	Esomeprazole	**In vitro** **In vivo PK study (rats)** **IVIVC**	• Sustained-release, enteric-coated pellets, • Functional coating: HPC-EF/HPMC-E5 (sublayer), Eudragit RS 30D/RL 30D (1st layer), Eudragit L 30D-55 (2nd layer), • Coated in fluidized bed
		In vitro **In silico (ANN, coating process)**	• Enteric-coated pellets, • Functional coating: HPMC (sublayer), Eudragit L 30D-55, • Coated in fluidized bed

Formulation	PPI	Development Stage	Description
Tablets	**Omeprazole**	**In vitro**	• Enteric-coated tablets
		In vitro	• Enteric-coated tablets, • Functional coating: HPMCP, Eudragit S 100 or CAP plasticized with dibutyl phthalate
		In vitro	• Lyophilized orally disintegrating tablets containing enteric-coated pellets, • Fast disintegration of tablets combined with gastric resistance of pellets and their immediate release in phosphate buffer
	Omeprazole + domperidone	**In vitro**	• Directly compressed fast disintegrating tablets, • Combination of two APIs in one tablet, • No stability considerations

Formulation	PPI	Development Stage	Description
		In vitro	• API complex with rosin used to protect it from low pH, • Complexes directly tabletted with different superdisintegrants: sodium starch glycolate, crospovidone, croscarmellose sodium
		In vitro **In vivo antiulcer activity (rats)**	• Sustained-release, enteric-coated tablets, • Slow release was achieved by forming matrix using HPMC, cassava starch or PVP, • Enteric coating: cellulose acetate phthalate (CAP) or Eudragit L 100, • No degradation of API in acid phase detected; prolonged release for 10 h in a buffer stage (first-order kinetic)
	Pantoprazole	**In vitro**	• Pulsatile drug delivery system, • Immediate-release tablets press-coated with ethylcellulose and HPMC mixed in different ratios, • Drug release lag time from 1.5 up to 3 h was achieved
		In vitro	• Multiunit particulate system tablets (MUPS), • Pantoprazole pellets coated with Eudragit L and with cushion layer, • Fast-disintegrating tablets were achieved with a drug release in the acid phase lower than 6%, followed by immediate release in the buffer
		In vitro	• Orodispersible tablets with crospovidone or sodium starch glycolate were directly compressed with API, • Stability issues were not considered

Formulation	PPI	Development Stage	Description
	Lansoprazole		
		In vitro	• Delayed-release tablets, • Immediate-release tablets press-coated with ethylcellulose and two different grades of HPMC, • Drug release lag time from 2 up to 4 h was achieved
		In vitro	• Hot-melt extrusion used to combine lansoprazole with PVP, Lutrol F68 and magnesium oxide, • Extrudates compressed to core tablets, which were coated with Eudragit L100-55, • No drug release during 1 h acid stage, followed by immediate release to a buffer
		In vitro **In vivo absorption studies (dogs), disintegration time in the mouth (human)**	• Orodispersible tablets containing enteric coated microgranules, • Enteric coating: Eudragit L30D-55 and Eudragit NE30D, • Bioequivalence was demonstrated with a manufactured drug
		In vitro	• Fast-dissolving tablets, • For solubility improvement solid dispersions of lansoprazole with PEG 4000/6000 or drug-β-cyclodextrin complexes were formed, • Tablets prepared by direct compression with superdisintegrants, • Degradation of API in acid was not considered in the study
		In vivo (human) **Clinical trials**	• Orodispersible tablets, • A review of studies on the clinical effectiveness of orodispersible tablets with lansoprazole
		In vivo (human)	• In the study the effect of water intake on lansoprazole absorption from orodispersible tablets was evaluated, • No significant difference between administration with or without water was observed

Formulation	PPI	Development Stage	Description
		In vivo bioequivalence studies (human)	• Bioequivalence studies on orodispersible tablets and capsules containing lansoprazole, • No significant differences between C_{max} and AUC values of tested formulations were observed
		In vitro **In vivo (human)**	• Comparison of branded and five generic orodispersible tablets containing lansoprazole, • Formulation quality (stability in saliva, dissolution in acidic and intestinal media) and ingestibility were tested
		In vitro	• Study on physical properties of six different orodispersible tablets containing lansoprazole

Formulation	PPI	Development Stage	Description
		In vitro **In vivo PK studies (beagle dogs)**	• Immediate-release formulation containing rabeprazole core tablet dry-coated with sodium bicarbonate, • Faster onset of action in comparison to reference tablets
		In vitro	• Enteric-coated tablets, • DrugCoat L100 (anionic copolymer based on methacrylic acid and ethyl acrylate) used as a coating polymer
		In vitro	• Enteric-coated tablets, • Core tablets prepared by direct compression or after wet granulation, • Coating with HPMCP (Instacoat EN-HPMCP)
	Rabeprazole	**In vitro**	• Enteric-coated tablets, • Coating with HPMCP, • Drug release in buffer stage extended up to 12 h
		In vitro	• Sustained-release tablets, • Matrix tablet were prepared after wet granulation of API with HPMC, Carbopol or sodium carboxymethyl cellulose, • Degradation of API in acid was not considered in the study
		In vitro	• Orodispersible tablets, • Different superdisintegrants evaluated: crospovidone, croscarmellose sodium, pregelatinized starch, L-HPC, treated agar , • Degradation of API in acid was not considered in the study

Formulation	PPI	Development Stage	Description
		In vitro	• Enteric-coated tablets , • Coating with Eudragit L 30D-55, HPMCP, CAP or Acryl-EZE
		In vitro	• Enteric-coated tablets , • Core tablets prepared after wet granulation, • Coating with Instacoat EN-Super-II
	Esomeprazole	**In vitro** **Ex vivo permeation studies (porcine mucosa)** **In vivo pharmacokinetics studies (rats)**	• Immediate-release tablets containing magnesium oxide or sodium bicarbonate as an acid protective ingredients, • Minitablets with esomeprazole and sodium bicarbonate coated with Eudragit L100-55, • Addition of bicarbonate promoted esomeprazole permeation and its immediate absorption
		In vitro	• Colon-specific drug delivery system, • Core tablets were press-coated with a mixture of HPMCP and ethyl cellulose, • Drug release sustained up to 6 h in buffer stage
		In vitro	• Multiunit particulate system (MUPS) tablets, • Enteric-coated pellets compressed with different excipients (lactose, dibasic calcium phosphate) to form of tablet, • High resistance to acid degradation, followed by immediate API release in buffer
	Dexlansoprazole	**In vitro**	• Extended-release tablets, • Directly compressed tablets containing HPMC and HPMCP were coated with shellac, • Drug release extended up to 12 h,

Formulation	PPI	Development Stage	Description
	Tenatoprazole	In vitro	• Enteric-coated tablets, • Directly compressed tablets were coated with HPMCP, Eudragit L 30D-55, or HPMCAS, • Drug release extended up to 12 h
		In vitro	• Extended-release matrix tablets, • Direct compression of API with polymers such as Carbopol, Methocel or Eudragit, and sodium bicarbonate as a pH controlling agent, • Drug release extended up to 12 h
	Ilaprazole	In vitro	• Enteric-coated tablets, • Compression of the core tablets after wet granulation, • Coating with Eudragit L 100 or HPMCP, • Efficient gastric protection followed by immediate release in buffer stage was achieved
		In vitro	• Extended-release tablets, • Direct compression of the core tablets containing different superdisintegrants, • Coating with HPMCP and Eudragit L 100, • Efficient gastric protection followed by drug release extended up to 12 h was achieved
Fixed-dose combination products	Esomeprazole + naproxen	In vitro	• Hot-melt co-extrusion was used to produce cylindrical systems, • The core of the cylinder contained naproxen with enteric polymers like Eudragit, HPMC-AS-LF, HPMCP or Eudragit L100-55, • The outer layer of the cylinder contained esomeprazole with immediate release polymers such as Kollidon, Klucel, Methocel or PEO, • Degradation of esomeprazole in acidic medium was not considered in the study

Formulation	PPI	Development Stage	Description
Bilayer tablets	Lansoprazole + amoxycillin	In vitro	• Bilayer tablets, • Immediate-release layer containing lansoprazole, sodium starch glycolate and MCC, • Sustained release layer with amoxicillin, HPMC and EC, • Degradation of lansoprazole in acidic medium was not considered in the study
	Esomeprazole + aceclofenac	In vitro	• Bilayer floating tablets, • Immediate-release layer contained esomeprazole, sodium bicarbonate, citric acid, and sodium starch glycolate, • Sustained release layer contained HPMC in different grades and xanthan gum, • Degradation of esomeprazole in acidic medium was not considered in the study
	Esomeprazole + clarithromycin	In vitro	• Controlled-release floating effervescent bilayer tablets, • Combination of Eudragit RS 100 and Carbopol was used to control drug release in both layers, • Sustained release for up to 24 h was achieved, • Degradation of esomeprazole in acidic medium was not considered in the study
	Esomeprazole + levosulpiride	In vitro	• Bilayer tablets, • Immediate-release layer containing esomeprazole with superdisintegrants such as croscarmellose sodium, crospovidone or sodium starch glycolate, • Sustained release floating layer contained levosulpiride, HPMC, sodium bicarbonate and citric acid, • Immediate release of esomeprazole and 12 h release of levosulpiride were achieved, • Degradation of esomeprazole in acidic medium was not considered in the study

Formulation	PPI	Development Stage	Description
Floating tablets	**Pantoprazole**	**In vitro**	• Floating effervescent tablets, • Tablets contained pectin, HPMC, sodium bicarbonate, calcium carbonate and citric acid granulated with isopropyl alcohol prior to compression, • Pantoprazole release was extended up to 8 h, • Degradation of pantoprazole in acidic medium was not considered in the study
		In vitro	• Sustained release floating tablets, • Direct compression used to prepare tablets containing API, HPMC or sodium alginate with MCC and sodium bicarbonate, • Pantoprazole release was extended up to 8 h, • Degradation of pantoprazole in acidic medium was not considered in the study
	Lansoprazole	**In vitro**	• Sustained release floating tablets, • Direct compression used to prepare tablets containing API, HPMC and sodium bicarbonate, • Lansoprazole release extended to 10 h, • Degradation of API in acidic medium was not considered in the study
		In vitro	• Sustained release effervescent floating tablets, • Direct compression used to prepare tablets containing API, xanthan gum, gellan gum, Carbopol or chitosan, citric acid and sodium bicarbonate, • Lansoprazole release extended to 12 h, • Degradation of API in acidic medium was not considered in the study

Formulation	PPI	Development Stage	Description
	Rabeprazole	**In vitro** **In vivo pharmacokinetic and antiulcer activity studies (rats)**	• Immediate-release floating tablets, • Wet granulation with ethanolic solution of HPMC was used to prepare granules containing API, pectin, mannitol, PEG 400, sodium bicarbonate, calcium carbonate and citric acid, • Floating tablets neutralize gastric acid to protect API from degradation, • Faster onset of action and better antiulcer activity was achieved as compared to the commercial rabeprazole delayed-release capsules

Formulation	PPI	Development Stage	Description
Hydrogel formulations		**In vitro**	• Colon-specific controlled release hydrogel, • Gum tragacanth and acrylic acid based hydrogel was prepared by graft copolymerization, • pH-sensitive drug release rate was achieved, • Pantoprazole released extended up to 30 h
	Pantoprazole	**In vitro**	• Superporous hydrogel with pantoprazole, • Methacrylic acid and acrylamide were polymerized in the presence of N,N-methylene-bis-acrylamide as crosslinking agent, • High acid resistance and extended pantoprazole release up to 6 h was achieved
		In vitro **In vivo studies on hydrogel gastro-retention (mice)**	• In situ gelling formulation, • Gellan gum, sodium alginate and HPMC were used as a gelling agents, • Pantoprazole release extended to 12 h, • Degradation of API in acidic medium was not considered in the study
	Rabeprazole	**In vitro**	• Hydrogel beads intended for the colon delivery of rabeprazole, • Hydrogel beads were prepared by ionotropic gelation of sodium alginate with calcium chloride, • Eudragit S100 used for enteric-coating of beads, • Gastric protection of rabeprazole was achieved followed by 8 h drug release

Formulation	PPI	Development Stage	Description
Mucoadhesive tablets		**In vitro**	• Mucoadhesive tablets with pellets inside, • Tablets were coated with mucoadhesive polymer: HPMC K4M, sodium carboxymethylcellulose, ethyl cellulose or Carbopol 934P, and then with Eudragit L100 to achieve final enteric coating
		In vitro **In vivo studies on absorption from the oral cavity and tablets adhesion to the oral mucosa (human)**	• Buccal adhesive tablets, • Sodium alginate and HPMC were used as a mucoadhesive polymers, • Magnesium oxide, potassium phosphate monobasic, sodium phosphate monobasic and dibasic were used as a pH-stabilizers, • Stability of API in human saliva for 4 h was achieved
	Omeprazole	**In vitro** **In vivo pharmacokinetic studies (hamsters)**	• Omeprazole buccal adhesive tablets, • API was directly compressed with sodium alginate, HPMC, magnesium oxide, and croscarmellose sodium, • Sustained drug release was confirmed in pharmacokinetic studies; constant omeprazole level in blood was maintained for 6 h
		In vitro **In vivo pharmacokinetic studies (hamster), mucoadhesive force measurement (human)**	• Buccal adhesive tablets with omeprazole, • API was directly compressed with sodium alginate, HPMC, magnesium oxide, and croscarmellose sodium, • Sustained drug release was confirmed in pharmacokinetic studies; constant omeprazole level in blood was maintained for 6 h
		In vitro	• Pediatric buccal film, • Casting method was used to prepare films with omeprazole, HPMC, MC, sodium alginate, carrageenan, metolose, PEG 400 and L-arginine

Formulation	PPI	Development Stage	Description
Oral liquid suspensions	Pantoprazole	In vitro	• Sustained release mucoadhesive gastroretentive system, • Tablets containing API, MCC, PVP, and HPMC, Carbopol, or guar gum were prepared with direct compression, • Extended release of pantoprazole was achieved for 10 h, • Degradation of API was not analyzed in the study
	Omeprazole	In vitro	• Study on physicochemical and microbiological stability, • Suspension composed of crushed omeprazole pellets or pure omeprazole in a complex vehicle
		In vitro	• Enteric-coated particles for suspension in syrup (extemporaneously), • Functional polymes: Eudragit E 100, Eudragit L100-55, • Particles obtained by fluid bed coating
		In vitro In vivo preliminary toxicity and antiulcer activity studies (mice)	• Enteric-coated nanoparticles for oral liquid suspension, • Functional polymes: Eudragit RS 100 (1st layer), Eudragit L100-55 (2nd layer), • Obtained by interfacial deposition of the preformed polymers method

Formulation	PPI	Development Stage	Description
Transdermal delivery	Omeprazole	In vivo PK study (human)	• Study on omeprazole transdermal absorption, • Transdermal gel formulation: pleuronic lecithin organogel (PLO) containing omeprazole (50 mg/mL)
	Lansoprazole	Ex vivo penetration study (pigs) In vivo PK study (rats)	• Nanostructured lipid carriers (NLCs) for hydrogel formulations, • Functional excipients: glyceryl monostearate, stearylamine, SDS, isopropyl myristate, menthol
	Rabeprazole	Ex vivo penetration study (snake)	• Transdermal patches, • Film forming polymers: HPC-EF, PVP K30, PVP K90, • Obtained by solvent casting method
Suppositories	Omeprazole	In vitro	• Pediatric suppository, • Functional excipients: witepsol H15, arginine (L) base
		Clinical trial (efficacy, PK)	• Study on efficacy and pharmacokinetics of omeprazole administered in form of suppositories in infants
Intravenous formulations	Omeprazole	In vitro	• Powder for solution for infusion with cyclodextrins as stability enhancers, • Obtained by lyophilization
		In vitro	• Nanosuspension, • Suspension components: 8.4% sodium bicarbonate solution, Poloxamer 188 (1%), • Obtained by DissoCubes® technology

5. Future Perspectives

Despite more than 30 years of application of proton pump inhibitors in the pharmacotherapy of many gastrointestinal disorders, there are still multiple unresolved issues that needs to be met to ensure the stability, efficacy and above all safety of the application of PPIs. There are many approaches to alleviate PPIs' disadvantages, but there is still room for improvement when both patient experience and therapeutic efficacy and safety are at stake.

Probably one of the most important issues is the availability of PPIs to children of all ages and medical conditions. Although there are some dosage forms with PPIs intended for children, there is still no universal one, which might be convenient for all pediatric groups. There seems to be a great deal of hope in the incorporation of micro- and nanoparticles into orodispersible tablets (ODTs), minitablets (MODTs), films (ODFs), or granules. However, this is still an unexplored field in the case of PPIs and needs to be investigated more deeply.

Another great opportunity is the design and development of more stable PPIs such as AGN 201904-Z, which is actually a prodrug converted in the systemic circulation to omeprazole. It is acid stable and therefore does not require an enteric coating or other protection from the acidic environment in the stomach. However, as a new drug moiety, it is still necessary to prove its safety and efficacy in a larger group of patients, including children and the elderly [31][32][33].

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