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Recent advancements in solubilization and Gastroretentive techniques for Oral Drug Delivery of Proton Pump inhibitors: A comprehensive review

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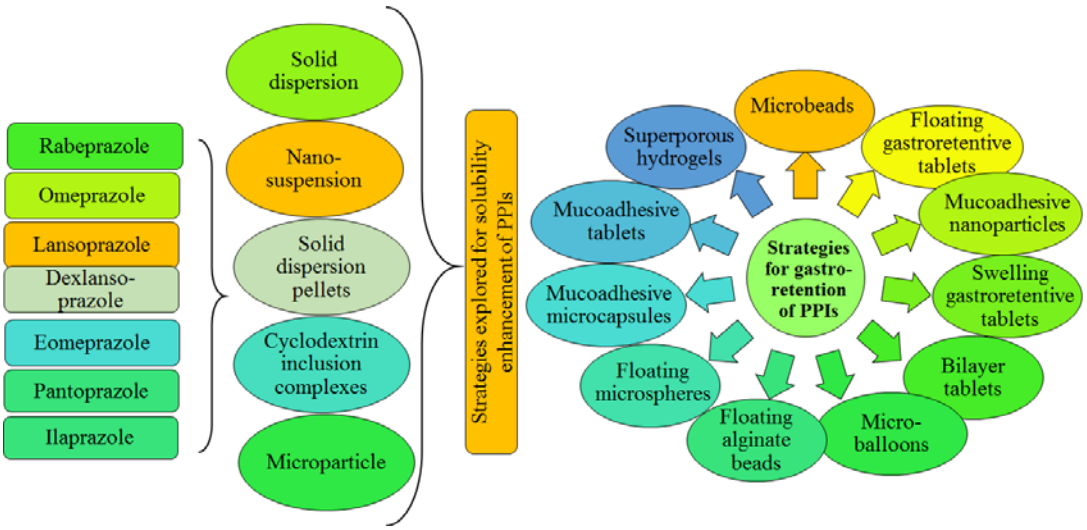
Review Article

ABSTRACT



Proton pump inhibitors (PPIs) have been considered as safe and proficient therapeutic drugs enormously prescribed globally for management of acid-related disorders. PPIs have tendency to blockage proton pumps directly and therefore, considerably reduce gastric acid secretions. PPIs like lansoprazole, omeprazole, esomeprazole and dexlansoprazole are BCS class II medicines and meet challenge of inadequate drug dissolution in oral drug delivery and thus, require solubilization through various strategies like cyclodextrin inclusion complexes, nanosuspension, solid dispersion, microparticles, and solid dispersion pellets. PPIs also undergoes challenge of inadequate gastric residence time and therefore, development of gastroretentive drug delivery systems *i.e.* microbeads, microballoons, mucoadhesive and gastroretentive formulations, bilayer tablets, and super-porous hydrogel of PPIs has been crucial for acquiring vital local drug delivery in the gastrointestinal tract. This review provides comprehensive detail with regard to mechanism of action, pharmacokinetics/pharmacodynamics and physiochemical profile of PPIs. The primary objective of current review is recapitulation of research studies explored previously in order to overcome certain challenges in oral drug delivery of PPIs like low water solubility and inadequate gastric residence time.

Keywords: proton pump inhibitors, solubilization, nanosuspension, solid dispersion, gastroretentive drug delivery systems, microballoons

INTRODUCTION

Proton pump inhibitors (PPIs) are among highly prescribed medicines worldwide for treatment of acid-related illnesses like gastroesophageal reflux disease (GERD), duodenal ulcers, stomach ulcers, Zollinger-Ellison syndrome and Barrett's esophagus.[1] PPIs have been established as essential, safe and efficient treatments for range of acid-related disorders since their clinical inception of more than twenty five years because of high degree of effectiveness and low level of toxicity. The therapeutic applications of PPIs has emerged as customary among primary care physicians and gastroenterologists.[2,3] Gastric acidity demonstrates fundamental function role as defensive system in body since acidic conditions sterilizes food and drink before entering into digestive tract, prevent bacteria from colonizing in upper gastrointestinal tract (GIT) and modifies build of typical intestinal flora. PPIs elevates gastric pH which tend to cause augmentation in bacterial population within stomach through increasing neutrophils basal cytosolic amount and decreases intracellular and extracellular reactive oxygen species; and reduces bactericidal activity.[4] In spite of that, PPIs have been widely used for treatment of adult and pediatric patients over past three decades and number of PPIs

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prescriptions amplified 7.5-times between 1999 and 2004.[5,6] The main concerns with PPI are achlorhydria and hypergastrinemia, despite the fact that they have few acute and obvious side effects. The short-term effects of hypergastrinemia include rebound hyperacidity which may exacerbate GERD symptoms and induce dyspepsia while long-term effects include enterochromaffin cell-hyperplasia which may increase risk of neuroendocrine tumors.[7–9] Individuals on prolonged exposure of PPI might experience serious adverse effects like electrolyte imbalance, renal insufficiency; fractures, vascular dysfunction, and cardiovascular events.[10] PPIs are often utilized in many nations due to their stability in suppressing stomach acid compared to histamine H2 antagonists. In 2009, PPIs have been third-highest selling medication in USA.[11] However, PPIs have two basic challenges *i.e.* (i) solubility issue and (ii) limited gastric residence time for local drug delivery in GIT. PPIs include lansoprazole, omeprazole, rabeprazole, pantoprazole, esomeprazole and dexlansoprazole and literature supports that PPIs except rabeprazole, pantoprazole belong to BCS Class II having poor aqueous solubility and high permeability. The BCS class II drugs encounters challenge of limited dissolution and bioavailability and therefore, prerequisite solubility improvement by solubility enhancement strategies.[12–14] The second challenge for PPIs is limited gastric residence time and therefore, development of gastroretentive formulation of PPIs has become necessary for achieving requisite local drug delivery in GIT *via* oral administration.

The salt generation is a typical approach used by pharmaceutical firms to solve concerns such as low water solubility, stability, toxicity, poor absorption, and challenges connected to production procedures.[15] The salts forms of PPIs are highly soluble in water and therefore, these can be administered *via* intravenous (IV) route. For example, pantoprazole, lansoprazole, rabeprazole, dexlansoprazole and esomeprazole in their sodium salt form are highly soluble; therefore, their salts forms are used to manufacture IV dosage forms and are available as marketed product in the form of lyophilized powders either for infusions or injections. The alkaline aqueous solution of PPI is manufactured using sodium hydroxide at a pH of 11. The solution is then filtered, divided into vials measuring 5 or 10 mL, and freeze-dried in an aseptic environment. The omeprazole sodium (42.6 mg) equivalent to omeprazole (40 mg) has been marketed as powder for solution for infusion. The pantoprazole sodium sesquihydrate has been marketed as powder for solution under brand name Protium I.V. and Protonix I.V. Esomeprazole sodium is available as powder for solution for infusion/injection under brand name Nexium IV.[16]

This review highlights about mechanism of action, metabolism and physiochemical profile of PPIs. The primary objective of this review includes recapitulation of research outcomes explored previously to overcome poor aqueous solubility and minimal gastric residence time of PPIs. The patents related to formulation and production methodology for PPIs published in previous decades are also recapitulated in this review.

MECHANISM OF ACTION OF PROTON PUMP INHIBITORS

The prime regulator responsible for gastric acid secretion in parietal cells is H^+K^+ ATPase proton pump which exchange protons from parietal cells to gastric lumen in replacement of potassium ions. Therefore, the proton pumps are foremost acidifying aspects in gastric fluids. The binding of gastrin molecules with cholecystokinin-2 receptors initiates cascade reactions resulting in proton-pump activation and increase in gastric acid secretions. PPIs cause direct blockage of proton pumps via covalent bonding with sulfhydryl group of proton pump and therefore, significantly decrease gastric acid secretions (Figure 1).[17–19]

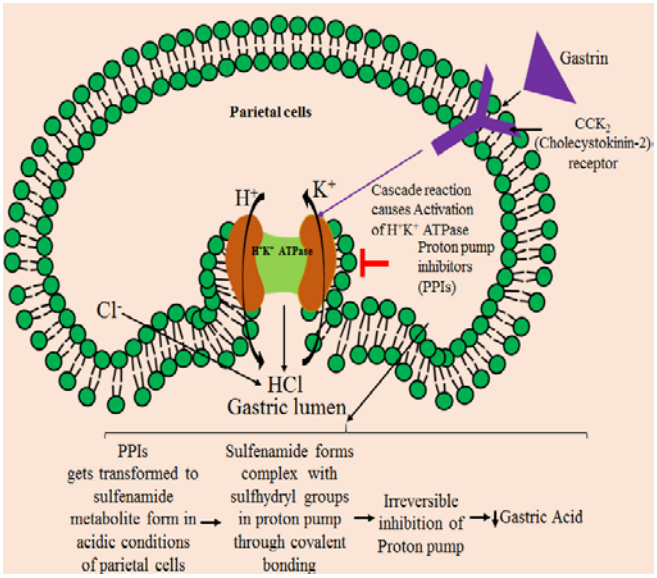

Figure 1. Schematic illustration of mechanism of action of proton pump inhibitors.

PHARMACOKINETICS AND PHARMACODYNAMICS OF PROTON PUMP INHIBITORS

The PPIs decreases the gastric acid secretion via inhibition of hydrogen-potassium ATPase (H+/K+ ATPase) enzyme which catalyses the last step in acid secretion within the gastric parietal cells. This decreases acid production in the stomach and, as a result, reduces gastroesophageal reflux.[20–24] The maximum plasma concentration (C_{max}) of lansoprazole is attained about 1.7 hours after oral administration, and oral absorption ranges between 80 and 90%.[25] The observed volume of distribution of lansoprazole was 0.4 litres per kilogram. Lansoprazole sulfone and 5-hydroxylansoprazole are the two primary excretory metabolites of lansoprazole which are produced through CYP3A4 and CYP2C18.[26–29] The amount of lansoprazole excreted in the urine ranges from 14 to 23%.[28] The half-life of lansoprazole ranges from 0.9 to 1.6 hours.[25] It has been reported that lansoprazole is eliminated at a rate of 400 to 650 mL/minutes.[22] The treatment of duodenal ulcers with lansoprazole is successful in reducing ulcer-related discomfort and reflux symptoms.[30]

Omeprazole must be protected from acidic gastric fluid when taken orally since it is acid-labile. The omeprazole is

quickly absorbed, reaching its peak plasma concentrations within 30 minutes of delivery.[31] Omeprazole has a 0.3 litre/kg volume of distribution and is quickly removed from plasma. Omeprazole has a half-life of less than an hour, and it takes the drug three to four hours to acquire complete elimination from plasma.[5] Omeprazole undergoes extensive first pass metabolism into hydroxyomeprazole, 5'-O desmethyl omeprazole and omeprazole sulfone by CYPP450, CYP3A4 and CYP2C19 enzymes.[32–38] The majority (80%) of the dosage is excreted in the urine, with the liver secreting the remaining 20%.

The ingestion of food or the use of antacids has no impact on the absolute bioavailability of rabeprazole, which is approximately 52%. The consumption of food or the use of antacids had no impact on the medication's 52% absolute bioavailability. After approximately 3–4 hours, maximum plasma concentrations are attained. Rabeprazole predominantly undergoes non-enzymatic reduction to rabeprazole thioether while minor metabolism involves CYP2C19 and CYP3A4.[38–41] The elimination half-life of rabeprazole is approximately one hour.[42]

Maximum plasma concentrations of pantoprazole are acquired within 2 to 3 hours after oral administration of an enteric-coated tablet [43]. Pantoprazole is significantly beneficial for patients receiving co-medication having least potential for metabolic reactions with CYP450-dependent oxidase.[44–48] The hepatic cytochrome enzyme CYP2C19 performs demethylation, the main metabolic step, which is followed by sulfation. Oxidation is another metabolic pathway that is carried out by CYP3A4. The remaining 20% of a dose administered orally or intravenously is excreted in the faeces via bile excretion, with about 80% of the dose being removed as metabolites in urine.[49,50]

The maximum drug concentration in the blood is reached after oral esomeprazole dosing in around 1.5 hours (Tmax).[31] Esomeprazole has a better pharmacokinetic profile than omeprazole and is available as an optical isomer. After oral treatment, esomeprazole is quickly absorbed, and the area under the curve rises nonlinearly with dosage. The CYP2C19 isoenzyme produces the primary components of the metabolites hydroxy and desmethyl, while CYP3A4 produces the metabolite sulphone.[51–53]

The dexlansoprazole is *R*-enantiomer of lansoprazole which exhibits twofold delayed drug release mechanism.[54] Compared to its *S*-enantiomer or racemic combination, dexlansoprazole has a longer clearance time and maintains plasma concentration for a greater duration.[55] Oxidative metabolites of dexlansoprazole like 5-hydroxydexlansoprazole and dexlansoprazole sulfone are generated by CYP2C19 and CYP3A4, respectively.[56] Ilaprazole is another novel PPI which have half-life of 3.0–3.4 hours, t_{max} of 0.75–1.0 hours and C_{max} of 4.2–5.1 µmol/L on administration of 20 mg of Ilaprazole via per oral route.[16]

PHYSIOCHEMICAL PROFILE OF PROTON PUMP INHIBITORS

The physiochemical parameters like molecular weight (Daltons), melting point (°C), partition coefficient and solubility of PPIs have been summarized in Table 1 and chemical structures has been depicted in Figure 2. Among all PPIs, rabeprazole and pantoprazole are BCS class III drugs and exhibits high aqueous solubility. The molecular weight of PPIs is less than 500 Daltons as required for oral drug administration.[56–58]

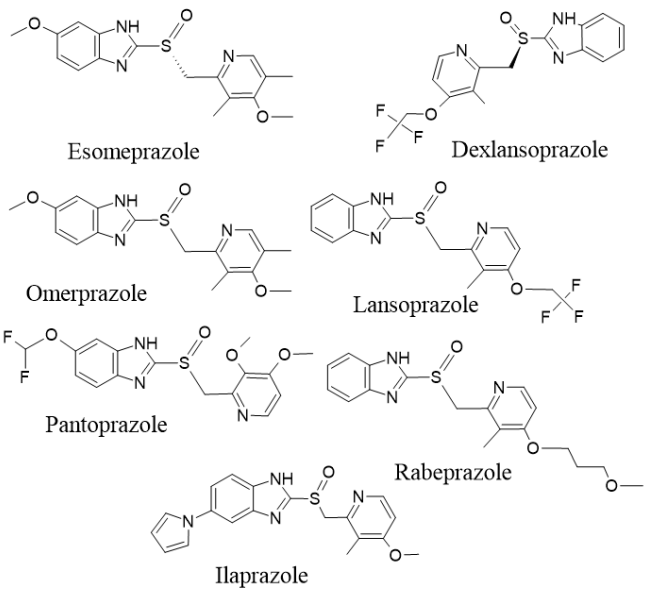

Figure 2. Chemical structures of proton pump inhibitors

Table 1. Physiochemical properties of proton pump inhibitors

Drug & BCS Class	Empirical formula [*Mol. Wt. (Daltons)]	Melting point (°C) & [Log P]	Solubility
Lansoprazole [II]	$C_{16}H_{14}F_3N_3O_2S$ [369.4]	178-182 [2.84]	Freely soluble in dimethylformamide and practically insoluble in water.[59]
Omeprazole [II]	$C_{17}H_{19}N_3O_3S$ [345.4]	155 [1.66]	Very slightly soluble in water (0.359 mg/ml), freely soluble in ethanol and methanol; Slightly soluble in acetone.[60]
Rabeprazole [III]	$C_{18}H_{21}N_3O_3S$ [359.4]	99-100 [2.04]	Very soluble in H_2O (10 mg/ml) and methanol, freely soluble in chloroform and ethanol and; insoluble in n-hexane.[61,62]
Pantoprazole [III]	$C_{16}H_{14}F_2N_3NaO_4S$ [405.4]	>30 [2.11]	Freely soluble in water; practically insoluble in n-hexane.[63]
Esomeprazole [II]	$C_{17}H_{19}N_3O_3S$ [345.4]	155 [1.66]	Slightly soluble in water (0.353 mg/ml) and soluble in ethanol.[64]

Dexlansoprazole [II]	$C_{16}H_{14}F_3N_3O_2S$ [369.4]	Decomposes at 140 [2.84]	Freely soluble in ethanol, methanol, dichloro-methane; soluble in acetonitrile; slightly soluble in ether; very slightly soluble in water (0.25 mg/ml) [65].
Ilaprazole [N/A]	$C_{19}H_{18}N_4O_2S$ [366.4]	>120°C (decomposition)	Slightly soluble in dichloromethane and methanol; solubility in water (0.0934 mg/ml).[66]

*Mol. Wt.: Molecular weight; N/A: Not available; The definition of solubility as per Indian Pharmacopoeia in terms of parts of solvent required to dissolve one part of solute, Freely soluble: 1 to 10 parts; Soluble: 10 to 30 parts; Slightly soluble: 100 to 1000 parts; Very slightly soluble: 1000 to 10000 parts; Practically insoluble: > 10000 parts.

STABILITY OF PROTON PUMP INHIBITORS

Proton pump inhibitors exhibit sensitivity to various environmental factors such as acidity, light, temperature, oxidation, and the coexistence of other salts. Proton pump inhibitors are considered inert substances that necessitate activation through protonation within the acidic surroundings of parietal cells.[16,67] Consequently, it is essential to prevent PPIs from premature activation in the gastric environment following their oral administration. The stability of the PPI is comparatively higher at pH value of 7; however, it undergoes rapid decomposition in the presence of acidic solutions. The order of acid stability is pantoprazole > omeprazole > lansoprazole > rabeprazole.[68] Omeprazole undergoes degradation under acidic conditions within a time frame of 24 hours, whereas it exhibits maximum stability at a pH of 11. It was discovered that the decomposition of this PPI followed the first-order dynamics in solutions with a pH that was greater than 7.8. It was discovered that the decomposition of this PPI followed the first-order dynamics in solutions with a pH that was greater than 7.8.[69,70] Proton pump inhibitors are inactive compounds which exist in the form of prodrugs that must be activated in the acidic pH of parietal cells to inhibit proton pump activity.[25,69,70] Following absorption, they are carried by the systemic circulation to the canaliculi of parietal cells.[73]

SOLUBILIZATION TECHNIQUES IN ORAL DRUG DELIVERY OF PROTON PUMP INHIBITORS

Proton PPIs like Lansoprazole, Omeprazole, Esomeprazole and Dexlansoprazole belong to BCS class II category and therefore, come across dissolution-limited GIT absorption and limited bioavailability.[56] Therefore, this has been essential to augment solubility and dissolution profile of such medications to acquire improved therapeutic efficacy in treatment of gastric-ulcer related disorders.[74] In previous years, several techniques and formulation approaches like cyclodextrin inclusion complexes, nano-suspension, solid dispersions, microparticles, solid dispersion pellets and multi-layer film coated pellets has been investigated for PPIs in order increase dissolution and solubility profile of hydrophobic drugs (Figure 3). Table 2 summarizes the excipients used, methodology and research outcomes from earlier investigations performed for solubility enhancement of PPIs.

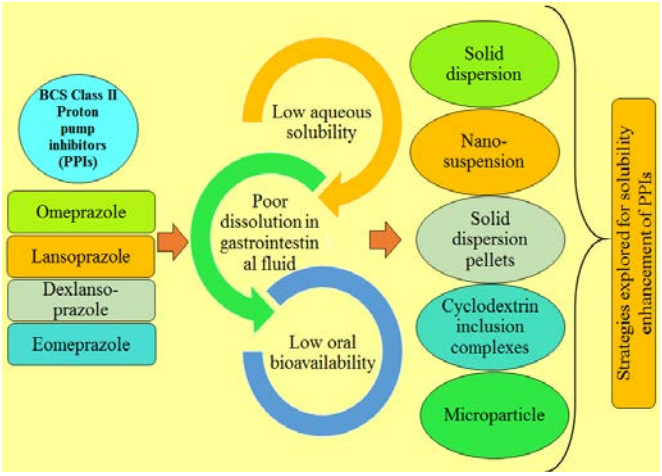

Figure 3. Schematic representation of techniques explored for solubility enhancement of proton pump inhibitors

Nanosuspension

Nanosuspensions are colloidal biphasic dispersion of drug particles scattered in aqueous vehicle having suspended drug exists in nanometer size range and are stabilized by surfactants.[74,75] Nanosuspensions have emerged as feasible solution to challenges faced for delivery of hydrophobic drugs due to simplicity in manufacturing. Drug particle reduction to nanoscale range tends to increase drug dissolution rate not only due to increased surface area but also caused by increase in saturated solubility which is because of increase in vapor pressure and velocity of drug particles due to nanometric size range.[76,77] Incorporation of stabilizers in nanosuspension formulations is crucial to circumvent particle agglomeration. Polymers like polyvinylpirrolydone, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyethylene glycol, polyvinyl alcohol, and d-tocopherol polyethylene glycol 1000 succinate are commonly used stabilizers in nanosuspension formulation.[78] Top-down and bottom-up technologies are frequently used approaches for synthesis of nanosuspension. In bottom-up methods, precipitation technique is commonly used for synthesis of nanoparticles which involves drug dissolution in suitable solvent which is further introduced into non-solvent to precipitate out drug particles at nanoscale.[79,80] Media milling, high-pressure homogenization, emulsion diffusion, and supercritical fluid method are among top-down technologies which are preferred over precipitation techniques.[81]

Solid dispersion

The term "solid dispersion" refers to the dispersion of drug in hydrophilic polymeric solid matrix and can be developed as eutectic mixtures, crystalline solutions, glass solutions and crystalline or amorphous or suspension.[82,83] The polymeric carrier gets dissolved in aqueous environments promptly and releases the drug as fine colloidal suspension which cause enhancement in surface area for producing higher dissolution rate and bioavailability of poor water-soluble drugs.[84] The

examples of water-soluble or water-miscible polymers commonly used as carrier for solid dispersion synthesis includes polyvinylpirrolydone, polyethylene glycol, gelucire 44/14, and Labrasol.[85,86] The solid dispersions are prepared by techniques such as melting or fusion method, melt agglomeration, spraying on sugar beads using fluidized bed coating, supercritical fluid technology, hot-melt extrusion, direct capsule filling, electrostatic spinning and solvent evaporation technique.[87,88]

Microparticles

Microparticles are described as particles with sizes ranging from 1-1000 µm and exist in variety of forms with matrix (microspheres) or reservoir (microcapsules) structure based on their interior design.[89,90] Microspheres are often created as homogeneous matrix systems in which core and membrane cannot be distinguished and active pharmaceutical ingredient is dispersed in polymer matrix either molecularly or in form of tiny clusters. Microcapsules are comprised of continuous polymer coating surrounding central liquid, solid or semisolid core carrying active pharmaceutical ingredient alone or in conjunction with excipients.[91,92] The polymers which are generally used for preparation of microparticles for solubility enhancement includes *beta*-cyclodextrin (*β*-CD),[93] poloxamer 407,[94] methylcellulose, sodium alginate, and chitosan.[95,96] The single emulsion, double emulsion, nano-precipitation, salting out, spray drying and hot melt extrusion are usually used techniques for preparation of microparticles.[97,98]

Cyclodextrin inclusion complexes

Cyclodextrin inclusion complexes are cyclic oligosaccharides with toroidal form made up of (-1,4)-linked d-glucopyranose units and have hydrophilic cavity inside and lipophilic surface outside.[99,100] The drug encapsulation in hydrophobic cavity of cyclodextrins tends to positively affect the physical and chemical properties of guest molecules upon formation of inclusion complexes. The characterization of inclusion complex involves determination of stoichiometry and complex formation constant.[101] Cyclodextrins are flexible and crystalline complexing agents used in pharmaceutical industry which have tendency to augment solubility, bioavailability and stability of drug.[102] The cyclodextrin are usually available in three forms *i.e.* *α*-, *β*- and *γ*-forms which are comprised of six, seven and eight glucopyranose units, respectively. The *β*-CD and their derivatives like hydroxypropyl-*β*-CD and methyl-*β*-CD are commonly employed for production of *β*-CD complexes.[103] The *β*-CDs are highly valuable cyclodextrin among three forms which is attributable to its appropriate complexing capacity, low cost, and appropriate size. Appropriate techniques for production of inclusion complexes includes kneading method, roll mixing, co-evaporation, freeze drying and spray drying.[104–106]

Solid dispersion pellets

Solid dispersion pellets technique is basically blend of solid dispersion with pelletization technology to achieve better drug dissolution rate along with improved flow characteristics without necessitate of milling process which therefore avoids milling challenges. The solid dispersion is synthesized by solvent evaporation technique followed by loading of dispersion into neutral pellets through pelletization technique to produce larger and spherical agglomerations of particles which are known as solid dispersion pellets.[107,108] The pelletization technique generally used includes extrusion-spheronization, spray drying, and powder layering procedure. In comparison to tablets and capsules, solid dispersion pellets have larger surface area to interact with solvent environment which therefore accelerates dissolution rate.[109,110] Pellets are superlative oral solid dosage forms since they can easily cross *via* GIT, causing less irritation and improving drug absorption. These tend to decrease dose dumping which thereby reduces side effects and plasma concentration fluctuation.[111,112] Extrusion-spheronization technique is commonly used for manufacturing of pellets in industries since this technique has excellent ability to prepare pellets with high drug content and uniform consistency without requirement of inactive core material as pelletization starters.[113] Rotoprocessor equipment has closed system which is competent in executing entire pelletization process. The advantages of rotoprocessor over extrusion-spheronization includes minimum dust issues, least contamination risks along with saving of time, money, equipment, energy, machine operators and laboratory space.[114]

Table 2. Outline of methodologies investigated for solubility enhancement of proton pump inhibitors, excipients used and research outcome

Formulation (Methodology)	Excipients	Outcome of research
Lansoprazole		
Cyclodextrin inclusion complexes (Fluid bed coating technique)	*β*-Cyclodextrin	Pure lansoprazole exhibited less than 5% dissolution within 1 hour. Cyclodextrin inclusion complex synthesis leads to ~80% drug dissolution in 15 Minutes.[115]
Solid dispersion pellets (Fluid-bed coating technique)	Polyvinylpyrrolidone (Plasdone®K29/32)	On increasing ratio of drug: polymer from 1/1.75 to 1/5, dissolution rate increased to ~80% within 5 minutes.[116]
Nanosuspension (High shear homogenization)	Hydroxypropyl methylcellulose E15, Sodium Lauryl Sulfate	Nearly 80% of drug was released within 10 minutes from nanosuspension.[117]
Fast dissolving tablet (Direct Compression tablets)	Sodium Starch Glycolate, Crospovidone, Crosscarmellose Sodium	The formulation showed 49.12% and 99.92% drug release with 5 and 15 Minutes, respectively.[118]
Solid dispersion (Solvent evaporation method)	PVP K-30	Solid dispersions dissolved 26.7 times more quickly than the pure drug within 30 Minutes.[119]

Nanosuspension (High pressure homogenization)	β-cyclodextrin, pyromellitic dianhydride	Exhibited increased solubility of ~20% and 50% was observed with β-cyclodextrin based nanosupension and nanosponge based nanosuspension.[120]
Enteric-Coated Lansoprazole Pellets	HPMCAS, Eudragit L	Improved the drug stability and oral bioavailability.[121]
Omeprazole		
Gastro Resistant Omeprazole Tablets (wet granulation method)	Sodium lauryl Sulfate, triethyl citrate, hydroxypropyl methylcellulose acetate succinate	Release profile showed 91 to 98% drug release within 1hour in acetate buffer, pH 6.8.[122]
Solid self-nanoemulsifying drug delivery system (Solid-SNEDDS)	Capryol 90, Cremophor RH 40, Neusilin® US2	Solid-SNEDDS filled in enteric coated hard gelatin capsules improved the dissolution profile and stability under acidic medium.[123]
Multi-layer film coated pellets (Extrusion-spheronization and fluidized bed coating)	MCC, SDS, PEG 6000, PVP K-30, HPMC, Eudragit® L 30D-55	Drug-layered pellets with multilayer film coatings not only provided delayed and rapid release of omeprazole, but also could provide a good stable property for omeprazole.[124]
Esomeprazole		
Nanosuspension (Evaporative precipitation-ultrasonication method)	Poloxamer 188 and Poloxamer 407	Plain Esomeprazole showed dissolution of 24% in 60 minutes while nanosuspensions showed enhanced release rate, 65% of the drug diffused in 30 min and 100% diffused in the 60 min test period.[125]
Nanosuspension (Top-down and Bottom-up)	Poloxamer 188	Crude drug and nanosupension revealed 31% and 92% release within 90 minutes, respectively which showed three times dissolution enhancement.[126]

HPMC: Hydroxypropyl methyl cellulose; PVP K-30: Polyvinylpirrolydone K-30; PEG 6000: Polyethylene glycol; MCC: Microcrystalline cellulose; SDS: Sodium dodecyl sulfate; SLS: Sodium lauryl sulphate

GASTRORETENTIVE TECHNIQUES IN DRUG DELIVERY OF PROTON PUMP INHIBITORS

Oral drug delivery systems have been predominant route of drug delivery because of the many benefits associated with using them. These benefits include simplicity of usage, highest patient compliance, formulation versatility, cost-effectiveness, convenience in storage and transportation. However, the limited oral bioavailability challenges may make oral drug delivery systems difficult to develop and application.[127] Conventional drug delivery of PPIs might be inefficient to solve the problems caused by GIT, which include insufficient drug release, reduction in drug efficacy, and the need for more frequent dosing which have encouraged establishment of gastroretentive drug delivery systems of PPIs.[128] The gastroretentive formulations of PPIs provide numerous advantages like extended gastric residence time for several hours, higher therapeutic efficacy attributable to increase in drug absorption and for achieving drug targeting within GIT.[129] Furthermore, gastroretentive drug delivery systems can improve the drug release for extended period in GIT until the drug is completely released from dosage form. The development of gastroretentive formulations for PPIs is viable alternative and highly required.[127,128,130,131] The different research investigations which have been executed in previous years for development of gastroretentive formulations of PPIs are summarized in Figure 4 and Table 3. In order to provide a prolonged or controlled release of the medicinal ingredient, gastroretentive formulations are primarily manufactured. The pH of gastric juice momentarily rises due to the alkaline ingredient sodium bicarbonate, which is present in the tablet formulation. Together with preventing PPIs from breaking down in the stomach, this function can be utilised for quick relief from GERD symptoms.[16]

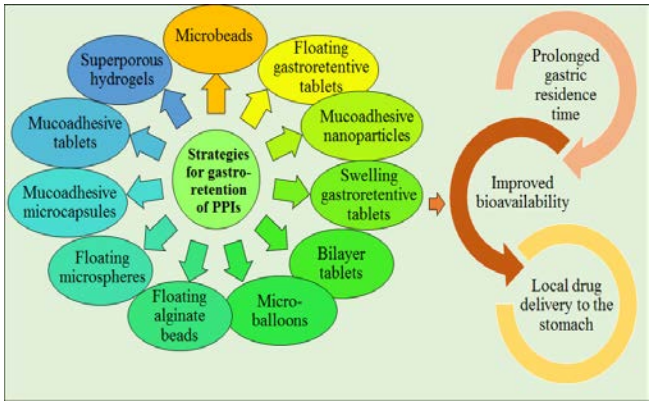

Figure 4. Diagrammatic illustration of techniques for development of gastroretentive drug delivery system of proton pump inhibitors

Table 3. Demarcation of formulation approaches investigated for gastroretention of proton pump inhibitors with reference to excipients, methodology employed and research outcome

Formulation (Methodology)	Excipients	Outcome of research
Lansoprazole		
Floating Microbeads (Ionic gelation method)	Pectin, zinc acetate, calcium silicate, neem gum	Floating microbeads showed 87.47% entrapment efficiency and delayed drug release of 69.20% till 8 hours due to strong polymer network.[132]
Microspheres (Modified non-	Span 80, ethyl cellulose, hydroxy	The porous cavities over outer surface of

aqueous solvent evaporation method)	propyl methyl cellulose (HPMC)	microspheres caused microspheres to float over dissolution medium for prolonged periods and buoyancy of microspheres was 90.4%-98.4%.[133]
Floating tablets (Compression)	HPMC K4M, HPMC K15M, microcrystalline cellulose, sodium bicarbonate, citric acid	The formulation F4 containing HPMC K4M and formulation F6 containing of HPMC K15M exhibited sustained drug release till 24 hours which highlighted that mixture of polymers and gas producing agent had significant effect on floating potential and drug release.[134]
Gastroretentive Sustained Release Tablets (Direct compression)	Xanthan gum, chitosan, carbopol 940, gellan gum, citric acid	F7 showed sustained drug release and the cumulitative drug release was upto 99.74% for up to 12 hours.[135]
Polymeric mucoadhesive nanoparticles (Ionotropic gelation method)	Chitosan, sodium tripolyphospate, acetic acid	*In-vitro* release from mucoadhesive nanoparticles followed zero-order kinetics and demonstrated sustained release behaviour till 24 hours.[136]
Trilayer swelling gastro retentive tablets (Wet granulation method)	PVP K30, cross povidone, cross carmellose sodium, sodium starch glycolate	Swelling of tablets prolonged for 24 hours for optimized trilayer swelling gastroretentive tablets.[137]
Omeprazole		
Gastroretentive floating tablets (Direct compression technique)	HPMC K4 M, HPMC K15 M, sodium bicarbonate, citric acid	*In-vitro* drug release from floating tablets comprised of HPMC-K4M and HPMC-K15M showed floating time of 81seconds and prolonged floating for >10 hours with sustained release of 94% for 7 hours.[138]
Microspheres (Emulsification-solvent evaporation method)	Ethyl cellulose, HPMC, piperine, light liquid paraffin, span 80	Exhibited increased absorption and decreased metabolism of omeprazole attributable to presence of piperine in gastroretentive microspheres.[139]
Bilayer tablets (Direct compression method)	PVP K30, crosscarmellose sodium, HPMC K15M, HPMC K4M, citric acid, crospovidone	Increased bioavailability and reliability for treating *H. pylori* with minimal fluctuations observed with conventional dosage form. Final Optimised bilayer formulation released 98.23 % in 12 hours.[140]
Floating microspheres (Solvent diffusion method)	Ethyl cellulose, PVP K-90	Exhibited drug release in range of 39.64 to 93.64% till 6 hours.[141]
Floating Tablet (Wet granulation)	HPMC KI5M, HPMC K100M, sodium bicarbonate	Revealed increased drug release in 0.1N hydrochloric acid having 1.2 pH; increased gastric retention time.[142]
Microballoons (Emulsion solvent diffusion method)	HPMC K4M, ethyl cellulose, dichloromethane	Enhanced bioavailability due to increase in gastric residence time.[143]
Esomeprazole		
Microspheres (Double emulsion solvent diffusion method)	HPMC K4M, K15M, sodium bicarbonate, span 80	Microspheres remained buoyant for > 10 hours and *in-vitro* release profile followed first order non-fickian release which showed diffusion as well as dissolution-controlled release pattern.[144]
Mucoadhesive Microballoons	HPMC, chitosan, carbopol 934, ethyl cellulose	Formulations showed floating for 7-12 hours and 81.71-93.51 percentage drug entrapment efficiency.[145]
Super porous hydrogel	Chitosan, polyvinyl alcohol, tween 80, glutaraldehyde	Super porous hydrogel revealed extended gastro-retention up to 18 hours.[146]
Bilayer tablet (Direct compression method)	Crosscarmellose sodium, PVP K30, HPMC K15M, HPMC K4M, cross-povidone	Showed release of 89.98 % Esomeprazole from immediate release layer in 15 minutes and 98.89±0.47% Clarithromycin from sustained release floating layer in 12 hours.[147]
Rabeprazole		
Floating alginate beads (Ionotropic Gelation Technique /Simple dripping method)	Sodium alginate, HPMC, calcium chloride, sodium bicarbonate	Preparations remained buoyant and exhibited controlled release till 10 hours.[148]

Floating microspheres (emulsion solvent evaporation method)	HPMC K15M and ethyl cellulose	Provided controlled drug delivery, reduced the dosing frequency and improved oral bioavailability.[149]
Floating microspheres (Solvent evaporation technique)	HPMC, chitosan, tween 80	Formulations floated for more than 12 hours over the surface of dissolution medium and showed improved absorption and bioavailability.[150]
Mucoadhesive microcapsules (Solvent evaporation technique)	Light liquid paraffin, tween 80, eudragit L100, ethyl cellulose, HPMCK100M	Exhibited controlled drug release for prolonged period with fitting in higuchi model. Pharmacodynamics studies demonstrated enhancement in ulcer protection potential in rat model.[151]
Floating tablet (Direct compression technique)	HPMC K15M, HPMC K100M, ethyl cellulose, sodium bicarbonate	Floating tablet exhibited floating time >12 hours.[152]
Pantoprazole		
Mucoadhesive gastroretentive tablets (Direct compression method)	Carbopol 940, Guar gum, HPMC K4M	Showed excellent mucoadhesive potential with sustained drug release pattern.[153]
Superporous hydrogels	Acrylamide, methacrylic acid, sodium bicarbonate, tetramethyl ethylenediamine	Exhibited higher swelling ratio and further, this was observed that alteration in pH from acidic to alkaline conditions caused significant rise in swelling of super-porous hydrogel.[154]
Microspheres (Nonaqueous solvent evaporation method)	Eudragit S100, HPMC K 100M, liquid paraffin	Microspheres exhibited the percentage yield, entrapment efficiency and buoyancy percentage of 84.43-91.93%, 65.83-90.03% and 61.7-78.46%, respectively.[155]
Floating microspheres (Coacervation technique)	PVP, HPMC	Showed drug release and incorporation efficiency of 92.8% and 91.2%, respectively.[156]
Floating tablets (Direct compression method)	Sodium bicarbonate, citric acid, hydroxyethyl cellulose	Formulations exhibited strong floating characteristics except few batches which showed moderate floating. Best batch exhibited highest drug release of 86.17% within 12 hours.[157]
Dexlansoprazole		
Super-porous hydrogel tablets (Direct compression method)	Chitosan, microcrystalline cellulose, sodium alginate, pectin, acrylic acid	Formulation revealed good swelling index and mechanical strength with enhanced drug release.[158]

MARKETED PRODUCTS OF PROTON PUMP INHIBITORS

The proton pump inhibitors are available in the market in the form of delayed release tablets or capsules in various dosage strengths. PPIs are also available in the form of lyophilized powder for solution for intravenous injection. Table 4 summarizes marketed products of PPIs manufactured by various pharmaceutical industries.[159]

Table 4. The description of some commercially available tablet/capsules/lyophilized powder formulations of proton pump inhibitors

Dosage	Strength	Route	Manufacturer
Omeprazole			
Tablet, delayed release	20 mg	Oral	Ranbaxy Inc.
Granule, delayed release	10 mg	Oral	AstraZeneca Pharmaceuticals LP
Capsule, delayed release	40 mg	Oral	Torrent Pharmaceuticals Limited
Lansoprazole			
Capsule, delayed release	15 mg	Oral	Sivem Pharmaceuticals ULC
	30 mg	Oral	Takeda Pharmaceuticals America, Inc.
Tablet, delayed release	15 mg	Oral	Takeda
Rabeprazole			
Tablet, delayed release	20 mg	Oral	Woodward Pharma Services LLC
	10 mg	Oral	Janssen Pharmaceuticals
	20 mg	Oral	Pharmascience Inc
	20 mg	Oral	Lupin Pharmaceuticals, Inc.
	20 mg	Oral	Aurobindo Pharma Limited
Pantoprazole			
Tablet, delayed release	40 mg	Oral	Takeda
	40 mg	Oral	Sun Pharma Canada Inc
Powder, for solution	40 mg/vial	I.V	Auro Pharma Inc
Injection, powder, lyophilized, for solution	40 mg	I.V	Hikma Pharmaceuticals USA Inc
Esomeprazole			
Tablet, delayed release	40 mg	Oral	Pro Doc Limitee

Granule, delayed release	20 mg	Oral	AstraZeneca Pharmaceuticals LP
Capsule, delayed release	20 mg	Oral	AstraZeneca Pharmaceuticals LP
Injection	40 mg/5 mL	I.V	AstraZeneca Pharmaceuticals LP
Dexlansoprazole			
Capsule, delayed release	60 mg	Oral	Takeda Pharmaceuticals America, Inc.
	30 mg	Oral	Physicians Total Care, Inc.
	60 mg	Oral	Takeda

I.V: Intravenous

STATE-OF-THE-ART OF PATENT LITERATURE ABOUT PROTON PUMP INHIBITORS

Patent literature was compiled from World Intellectual Property Organization (WIPO) website with regard to formulation strategies explored for PPIs in last few years. Table 5 demonstrates comprehensive description about patent title, patent number, applicant and date of publication in organized mode.

Table 5. Depiction of patent literature pertaining to PPIs and formulation strategies

Patent Title	Patent number (Date of publication)	Applicant
Pharmaceutical composition comprising esomeprazole and sodium bicarbonate having excellent release properties.[160]	US20230084129 (16.03.2023)	Chong Kun Dang Pharmaceutical Corp.
Omeprazole sodium freeze-dried powder injection and preparation method thereof.[161]	CN115501191 (23.12.2022)	Nanjing Carvendish Bio-Engineering Technology Co., Ltd
Equine esomeprazole formulations and methods of use.[162]	US20220354836 (10.11.2022)	Kindred Biosciences, Inc.
Pantoprazole compositions and methods.[163]	US20220062253 (03.03.2022)	Nivagen Pharmaceuticals, Inc.
Omeprazole enteric-coated pellet and preparation method thereof.[164]	CN112999188 (22.06.2021)	Kamp Pharmaceutical Co., Ltd.
Rabeprazole sodium enteric-coated orally disintegrating tablets and preparation method thereof.[165]	CN112168800 (28.09.2020)	Nanjing C&O Pharmaceutical Science&Technology Co., Ltd.
Lansoprazole freeze-dried powder for injection and preparation method thereof.[166]	CN109394706 (01.03.2019)	Hangzhou Shanghe Health Technology Co., Ltd.
Method for preparing rabeprazole sodium enteric coated tablets.[167]	CN107303285 (31.10.2017)	Nanjing Qingluo Biotechnology Co., Ltd.
Method for preparing rabeprazole sodium by virtue of supercritical anti-solvent technique.[168]	CN106957302 (18.07.2017)	Shandong Yuxin Pharmaceutical Co., Ltd.
Pantoprazole sodium composition lyophilized powder for injection.[169]	US20160263094 (15.09.2016)	Hainan Wei-Kang Pharmaceutical (Qianshan) Company Limited
Pantoprazole enteric-coated pellets, pantoprazole enteric-coated controlled-release tablets and preparing method thereof. [170]	CN105816436 (03.08.2016)	Guangzhou Gonghe Medicine Technology Co., Ltd.
Lansoprazole special superfine powder freeze-dried preparation and preparing method thereof.[171]	CN104306341 (28.01.2015)	Youcare Pharmaceutical Group Co., Ltd.
Novel benzimidazole isomer preparation and preparation method thereof.[172]	CN104274421 (14.01.2015)	Dashengxiang (Wuhan) Tcm Investment Management Co., Ltd.
Pantoprazole sodium composition freeze-dried powder injection for injection.[173]	CN103550173 (05.02.2014)	Hainan Weikang Pharmaceutical (Qianshan) Co., Ltd.
Levorotatory-pantoprazole sodium composition freeze-dried powder for injection.[174]	CN103536563 (29.01.2014)	Hainan Weikang Pharmaceutical (Qianshan) Co., Ltd.
Rabeprazole sodium composition and preparation method thereof. [175]	CN101627996 (20.01.2010)	Shandong Luoxin Pharmaceutical Co., Ltd

CONCLUSIONS

Several PPIs such as lansoprazole, omeprazole, esomeprazole and dexlansoprazole belongs to BCS class II. These drugs countenance enormous challenge of inadequate aqueous solubility as well as lesser bioavailability and consequently needs solubility improvement. This review article highlights about previously explored approaches like *β*-cyclodextrin complexes, solid dispersion, nanosuspension, microparticles, solid dispersion based pellets and multi-layer film coated pellets. Furthermore, PPIs also meet challenge of limited gastric residence time and thus, necessitate fabrication of gastroretentive drug delivery systems *i.e.* microbeads, bilayer tablets, polymeric mucoadhesive nanoparticles, floating gastroretentive tablets, trilayer swelling gastroretentive tablets, microballoons, floating microspheres, floating alginate beads, mucoadhesive microcapsules, super-porous hydrogel and mucoadhesive tablets. This review article concludes that poor aqueous solubility challenge of PPIs could be successfully overcome by applying suitable formulation strategy. This has also been conclusively manifested that gastroretention drug delivery systems has enormous potential for overcoming challenge of limited gastric residence time.

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CONFLICT OF INTEREST STATEMENT

Authors do not have any financial or academic conflict of interest for publication of this work.

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