Research Article

Glimpse of Drug Delivery Systems for Proton Pump Inhibitors

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ABSTRACT

Proton pump inhibitors (PPIs) provide the most effective pharmacotherapy for treating acid-related disorders. By inhibiting gastric H+/K+ adenosine triphosphatase via covalent binding to the cysteine residues of the proton pump, they provide the most potent acid suppression available. Although PPIs are generally considered safe, numerous adverse effects, particularly associated with long-term use have been reported. Moreover, PPIs do not completely control acid over 24 h with once daily conventional dosing. Despite the efficacy of PPIs, overcoming PPI failure has become an important challenge in the management of GERD. Knowledge of key underlying mechanisms for PPI treatment failure has provided researchers with direction for discovering alternative therapeutic options to address unmet needs of patients on PPI therapy. In current era of sophisticated new drug delivery systems, the drawbacks associated with current PPIs treatment can be overcome. The present review highlights brief about of PPIs, novel drug delivery approaches for PPIs and glimpse of patent filed on delivery of PPIs.

Keywords: Proton pump inhibitors, drug delivery systems, patent, MUPS.

INTRODUCTION

Proton-pump inhibitors (PPIs) have emerged as the drug class of choice for treating patients with acid-related diseases, including gastroesophageal reflux disease (GERD), duodenal ulcer, and gastric ulcer. PPIs are also effective in treating patients with Barrett's esophagus and Zollinger-Ellison syndrome. Each member of the PPI class; omeprazole, lansoprazole, pantoprazole, and rabeprazole has been shown to be effective and well tolerated in randomized, controlled clinical trials. Proton pump inhibitors (PPIs) are among the most widely sold drugs in the world, and in the United States, they are the third most widely sold drug class, with annual sales of $13.9 billion.[1] Overall, they are considered safe and effective. PPIs are a class of medication that act on the H+/K+ pump along the basolateral membrane of the parietal cell. They accumulate and activate in an acid environment at the secretory canalicular surface of the parietal cell. Here, they bind irreversibly to H+/K+ adenosine triphosphatase, inhibiting acid production of the bound parietal cell in approximately 70% of active pumps.[2,3]

Pharmacology of PPIs

An understanding of pharmacology of PPIs aids an optimal use of same. PPIs are weakly acidic in nature and partially absorbed. They accumulate and activate in an acid environment at the secretory canalicular surface of the parietal cell. In this ambience, the inactive benzimidazole of the PPI is converted to a cationic tetracyclic sulfonamide, which covalently binds to cysteine residues on the alpha subunit of the H+, K+ - ATPase enzyme, inhibiting acid production of the bound cell in about 70% of active pumps.[2,3] Acid recovery depends on synthesis of new pumps and slow dissociation of the PPI from the cysteine. Differences in cysteine binding between drugs may thus affect the speed of acid recovery. In addition to new pump synthesis, recovery of acid secretion may be by reduction of the disulfide bond by extracellular glutathione. Secretory capacity is restored when new pumps are converted from their inactive status in the tubulovesicle to their active form at the canalicular surface,[4] which occurs on average in 36-72 hours. As a class, PPIs suppress daytime, nocturnal, and meal-stimulated acid secretion.[5]

Pharmacokinetics of PPIs

Proton pump inhibitors have short half-lives, typically 1 hour, but may last up to 24 hours because of the necessity of new pump synthesis for acid secretion. All PPIs are eliminated via hepatic P-450 CYP2C19, with CYP3A4 also playing a role.[6] Lansoprazole, pantoprazole, and dexlansoprazole have the greatest bioavailability and achieve the highest plasma levels. Rabeprazole is the most acid-labile PPI and therefore the most potent, whereas pantoprazole is the least reactive and therefore the least potent.[6-9] Numerous studies have evaluated whether these differences are of clinical significance and would therefore justify choosing one PPI over another.

The degree of acid inhibition with PPIs does not correlate with plasma concentration but to the area under the curve (AUC). The slower a PPI is cleared from the plasma, the more of it is available to be delivered to the proton

pump.[10] The clinical implications of this are difficult to discern. Although all PPIs have the same general mechanism of action, the nature of the pyridine and benzimidazole substituent may confer physical and chemical differences. Because of its higher pKa, rabeprazole is activated over a wider pH range than omeprazole, lansoprazole, or pantoprazole, and it converts to its sulfonamide faster than the other. This profile might explain why rabeprazole has a faster onset of inhibitory action with respect to H+, K+- ATPase and acid secretion. The main pharmacokinetic parameters of all PPIs are compared in Table 1.[7,11]

Table 1: Pharmacokinetic properties of proton pump inhibitors

Parameter	Omeprazole	Esomeprazole	Lansoprazole	Pantoprazole	Rabeprazole
tmax	[h]	1–6	1–3.5	1.2–2.1	2–4
F[%]	25–40 (↑upon multiple dosing)	50 (acute dosing) 70–80 (chronic dosing)	80–90	77	55
fu[%]	0.05	0.05	0.03	0.02	0.04
V [l/kg]	0.13–0.35	0.22–0.26	0.4	0.15	-
$t_{1/2}$ [h]	0.5–1.2	0.8–1.3	0.9–2.1	0.8–2.0	0.6–1.4
CL [ml/min]	400–620	330 (acute) 160–250(chronic)	400–650	90–225	-
CL/F [ml/min]	320		310	125	600
fe [%]	Negligible	Negligible	Negligible	Negligible	Negligible
Hepatic dysfunction	CL↓, t1/2 ↑, F↑	CL↓, t1/2 ↑	CL↓, t1/2 ↑	CL↓, t1/2 ↑, F↔	CL↓, t1/2 ↑

(tmax time to maximal plasma concentration, F oral bioavailability, fu fraction of drug unbound in plasma, V apparent volume of distribution, t1/2 elimination half life, CL systemic clearance, CL/F apparent oral clearance, fe fraction excreted in unchanged form into urine, ↑ increase, ↓ decrease, ↔ no significant change)

Clinical uses of PPIs: [12,13]

- To reduce acid reflux, which may cause heartburn or oesophagitis (inflammation of the oesophagus)
- In the short-term management of GERD and peptic ulcer disease.
- To prevent oesophagitis from recurring after the oesophagus has healed (maintenance therapy).
- To treat ulcers in the stomach and duodenum.
- To prevent and treat ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs).
- In combination with appropriate antibiotics to eradicate Helicobacter pylori, a bacterium found in the stomach, which may cause ulcers.
- To treat a rare condition called Zollinger-Ellison syndrome.
- In other conditions where it is helpful to reduce acid in the stomach.

Safety and tolerability

PPIs are generally well tolerated[14], and should only be used for appropriate indications, and not for a longer duration than what is essential.[12] However, with the long-term use of any medication, drug safety becomes an important issue. The three main concerns regarding the long-term safety of PPIs include the effects of prolonged hypochlorhydria and hypergastrinaemia, and the possible association of PPIs with gastric atrophy. In particular, hypochlorhydria is of concern since it may predispose to infections and malabsorption.[13] The long-term use of PPIs is also associated with hypomagnesaemia, and may increase the risk of fractures. PPIs have also been associated with an increased risk of Clostridium difficile-associated diarrhea.[12] The US Food and Drug Administration (FDA) has mandated revised safety information on all PPIs with regard to a possible increased risk of fractures to the hip, wrist and spine with the use of these medications. The FDA also recommends that healthcare professionals prescribing PPIs should consider whether or not a lower dose or shorter duration of therapy would adequately treat the patient's condition.[13]

Unmet need for drug delivery systems for PPIs

All PPI compounds are weak bases that are acid labile and are rapidly degraded, usually within minutes, in the acidic environment of the stomach. These compounds are known to degrade under certain conditions in solution. Their stability is affected by several factors, including type of solvent and pH. In aqueous solutions, the degradation is acid-catalyzed and below pH 5 total degradation can occur within a few hours or less. Maximum stability is observed in alkaline conditions. Furthermore, all conventional PPIs have a relatively short plasma half-life (1–2 h) and limited residence time in the systemic circulation.[15,16] Thus, with once-daily conventional dosing, systemic exposure to PPIs tends to wane until there is no circulating PPI present in plasma during the later stages of the 24-h interval.[17,18] This enables resumption of gastric acid secretion by uninhibited, restored or new pumps.[17] Additionally, pump turnover time varies greatly within and between individuals. Conventional PPIs typically require 3 days to achieve maximal acid suppression, thereby delaying the onset.[17]

Despite their clinical efficacy, once-daily administration of conventional single-release PPIs does not always adequately control intra gastric acidity over a 24-hour period in a significant proportion of GERD patients, leading to suboptimal symptom relief, particularly at night.[19] Although the time to peak plasma concentration for most PPIs is generally less than two hours, their relatively prolonged pharmacodynamic effect is reflected in sustained inactivation of the gastric proton pumps.[16] Pumps that are not activated by the first meal consumed after PPI administration may be activated later in the day when drug plasma levels are low, leading to breakthrough symptoms.[20] Approximately 25% of pumps are regenerated every day[21], and the largest number of new proton pumps are usually synthesized overnight after a prolonged fast.[22] Thus, the combination of previously unbound proton pumps and newly synthesized pumps in the absence of circulating PPI at the end of the dosing cycle effectively contributes to suboptimal 24-hour acid suppression and could provide a pharmacological explanation for nocturnal symptoms.

Approaches for delivery of PPIs

Various novel approaches can be employed for controlled delivery of PPIs to overcome the drawbacks associated with current conventional regimen. Scientists have contributed significantly in this line. Following section covers different possible approaches for delivery of PPIs and work done in this regard.

OD-PEP™ technology

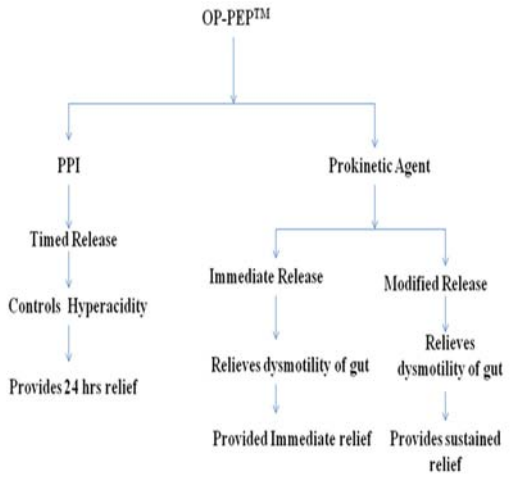

Figure 1: Release pattern of components of OP-PEP™

OD-PEP™ is a novel drug delivery based fixed dose combination therapy for Gastroesophageal Reflux Disease (GERD) and Non-ulcer Dyspepsia (NUD). It is a combination of a Proton Pump Inhibitor (PPI) and a prokinetic agent. Usually PPIs are administered once a day, while prokinetic agents are prescribed thrice daily. In OD-PEP™, an advance drug delivery system has been utilized to tackle the problem of different dosing frequencies of these two drugs. It not only ensures higher patient compliance through a convenient one a day dosage but also reduces acid secretion and increases gut motility. Prokinetic agents increase the tone of the lower esophageal sphincter and enhance gastric emptying. It facilitates gastrointestinal smooth muscle activity by inhibiting dopamine at the D1 receptors. A combination therapy of a prokinetic agent and a gastric acid lowering compound is rational and is more effective than mono therapy. Figure 1 depicts the release pattern of components of OP-PEP™.

Modified release oral unit dosage forms

Considering the current need and physicochemical and pharmacokinetics properties of PPIs, once a day modified dosage regimen is a viable approach. Also to prevent degradation of PPIs under acidic environment and increase bioavailability of the same, enteric coating is preferable solution.

Sriharsha Vardhan S and P.V.N. Sowmya prepared rabeprazole sodium dual drug release capsules by time release coating process varying the compositions of drug and polymer mixture in Film coating, water insoluble and enteric coating polymer mixture in lag time coating. Immediate release (IR) rabeprazole beads were prepared by drug layering process and barrier coated beads by providing an enteric coating membrane on IR beads.[23]

A. Badoni formulated and evaluated rabeprazole enteric coated mucoadhesive tablet. Delayed release tablets of rabeprazole were prepared by wet granulation method using HPMC, HPMC-P, Xanthan gum and Carbapol as polymer, Avicel PH 102 (MCC) as filler and starch as binder.

The prepared tablets were evaluated for hardness, weight variation, friability and drug content uniformity and it was found that the results comply with official standards. The prepared tablets were coated using enteric coating polymer such as Hydroxypropyal methyl cellulose-Phthalate by spray dried method. The *in vitro* release was studied using pH 1.2 acidic buffer and pH 7.2 phosphate buffer. The *in vitro* release study revealed that the prepared tablets were able to sustain release drug in to the intestine. An optimized rabeprazole sodium enteric coated formulation at a dose of 10 mg/kg body weight showed a protection index of 100%.[24]

Putta Rajesh Kumar have prepared and evaluated directly compressible esomeprazole magnesium trihydrate enteric coated tablets. Different tablets were prepared by super disintegrants like Ac-Di-Sol, Crospovidone, sodium starch glycolate and diluents like Pharmatose DCL11, Mannogem EZ. Tablets were enteric coated using Acryl-EZE. The tablets were evaluated for hardness, disintegration time and *in vitro* drug release.

The powder bed showed good rheological properties and enteric coated tablets showed acid uptake value <5 indicates significant protection of acid liable drug. The tablets with Pharmatose DCL11 released higher than Mannogem EZ which could be due to its hydrophilicity and due to swelling of the super disintegrant.[25]

MUPS

The tablets which are prepared by compaction of modified release coated pellets are called as MUPS (multi unit pellet system) tablets. Pellets are produced for the purpose of oral controlled-release dosage form having sustained release properties. For such purposes, coated pellets are administered in the form of MUPS tablets. The coating material used is either sustained release or enteric release. Different release profile can be achieved at same time at same site in GIT.

Senthil kumar investigated delayed release i.e., enteric coated pellets of Rabeprazole sodium by using hydroxypropyl methyl cellulose based sub coating and methacrylic acid copolymer based enteric coating. The different batches of pellets were prepared by drug suspension layering method. Comparative study of dissolution profile of final batch with market preparations was conducted and it was concluded that final batch shown good similarity with market products. The results of the accelerated stability of final formulation revealed that storage conditions were excellent.[26]

Renata P. Raffin prepared gastro resistant pantoprazole loaded microparticles by spray drying. One single oral dose (40 mg) was administered to dogs. Each dog received either a reference tablet or hard gelatin capsules containing the agglomerates. The plasma profiles were evaluated by non-compartmental and compartmental approaches, and the pharmacokinetic parameters were determined. The agglomerates presented 100% of drug particle loading and a production yield of 80.5%. The amount of drug absorbed after oral dosing was similar after reference or agglomerate administration, leading to a relative bioavailability of 108%. The agglomerated gastro-resistant pantoprazole-loaded microparticles reduced time to peak plasma. The agglomerates were equivalent to the reference tablets in terms of extent but not in terms of rate of absorption, showing that this formulation is an alternative to single-unit oral dosing with enteric coating and with the advantage of reducing time to effect.[27]

Orodispersible tablets

Pediatrics and geriatrics patients prefer fast dissolving tablet due to its swallowing conveniences. Many elderly persons face difficulties in administering conventional oral dosage forms because of hand tremors and dysphagia. Moreover, drug release in oral cavity and absorption through buccal mucosa into systemic circulation prevents degradation of PPIs in stomach. This is an innovative technology where the dosage form containing active pharmaceutical ingredients disintegrates rapidly usually in a matter of seconds without the need for water, providing optimal convenience to the patient.

Fabio Baldi have prepared Lansoprazole fast disintegrating tablet (LFDT) – a new, patient-friendly and more convenient formulation of lansoprazole which can be taken with or without water. It represents an innovative drug delivery system, comprising enteric-coated microgranules of lansoprazole compressed with an inactive, rapidly dispersing matrix to form a tablet. When the tablet is placed on the tongue and sucked gently it disintegrates rapidly in the mouth, releasing the enteric-coated microgranules which are swallowed with the patient's saliva without water. Alternatively, the tablet can be swallowed with a drink of water. Studies have shown that the bioavailability of LFDT is comparable to lansoprazole capsules, at both 15 and 30 mg doses; the indications and recommended dosages for LFDT are therefore identical to lansoprazole capsules.[28]

N. Jawahar developed fast disintegrating and rapid release tablets, (Ora-Solv tablets) of Pantoprazole using two different Superdisintegrants viz. Croscarmellose sodium and Sodium starch glycollate (SSG) by direct compression method. Evaluation of the tablets showed that all the tablets were found to be within official limits and the disintegration time for the formulations ranged from 15 s to 25 s. From the overall observations, formulation containing 15% w/w concentration of SSG was considered to be the optimized formulation which releases up to 100.70% of the drug in 15 minutes. The formulated OST's have potential advantages over conventional marketed tablets with their improved patient compliance, both in geriatrics and paediatrics, ease of administration and bio-availability.[29]

Buccal delivery

Buccal mucosa is an attractive route for systemic delivery of drugs as it is relatively permeable with a rich blood supply. Moreover, it has high robustness and accessibility. A drug can be easily applied and localized at the application site, and can also be removed from there if necessary.[30-32] Buccal delivery for the transmucosal absorption of drugs into the systemic circulation offers a number of advantages over oral delivery.

Raval J. A. have prepared and evaluated buccoadhesive tablets of rabeprazole sodium that avoid gastric degradation and first pass metabolism, thereby increasing the drug bioavailability and onset of action. Different ratios of Gantrez MS 955 along with HPMC K4M were studied to give bioadhesive strength. To stabilize the drug in human saliva different stabilizers were studied, of which sodium carbonate was found the best. A 3^2 full factorial design was applied to investigate the combined effect of Gantrez MS 955 concentration (X1) and HPMC K4M concentration (X2).

Results of the multiple regression analysis revealed that the independent variables significantly affected the dependent variables (bioadhesive strength (Y1) and t50 (Y2)).

From the *in vitro* diffusion study flux was calculated for the optimized batch. Result found that increase in prehydration time decreased in bioadhesive strength and increase in contact time increased bioadhesive strength.[33]

Rajput N prepared bilayered buccoadhesive tablets by direct compression technology, using different mucoadhesive polymers such as carbopol-934 (CP) as primary, xanthum gum and olibanum gum (OG) as secondary polymer, sodium deoxycholate as permeation enhancer. The tablets were evaluated for physical characterization, assay, swelling index, bioadhesion study, *in-vitro* residence time, microenvironment pH, *in-vitro* drug release and *in vitro* permeation. Bioadhesive strength tends to quite linear with increasing amount of each polymer. Percentage release of drug tented to very non-linear with polymer amount. The formulation with CP and OG containing 1:1 ratio including sodium deoxycholate was considered as an optimized formulation. The drug release of this formulation was found to be non-Fickian and approaching zero order kinetics.[34]

Varma D. K. formulated and evaluated Pantoprazole sodium sesquihydrate IR buccal films using solvent casting at various viscosity grades of HPMC (5cps, 100K, K5M). The formulation comprised of HPMC 100K (100mg) as water soluble polymer, PEG 400 and glycerol was found to be an optimized. The cumulative drug release was found to be 89.6% for 30min and 99% within 60min.[35]

Microspheres and Microcapsules

The micro particulate delivery systems are considered and accepted as a reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effect(s). Microspheres are characteristically free flowing powders consisting of solid spherical particles of size 1-1000µm. These are made up of polymeric substance in which the drug is dispersed throughout the particle i.e. internal structure is made up of drug matrix and polymeric excipients. Microcapsule is a spherical particle with size varying from 50nm to 2mm, containing a core substance.

Sunitha S. prepared microspheres for sustained release of ondansetron hydrochloride using various cellulose polymers such as ethyl cellulose, cellulose acetate phthalate, cellulose acetate by employing solvent evaporation technique. SEM revealed that microspheres were found spherical, free flowing and porous. The entrapment efficiency and wall thickness was found in between 69.44% & 40.35%, 117.57µ & 71.82µ respectively. The drug release was extended maximum upto 12 hours with ethyl cellulose. The curve fitting data revealed that the release followed first order kinetics and Higuchi's and peppa's plots stated non-fickian and diffusion controlled.[36]

Suryakanta Swain designed and characterized the rabeprazole sodium loaded microcapsules prepared by solvent evaporation technique using ethyl cellulose (EC) based various mucoadhesive polymer, followed by a triple coating with Eudragit L100. The Box-behnken design (BBD) was applied for optimization of formulations containing EC, HPMCK100M and Eudragit L100 as factors for selected responses like entrapment efficiency, mucoadhesive property and drug release in 24 h. SEM studies revealed that microcapsules were non-aggregated, spherical shape and smooth appearance. *In vitro* drug release was fitted to Higuchi model. *In vivo* antiulcer activity showed that the optimized microcapsules were able to protect rat stomach against ulcer formation vis-à-vis aqueous solution of the drug showed only negligible and minimum effect.[37]

A. Kishore Babuet developed double walled microspheres loaded with pantoprazole. The primary wall composed of muco adhesive polymer HPMC and a release controlling polymer sodium alginate. The second wall coating the primary microspheres was composed of eudragit RS 100. Eudragit RS 100 provides sustained drug release upto 14hrs with the influence of pH 7.4 buffer.[38]

Osmotic tablets

Osmotic systems use the principle of osmosis as delivery force to deliver the drug from the system, and the release rate is unaffected by the body's pH and other physiological factors. Sheikh S. have prepared osmotic tablet of pantoprazole using cellulose acetate as a coating material and castor oil as plasticizer. The tablet was evaluated for various pharmacopial specifications. Effect of different variables and drug release kinetics study of optimized batch were studied. Optimized batch followed Korsemeyer peppas equation and released the drug in controlled passion.[39]

Nanoparticles

Nanotechnology is the tool to increase the selectivity and efficacy of drugs at the infected site and to reduce the toxicity of biotechnological entities on other parts of the body.[40] Milind Sadashiv Alai developed the Eudragit RS100 based nanoparticulate system for sustained delivery of an acid-labile drug, lansoprazole (LPZ). LPZ-loaded Eudragit RS100 nanoparticles (ERSNPs) were prepared by oil-in-water emulsion-solvent evaporation method. All nanoparticles were spherical with particle size 198.9 ± 8.6 to 376.9 ± 5.6 nm and zeta potential +35.1 ± 1.7 to +40.2 ± 0.8 mV. The yield of nanoparticles was unaffected by change of these three variables. All nanoparticles prolonged drug release for 24 h which was dominated by a combination of drug diffusion and polymer chain relaxation.[41]

Recent trends in delivery of PPIs

Other strategies to increase the effectiveness of currently available PPIs have also been developed. Vecam (VB101) is an oral agent with pentagastrin like activity that stimulates proton pumps without the need for food ingestion and can be administered with any PPI.[42] VB101 is reported to be in phase 3 trials and is being tested in combination with omeprazole given 1 h before VB101. Immediate-release omeprazole (Zegerid, Santarus, San Diego, CA, USA), a currently available product, is a

combination of non-enterically coated omeprazole powder with sodium bicarbonate, which theoretically shields the uncoated drug from gastric acid degradation. It possibly provides a more rapid onset of action that may result from the activation of proton pumps caused by neutralization of intragastric pH by sodium bicarbonate.[43] Potassium-competitive acid blockers (PCABs), which target the K+ -binding region of the H+, K+ -ATPase, are another class of drug that has been investigated[22]. PCABs garnered interest because they achieve peak plasma concentrations rapidly after oral delivery and produce a fast onset of acid inhibition. Alternative delivery systems for some existing PPIs are being developed to prolong the duration of drug exposure and subsequently, acid suppression. Chemically metered absorption (CMA) formulations provide a novel mechanism for delivery that may be combined with any PPI to provide more sustained drug exposure.[44] In healthy subjects, CMA-omeprazole, administered as a 600 mg capsule [delivering approximately a 50 mg molar equivalent of an acid-labile sodium salt of a sulfonamide of omeprazole (Allergan, Inc., Irvine, CA, USA)], maintained intragastric pH > 4 significantly longer than esomeprazole 40 mg in healthy subjects.[45]

Patent status of delivery systems of PPIs

Table 2 presents the glimpse of few patents filed for novel approaches of drug delivery systems for PPIs.

Table 2: Patents filed for controlled delivery of PPIs

No.	Patent No.	Drug	Dosage form	Route	Reference
1	US20040006111A1	Omeprazole	Unidirectional release tablet	Buccal	46
2	US20070014875A1	Rabeprazole Sodium	Lyophilized injectable form	Parenteral	47
3	US6132768	Reversible PPIs	Pellets and tablet	Oral	48
4	US5708017	Omeprazole	Paste	Oral	49
7	US6613354B2	Fixed dose of PPIs and NSAIDs	Enteric coating layered tablet, capsule and multiunit tablet	Oral	50
8	US6132770	S- Omeprazole	Multiunit effervescent tablet	Oral	51
9	US6869615B2	Diclofenac and Omeprazole	Coated tablet	Oral	52
10	US6328993	Acid labile PPIs	Enteric coated tablet	Oral	53
11	US6013281	PPIs	Layered tablet	Oral	54
12	US8603520B2	PPIs	Multifunctional capsule	Oral	55
13	US8802139B2	PPIs	Multiparticulate systems in capsule	Oral	56
14	US6274173	Pentoprazole anti microbial agent	Pellets/Tablet	Oral	48
16	WO2006042277A2	PPIs	Osmotic tablet	Oral	57
17	WO2005097083A2	Omeprazole	Patch	Topical and Transdermal	58
18	US20100305163A1	Esomeprazole and Naproxen	Tablet	Oral	59
23	WO2004004690A1	PPIs	Micro granules in suspension	Oral	60
24	EP1156806B1	Omeprazole	Paste	Oral	61
26	WO2004066924A2	PPIs and Antacid	Multilayered tablet	Oral	62
27	US20080003281A1	PPIs	Modified release tablet	Oral	63
28	US20100222390A1	Prodrug of sulfonyl containing PPIs	Liquid	Oral	64
30	WO2006049564A1	PPIs	Enteric coated pellets	Oral	65
31	WO2002053097A2	Lansoprazole	Non enteric coated formulation with carbonates and bicarbonates	Oral	66

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