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Review Article

Analytical Methods with Clinical Trial and Future Aspects of Vonoprazan : A Systemic Review

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ABSTRACT

Nowadays, use of antacids has drastically increased due to an increase in the intake of drugs with certain side effects, in which the dominant 'acid release cycle' is disturbed. This resulted in the inclusion of Proton pump inhibitors in a major number of prescriptions. In individuals with gastroesophageal reflux disease and concurrent Helicobacter Pylori infection, proton pump inhibitors exhibit a significant limitation in providing relief from symptoms or adressing lingering issues associated with the sympathetic system, particularly during periods of rest such as sleep. Furthermore, this article summarises vonoprazan's effects on 'triple drug therapy'. Through its inhibition of the stomach's H+/K+ ATPase, Vonoprazan, a novel potassium-competitive acid blocker, has the potential to provide a reversible mechanism of action, leading to acid supression.It is anticipated that vonoprazan-based addiction therapy would be more effective for treatment for shorter period of time. In this study, the latest information provides a concise overview of the chemistry, biological properties, pharmacological, analytical methods, and clinical trials of Vonoprazan.

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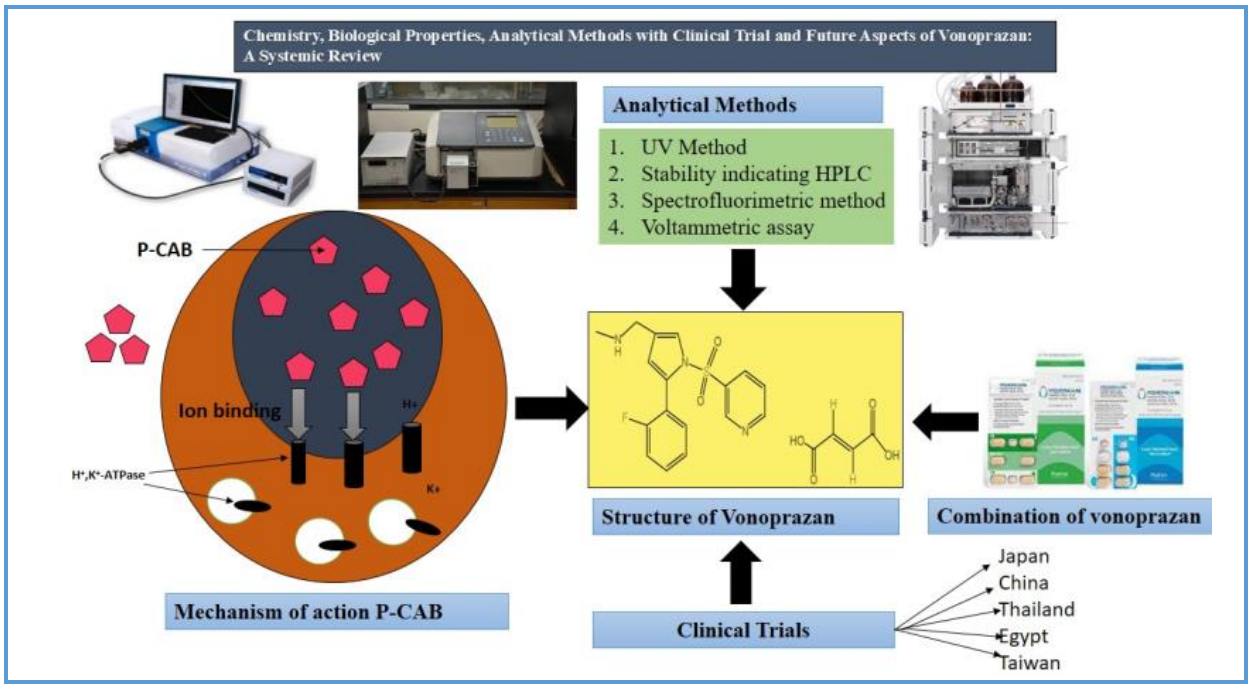
Graphical Abstract



Introduction

Conditions associated with excess acidity such as gastroduodenal ulcers and reflux require treatment to suppress gastric acid secretion. PPIs, available in the late 1980s, have become the preferred drug for most patients due to their potent acid-suppressing effects and better tolerability [1]. Helicobacter pylori are linked to peptic ulcer disease recurrence and potential gastric adenocarcinoma. Eradication therapy includes combination chemotherapy with amoxicillin and clarithromycin for enhanced antimicrobial effects [2]. PPIs revolutionized acid-related disorder pharmacotherapy, leading to doubts about developing a powerful anti-secretory drug [3]. PPIs, despite their effectiveness, may not completely control nighttime acid breakthrough, leading to approximately one-third of individuals suffering from gastroesophageal reflux disease requiring additional antacids to alleviate remaining symptoms [4]. PPIs' pharmacokinetics is influenced by CYP2C19 genetic polymorphisms, making standard doses insufficient for H. pylori eradication. Acid-resistant formulations are needed to prevent conversion to active protonated sulfonamides within the stomach's interior [5].

Helicobacter pylori are a worldwide health problem with a prevalence of 44.3%, affecting 40-50% of the global population, and a recurrence rate of 4.3-4.6% [6]. H. pylori infection is most prevalent in Africa, followed by Latin America and Asia [7]. Indonesia has a 22.1% H. pylori infection prevalence [8]. H. pylori infection is linked to gastritis, reflux, ulcers, MALT lymphoma, and malignancies [9-10].

The treatment of acid-peptic diseases requires rapid and effective acid inhibition upon the administration of acid-inhibitory medications such as proton pump inhibitors (PPIs). Improved cure rates for peptic ulcers, gastroesophageal reflux disease, non-erosive reflux illnesses, aspirin-induced

gastroduodenal mucosal damage, and Helicobacter pylori infection have been linked to therapies that neutralise intragastric pH values. To effectively treat acid-peptic illnesses, it is crucial to comprehend how to reduce stomach acid secretion [11].

VPZ, a potent acid-inhibitory drug, targets the gastric proton pump enzyme H^+,K^+-ATPase in gastric parietal cells. It has two advantages over PPIs: it doesn't require activation by gastric acid and has a longer half-life due to its slow dissociation kinetics. Vonoprazan provides rapid, strong, and long-lasting gastric acid inhibition after administration in a dose-dependent manner. Mechanism of action of PPIs works by irreversibly inhibiting the proton pump (H^+, K^+-ATPase) in the stomach lining. This enzyme is responsible for the final step in the production of gastric acid, and by blocking it, PPIs effectively reduce the acid secretion into the stomach when Vonoprazan is also a proton pump inhibitor, but it differs in that it acts in a reversible manner. It inhibits the proton pump by binding to a different site on the pump compared to PPIs. The duration of acid suppression with PPIs is influenced by the time it takes for the body to replace the proton pumps that have been inactivated. This process can take several days when vonoprazan due to its reversible inhibition, it may provide a more sustained and prolonged suppression of gastric acid compared to same PPIs.

This reversible binding may result in a more rapid and sustained suppression of acid secretion.Vonoprazan is taken orally in the following dosages: 20 mg once daily for healing gastroduodenal ulcers, 20 mg once daily for treating reflux esophagitis and 10 mg once daily for preventing its recurrence, 10 mg once daily for preventing peptic ulcers induced by low-dose aspirin or non-steroidal anti-inflammatory drugs, and 20 mg twice daily when used in combination with clarithromycin and amoxicillin to eliminate H. Pylori [12].

Class of Drug

H^+,K^+-ATPase transports protons to the canalicular space, regulating activity by balancing K^+ ions. Studies on H^+,K^+-ATPase's molecular mechanisms led to the discovery of potassium-competitive acid blockers (P-CAB), anti-secretory agents that competitively block K^+ availability for H^+,K^+-ATPase. Vonoprazan fumarate (known as TAK-438 or Takecab) is a Potassium-Competitive Acid Blocker (P-CAB) that received approval from the Japanese Ministry of Health, Labor, and Welfare in December 2014 and was introduced in February 2015 for the treatment of conditions related to high acidity and as a part of the treatment regimen for eliminating H.pylori. It became available in Russia in April 2021. Vonoprazan is pioneering potassium-competitive acid blockers (P-CAB), and studies have detailed its pharmacokinetic and pharmacodynamic effects in both Caucasian and Asian populations [12]. Chemical structure of vonoprazan is shown in Figure 1.

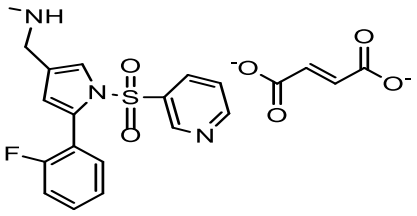


Figure 1. Chemical Structure of Vonoprazan

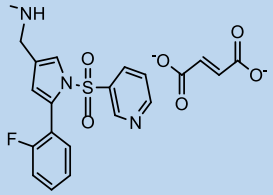
Physicochemical characteristics

White to virtually white crystals or crystalline powder, or vonoprazan fumarate melts at 194.8 °C. Vonoprazan fumarate dissolves in dimethyl sulfoxide, is hardly soluble in N-dimethylacetamide, is barely soluble in N,N-dimethylformamide, methanol, and water, is barely soluble in ethanol (99.5),

and is essentially insoluble in 2-propanol, acetone, 1-octanol, and acetonitrile. Physicochemical properties of vonoprazan are presented in Table 1. Vonoprazan, also known as TAK-438, is a pyrrole derivative that resists acidic conditions. As a pyrrole derivative, it contains a pyrrole ring in its molecular structure. This stability in acidic environments is particularly relevant to its pharmacological action, as Vonoprazan is commonly used to reduce stomach acid and treat conditions such as gastroesophageal reflux disease (GERD) and peptic ulcers. It was developed by Takeda Pharmaceutical Company Ltd. as a Potassium-Competitive Acid Blocker (P-CAB). Vonoprazan's distinctive feature is its ability to accumulate in higher concentrations within the canalicular space of gastric parietal cells when compared to the other P-CABs. This is primarily due to its elevated positive charge, with a pKa value of 9.06, which surpasses other potassium-competitive acid blockers (P-CABs) with varying chemical structures. The drug effectively binds to H^+, K^+-ATPase in a strictly potassium-competitive and reversible manner, as reflected by its Ki value of 10 nM at equilibrium [13].

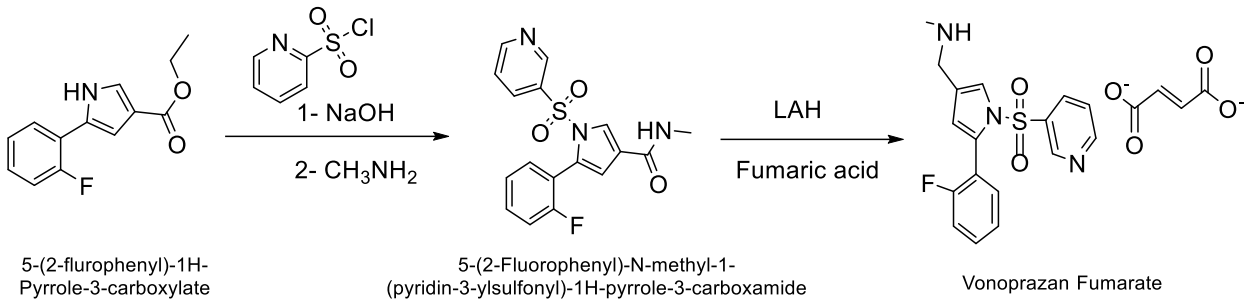
Vonoprazan exhibits greater effectiveness in inhibiting H^+, K^+-ATPase activity when compared to SCH28080 and lansoprazole in porcine gastric microsomes at pH 6.5. This heightened efficacy and longer-lasting suppression of acid secretion, as compared to lansoprazole, can be attributed to Vonoprazan's slower dissociation rate [14].

Table 1. Physicochemical properties [15]

properties	
Alternative names	TAK 438;Takecab; Vonoprazan fumarate
IUPAC Name	1-[5-(2-fluorophenyl)-1-pyridin-3-ylsulfonylpyrrol-3-yl]-*N*-methylmethanamine
Molecular formula	$C_{17}H_{16}FN_3O_2S{\cdot}C_4H_4O_4$
Molecular weight	345.4 g/mol
log P	2.74
pKa	9.3
Solubility	DMSO, Methanol

Synthesis

Vonoprazan fumarate, a recently developed potassium-competitive acid blocker, has been produced using an inventive and practical approach starting from 5-(2-flurophenyl)-1H-Pyrrole-3-carboxylate.[16] 5- (2-fluorophenyl) -1H-pyrrole-3-carboxaldehyde is used as a raw material, tetrahydrofuran is used as a solvent, sodium hydride is used as an acid binding agent, and crown ether is used as a phase transfer catalyst. -Pyridylsulfonyl chloride reacts to give intermediate 5- (2-fluorophenyl) -1- (3-pyridylsulfonyl) -1H-pyrrole-3-carboxaldehyde, and then salted with fumaric acid to form the final product, Vonolazan fumarate, as depicted in Scheme 1 [16].



Scheme 1. Synthesis of vonoprazan.

Clinical Pharmacology

Mechanism of Action

Proton pump inhibitors (PPIs) are a potential substitute for potassium-competitive acid blockers (P-CABs), a unique class of acid-suppressing medications, in the management of gastroesophageal reflux disease. When treating GERD, PPIs may serve as an alternative option to P-CABs. PPIs and P-CABs are both classes of medications designed to suppress stomach acid production, and their use may depend on factors such as patient preferences, tolerability, or specific clinical considerations. P-CABs are the "unique class of acid-suppressing medications" with a distinct mechanism of action compared to PPIs. P-CABs, such as Vonoprazan, competitively block the potassium channel of the proton pump, providing an alternative approach to acid suppression compared to the irreversible inhibition caused by PPIs. Unlike PPIs, PCABs are acid-stable H^+, K^+-ATPase inhibitors that non-covalently inhibit H^+, K^+-ATPase. As a potassium-competitive acid blocker (PCAB), vonoprazan prevents the H^+, K^+-ATPase enzyme systems from working. Through this mechanism, vonoprazan prevents both basal and provoked gastric acid production at the secretory surface of gastric parietal cells. Mechanism of action is displayed in Figure 2**.**

Despite the fact that both medication classes inhibit the H^+, K^+-ATPase, PCABs have a different mode of action than proton-pump inhibitors (PPIs) [17].

Comparison of the mechanisms of action of vonoprazan, a potassium-competitive acid blocker was done with lansoprazole, a traditional proton pump inhibitor. In the active phase, which comes after a meal, hydrogen potassium H^+, K^+-ATPases may be seen on the apical membrane of the secretory canaliculus. They are seen in tubulovesicles in quiescent phage.

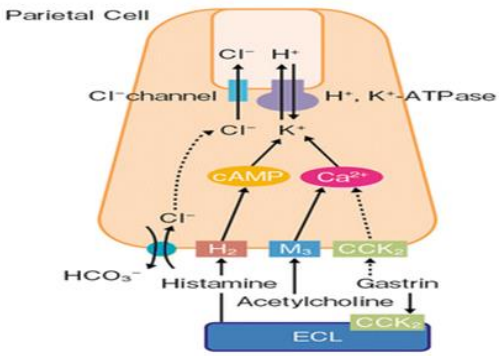


Figure 2. Mechanism of action.

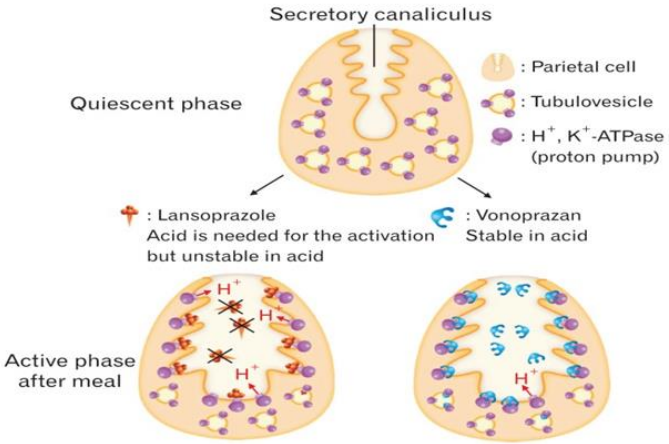


Figure 3. Mechanistic contrasts Between Lansoprazole and Vonoprazan.

Although it quickly dissolves, lansoprazole transforms into its active form in the secretory canaliculus (X). Lansoprazole's active form forms a covalent bond with the proton pump enzyme H^+, K^+-ATPase. Vonoprazan can inhibit newly exposed H^+, K^+-ATPase for a very long time and accumulate steadily in the acidic secretory canaliculus, as demonstrated in Figure 3. It non-covalently binds to H^+, K^+-ATPase with a very slow dissociation rate [18].

Pharmacokinetics

Absorption

Vonoprazan's intestinal absorption is rapid, with C_{max} increasing rapidly after single oral doses in both study populations. Consecutive oral administrations spanning seven days demonstrated that drug accumulation approached completion by the third day. During this process, the C_{max} and AUC0-inf factors exhibited a range of 1.14 to 1.32. Vonoprazan is quickly absorbed and reaches its peak plasma concentration 1.5 to 2 hours after oral dosing [12].

To predict vonoprazan's pharmacokinetics and its acid-supressind impact following human administration using *in vitro* data, we developed a physiologically based pharmacokinetics (PBPK)-PHARMACODYNAMIC (PD) model that specifically addresses the stomach. This model employed a simplified membrane representation to describe vonoprazan's distribution within the stomach. In addition, *in vitro* data was generated using hepatic microsomes and Caco-2 cells for metabolic and transport studies [19].

Distribution

Furthermore, the duration of vonoprazan's antisecretory impact was partially explained by the drug's sluggish rate of dissociation from the H^+, K^+-ATPase complex. In addition, it was discovered that, particularly at night, the anticipated changes in pH in the participants were greater than those in the actual data, which may be the result of nocturnal acid breakout [20].

Vonoprazan migrates into parietal cells via passive transport, becomes protonated, and accumulates in the acidic secretory canaliculus. It remains in a protonated state despite elimination, as illustrated in Figure 4 [21].

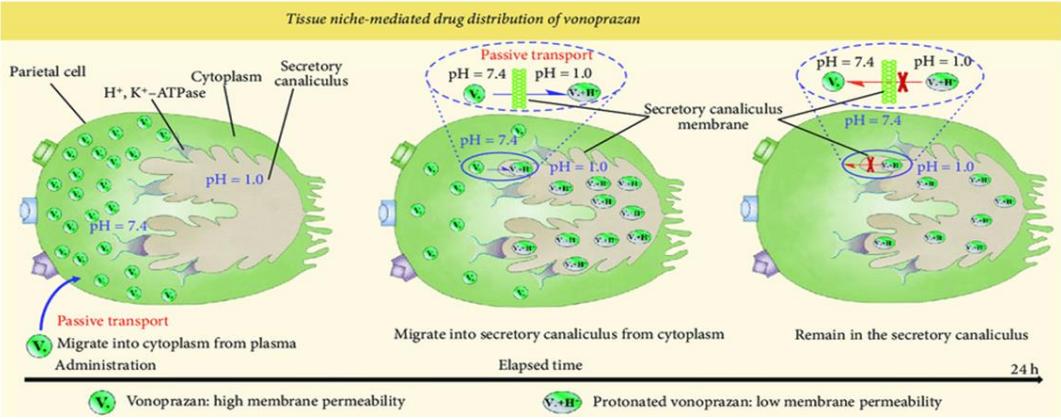


Figure 4. Tissue niche-mediated drug distribution (TNMDD) of vonoprazan

Plasma Protein Binding

Vonoprazan, a drug with a pKa of 9.6 and resistance to acidity, has 80% plasma protein binding in healthy individuals and 1050 liters of distribution. It concentrates in gastric parietal cells, suppressing gastric acid, and binds to albumin and alpha-1-acid glycoprotein [22].

Metabolism

Vonoprazan is divided into five active metabolites: N-demethylated vonoprazan, MI, M-II, M-III, and M-IV-Sul. M-I is the most toxic, with high levels in plasma, liver, and kidneys. M-IV-sul is the most secure and less toxic than the parent compound.

M-IV, a rapidly metabolized phase II compound, has potential pharmacological activity and TNMDD similar to vonoprazan. It could serve as a lead compound for developing new P-CABs with better stomach distribution and nontoxic metabolites. M-IV's *in vitro* inhibitory effect showed good activity against H^+,K^+- ATPase, providing an ideal position for substituents to insert [23].

Elimination

Vonoprazan has an average renal clearance of 6.4 L/h in healthy individuals, with only 4% excreted in urine. Its plasma half-life is longer than PPIs, extending to 7 hours. However, renal clearance for unbound form surpasses glomerular filtration rate, suggesting an active transport mechanism in vonoprazan's renal elimination [22].

Drug-drug interaction

A variety of cytochrome P450 (CYP) isoforms and conjugation pathways, including sulfo- and glucuronosyl-transferases, are used to highly metabolise vonoprazan. Recombinant CYP enzymes were used in *in vitro* tests to establish that CYP3A4 is the main enzyme responsible for the CYP-mediated processing of vonoprazan, with CYP2D6 and CYP2C19 making just a little contribution.Vonoprazan exposure increased 1.58-fold when given in conjunction with the potent CYP3A4 inhibitor clarithromycin in a clinical DDI study [24].

Clinical research assessed potential medication interactions using vonoprazan, clarithromycin, and amoxicillin combination regimens. Results showed vonoprazan exposure increased 1.8 times when clarithromycin and amoxicillin were co-administered. The PKs of amoxicillin did not alter, but when clarithromycin was given as

triple treatment, the exposure to the drug dose increased by 1.5 times. Due to potential safety concerns regarding probable nitrosamine impurities in rifampin clinical supplies, a clinical research examining the effect of powerful CYP3A inducer rifampin on vonoprazan exposure was halted [25,26].

Rifampin was explored as an alternative to other robust CYP3A inducers, such as phenytoin or carbamazepine, for the clinical DDI trial, but a modelling method was adopted in order to avoid any potential safety issues that may arise when these drugs are given to healthy participants. [27,28].

Clinical indication

Helicobacter pylori eradication therapy

Helicobacter pylori are prevalent human bacterial infections causing various gastric disorders, has been effectively addressed through diverse treatments, including bismuth quadruple therapy and vonoprazan-based triple therapy. Significantly, second-line triple therapy involving vonoprazan, amoxicillin, and metronidazole achieved a noteworthy 98% eradication rate for non-responsive cases following initial treatment. Studies also demonstrated the success and tolerability of vonoprazan-based first-line therapy, especially for patients previously unresponsive to rabeprazole first-line triple treatment. Emphasizing the importance of a swift and sustained increase in intragastric pH, this study provides valuable insights into effective strategies for H. pylori eradication, presenting alternatives for patients with resistant infections [29,30,31].

Prevention of Recurrence of Low-dose Aspirin/non-steroidal anti-inflammatory drug-related ulcers [18]

The co-administration of NSAIDs with H. pylori infection heightens the risk of gastric and duodenal ulcers and bleeding. Vonoprazan, a potent acid suppressant from the first dose, proves well-tolerated in combination with low-dose aspirin (LDA) or NSAIDs, showing no clinically significant interactions. Double-blind, randomized studies confirm the effectiveness and safety of vonoprazan (10 mg and 20 mg) in preventing NSAID-associated upper GI ulcer recurrence, aligning with prior research on PPIs. Extended use of vonoprazan for over a year reveals no unexpected adverse effects. In comparison to lansoprazole, vonoprazan reduces ulcer recurrence and upper GI hemorrhage risk, remaining safe and well-tolerated over at least 24 weeks of long-term usage.

Adverse Drug Reaction

ADRs such diarrhoea, nausea, dysgeusia, soft faeces, and rash were often observed. Immune system problems include drug eruptions, urticaria, and anaphylactic shock. Hepatic damage, liver failure, and jaundice are hepatobiliary illnesses. The common side effects (2%) of the VOQUEZNA TRIPLE PAK (comprising vonoprazan pills, amoxicillin capsules, and clarithromycin tablets) included altered taste sensation (dysgeusia), gastrointestinal issues such as diarrhoea, and vulvovaginal discomfort [32]. The most frequent side effects (2%) of the VOQUEZNA DUAL PAK (vonoprazan tablets;amoxicillin capsules) were diarrhoea, stomach pain, vulvovaginal candidiasis, and nasopharyngitis [32].

Reported Analytical Methods

Table 2 gives idea about reported analytical method available for vonoprazan [33-37].

Table 2. Analytical methods

Sr. No.	Technique	Matrix	Method description	Conclusion
1	UV (ratio difference) RD method	VON & ASPIRIN	**Wavelength**: ASP- amplitude values between 229 & 283 VON- amplitude values between255 & 212 **Accuracy** : ASP = 100.37, VON = 99.24	Utilising ratio spectra and other ultraviolet spectrophotometric techniques, ASP and VON in combination tablet formulations were analysed and quantified.
2	UV 1st derivative method	VON & ASPIRIN	**Wavelength**: ASP selective ƛ = 237.4 VON selective ƛ = 244 **Accuracy** : ASP = 99.82, VON = 100.01	Ultraviolet spectrophotometric techniques, ASP and VON in combination tablet formulations were analysed and quantified
3	Stability– indicating HPLC method for ten related substances	VON	**Mobile phase-A** 0.03 M sodium phosphate **buffer** (pH adjusted to 6.5), methanol and acetonitrile in the ratio of 72:25:3 **Mobile phase-B** 0.03 M sodium phosphate **buffer** (pH adjusted to 6.5) and acetonitrile in the ratio of 30:70 **Column**: Phenomenex Kinetex EVO C18 (250 mm × 4.6 mm, 5 mm) **Wavelength**: 230 nm	The method's capability to detect stability was illustrated through forced degradation studies. Under alkaline and oxidative stress conditions, vonoprazan experienced substantial degradation, whereas it remained stable when exposed to acidic, thermal, and photolytic degradation. Importantly, the presence of degradants did not disrupt the identification of vonoprazan fumarate and its impurities.
4	Spectrofluorimetric method	Human plasma	**Wavelength**: Measure at 530 nm, Excitation at 465 nm C_{max}: 71.03 ng mL−1 T_{max}: equal to 1.5±0.15 h	This technique was effectively used to estimate Vonoprazan in research on content uniformity and pharmacokinetics (PK).
5	Voltammetric assay	Serum	**Electrode**: carbon paste electrodes integrated with copper oxide nanoparticles **Chromatographicanalysis**: UV detection at 230 nm **LOD** : 0.24 µg/ml	This technique demonstrates a higher degree of sensitivity and selectivity against Vonopazan within the concentration range from 0.99 to 20.00 µg/ml with LOD 0.24 µg/ml.

VON = Vonoprazan, ASP= Aspirin

Marketed Formulation

In 2022, the FDA aprroved two products containing vonoprazan: voquezna triple pak (vonoprazan,amoxicillin and clarithromycin) and voquezna dual pak (vonoprazan,amoxicillin) for the treatment of H.pylori infection in adults [38].

Recommendations of the SEC (gastroenterology & hepatology) made in the

56th meeting held on 17/01/2023 at cdsco New Delhi. After detailed delibration, the committee permission to conduct the proposed phase 3 clinical trial as per the proposed protocol.

Different Approaches of Synthesis (PSAR SUMMURY)

This Schematic diagram represents different ways of synthesis of vonoprazan from patent search analysis, as depicted in Figure 5.

Clinical Trial Study Future Aspects

The future of clinical research is an exciting and rapidly evolving field. The researcher envisions the future of clinical research, emphasizing key areas of improvement in clinical trial design, conduct, and the generation of evidence. Table 3 presents the information on clinical trial study future aspects [45].

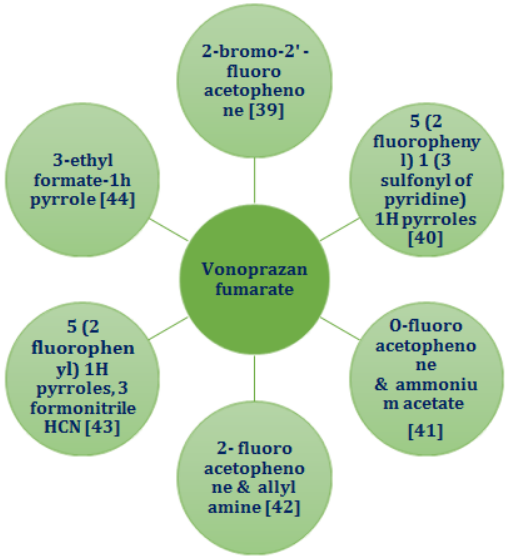


Figure 5. Different ways of synthesis of vonoprazan.

Table 3. Clinical trial study.

Sr No.	Title	Country	Disease	C.T.status	Phase
1	A RCT of the Efficacy of Vonoprazan 20mg QD	China	H.Pylori Infection	Recruting	IV
2	Helicobacter Pylori and Vonoprazan Dual Therapy	China	H.Pylori	Not yet recruiting	IV
3	Vonoprazan Hp Dual or Triple Eradication Regimes	China	H.Pylori	Recruting	IV
4	Vonoprazan-based Therapy Versus Standard Regimen for Helicobacter Pylori Infection Managemen	Egypt	H.Pylori	Recruting	IV
5	Optimization of Vonoprazan-based Dual Therapy for Helicobacter Pylori	China	H.Pylori	Recruting	IV

Table 3. Continued…

Sr No.	Title	Country	Disease	C.T.status	Phase
6	Optimization of Vonoprazan--amoxicillin Dual Therapy for Eradicating Helicobacter Pyloriinfection	-	H.Pylori Eradication Rate	Not yet recruiting	III
7	Vonoprazan-Based Triple Therapy in Comparison With Extended Sequential Therapy	Taiwan	H.Pylori	Recruting	IV
8	Vonoprazan Fumarate in Combination With Amoxicillin for the First-line Eradication of Helicobacter Pylori-a Multicenter, Randomized, Parallel Controlled Study	-	H.Pylori Eradication Rate	Not yet recruiting	IV
9	The Need of Revisiting to an Outpatient Clinic After the Prescription of Vonoprazan or Esomeprazole	Japan	Gastroesophageal Reflux	Recruting	Not applicable
10	Efficacy and Safety of Dual Therapy for Helicobacter Pylori Eradication	China	H.Pylori	Recruting	IV
11	Vonoprazan-containing Triple Therapy Versus Empiric Bismuth Quadruple Therapy for First-line Helicobacter Pylori Treatment: a Randomized Clinical Trial	China	H.Pylori	Not yet recruiting	IV
12	The Effect of Probiotics on Gut Microbiotain After Helicobacter Pylori Eradication	China	H.Pylori	Not yet recruiting	IV
13	Efficacy of Vonoprazan Versus Intravenous Proton Pump Inhibitors for Prevention of Rebleeding in High Risk Peptic Ulcers Bleeding After Successful Endoscopic Hemostasis	Thailand	Peptic Ulcer With Haemorrhage	Recruting	Early phase 1
14	Comparison of Vonoprazan-based Versus Lansoprazole-based Triple Therapy, High Dose Dual Therapy, Bismuth, and Non-bismuth Quadruple Therapy in the First-line Treatment of Helicobacter Pylori Infection	Taiwan	H.Pylori	Recruting	IV
17	Helicobacter Pylori and Lacidophilin Tablets in Combination With Vonorazan Dual Therapy	-	H.Pylori	Not yet recruiting	IV

Conclusion

To sum up, vonoprazan's chemistry, biological properties, analytical methods, and

future prospects of clinical trials colletively. Its importance as a groundbreaking advancement in the managment of acid–related conditions. Its unique mechanism of action, improved pharmacokinetics and potential for diverse therapeutic applications position Vonoprazan as a valuable asset in modern medicine. Continued research and clinical investigations will illuminate new avenues for maximizing the benefits of Vonoprazan while ensuring patient well-being. The study of vonoprazan in combinational therapy showcases its versatility and potential to revolutionize treatment strategies for gastrointenstinal disorders. As clinical experience grows, vonoprazan-based combinational therapies are poised to make a significant impact on the field of gastroenterology.

List of Abbreviations

P-CABs: Potassium-competitive acid blocker
PPIs: Proton pump inhibitors
H.pylori: Helicobector pylori
MALT: Mucosa associated lymphoid tissue
VPZ: Vonoprazan
DMSO: Dimethyl sulfoxide
TNMDD: Tissue niche-mediated drug distribution
GERD: Gastroesophageal reflux disease
ADR: Advers drug reaction
PBPK: Physiologically based pharmacokinetic
DDI: Drug drug interation
LDA: Low dose aspirin
NSAIDs: Non-steroidal anti-inflammatory drugs
RD: Ratio difference

Disclosure Statement

There is no conflict of interest to expose.

Orcid

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References

[1]. Soll A.H., Achord J.L., Bozymski G., Brooks S., Lanza F., Lyon D., Meyer G., Reinus J., Schuster M., Achord J. *Jama*, 1996, **275**:622 [Crossref], [Google Scholar], [Publisher]
[2]. Axon A. *Helicobacter*, 2014, **19**:68 [Crossref], [Google Scholar], [Publisher]
[3]. Fock K.M., Ang T.L., Bee L.C., Lee E.J.D. *Clin. Pharmacokinet.*, 2008, **47**:1 [Crossref], [Google Scholar], [Publisher]
[4]. Cheng H.C., Sheu B.S. *World J. Gastrointest. Endosc.*, 2011, **3**:49 [Crossref], [Google Scholar], [Publisher]
[5]. Furuta T., Sugimoto M., Shirai N. *Mol. Diagn. Ther.*, 2012, **16**:223 [Crossref], [Google Scholar], [Publisher]
[6]. Soll A.H., Achord J.L., Bozymski G., Brooks S., Lanza F., Lyon D., Meyer G., Reinus J., Schuster M., Achord J. *Jama*, 1996, **275**:622 [Crossref], [Google Scholar], [Publisher]
[7]. Hooi J.K., Lai W.Y., Ng W.K., Suen M.M., Underwood F.E., Tanyingoh D., Malfertheiner P., Graham D.Y., Wong V.W., Wu J.C. *Gastroenterology*, 2017, **153**:420 [Crossref], [Google Scholar], [Publisher]
[8]. Syam A.F., Miftahussurur M., Makmun D., Nusi I.A., Zain L.H., Zulkhairi, Akil F., Uswan W.B., Simanjuntak D., Uchida T. *PloS one*, 2015, **10**:e0140186 [Crossref], [Google Scholar], [Publisher]
[9]. Suzuki H., Mori H. *J. Gastroenterol.*, 2018, **53**:354 [Crossref], [Google Scholar], [Publisher]
[10]. Miftahussurur M., Pratama Putra B., Yamaoka Y. *Pharmaceuticals*, 2020, **13**:276 [Crossref], [Google Scholar], [Publisher]
[11]. Sugimoto M., Yamaoka Y. *Front. Pharmacol.*, 2019, **9**:1560 [Crossref], [Google Scholar], [Publisher]

[12]. Jenkins H., Sakurai Y., Nishimura A., Okamoto H., Hibberd M., Jenkins R., Yoneyama T., Ashida K., Ogama Y., Warrington S. *Aliment. Pharmacol. Ther.*, 2015, **41**:636 [Crossref], [Google Scholar], [Publisher]
[13]. Shin J.M., Inatomi N., Munson K., Strugatsky D., Tokhtaeva E., Vagin O., Sachs G. *J. Pharmacol. Exp. Ther.*, 2011, **339**:412 [Crossref], [Google Scholar], [Publisher]
[14]. Hori Y., Imanishi A., Matsukawa J., Tsukimi Y., Nishida H., Arikawa Y., Hirase K., Kajino M., Inatomi N. *J. Pharmacol. Exp. Ther.*, 2010, **335**:231 [Crossref], [Google Scholar], [Publisher]
[15] Drug profile and information pf Vonoprazan [Publisher]
[16] Yu Q.Y., Zeng H., Yao K., Li J.Q., Liu Y. *Synth. Commun.*, 2017, **47**:1169 [Crossref], [Google Scholar], [Publisher]
[17]. Ishida M., Tsuchiya M., Naito J., Kawazoe H., Watanabe D., Nonaka Y., Sano M., Sakai H., Suzuki A., Kumada K. *Kidney Int.*, 2022, **102**:666 [Crossref], [Google Scholar], [Publisher]
[18]. Oshima T., Miwa H. *J. Neurogastroenterol. Motil.*, 2018, **24**:334 [Crossref], [Google Scholar], [Publisher]
[19]. Sakurai Y., Shiino M., Okamoto H., Nishimura A., Nakamura K., Hasegawa S. *Adv. Ther.*, 2016, **33**:1519 [Crossref], [Google Scholar], [Publisher]
[20]. Kong W., Sun B., Wang Z., Zheng X., Zhao K., Chen Y., Zhang J., Liu P., Zhu L., Xu R.. *Acta Pharmacol. Sin.*, 2020, **41**:852 [Crossref], [Google Scholar], [Publisher]
[21]. Wang M.S., Gong Y., Zhuo L.S., Shi X.-X., Tian Y.-G., Huang C.-K., Huang W., Yang G.-F. *Research*, 2022, [Crossref], [Google Scholar], [Publisher]
[22]. Echizen H. *Clin. Pharmacokinet.*, 2016, **55**:409 [Crossref], [Google Scholar], [Publisher]
[23]. Yamasaki H., Kawaguchi N., Nonaka M., Takahashi J., Morohashi A., Hirabayashi H., Moriwaki T., Asahi S. *Xenobiotica*, 2017, **47**:1027 [Crossref], [Google Scholar], [Publisher]
[24]. Jenkins H., Jenkins R., Patat A. *Clin. Drug Investig.*, 2017, **37**:311 [Crossref], [Google Scholar], [Publisher]
[25]. van Haarst A., Smith S., Garvin C., Benrimoh N., Paglialunga S. *Clin. Pharmacol. Ther.*, 2023, **113**:816 [Crossref], [Google Scholar], [Publisher]
[26]. Bolleddula J., Gopalakrishnan S., Hu P., Dong J., Venkatakrishnan K. *Clin. Transl. Sci.*, 2022, **15**:2075 [Crossref], [Google Scholar], [Publisher]
[27]. Greenberg R.G., Melloni C., Wu H., Gonzalez D., Ku L., Hill K.D., Hornik C.P., Zheng N., Jiang W., Cohen-Wolkowiez M. *Clin. Neuropharmacol.*, 2016, **39**:232 [Crossref], [Google Scholar], [Publisher]
[28]. Mulford D.J., Ramsden D., Zhang L., Michon I., Leifke E., Smith N., Jones H.M., Scarpignato C. *CPT Pharmacometrics Syst. Pharmacol.*, 2023, **12**:532 [Crossref], [Google Scholar], [Publisher]
[29]. Inaba T., Iwamuro M., Toyokawa T., Okada H. *Aliment. Pharmacol. Ther*, 2016, **43**:179 [Crossref], [Google Scholar], [Publisher]
[30]. Kawashima K., Ishihara S., Kinoshita Y. *Dig. Liver Dis.*, 2016, **48**:688 [Crossref], [Google Scholar], [Publisher]
[31]. Suzuki S., Kusano C., Horii T., Ichijima R., Ikehara H. *Digestion*, 2022, **103**:62 [Crossref], [Google Scholar], [Publisher]
[32]. FDA Approved drug products: VOQUEZNA TRIPLE PAK and VOQUEZNA DUAL PAK co-packaged for oral use [Publisher]
[33]. Abdelazim A.H., Abdel-Fattah A., Osman A.O., Abdel-Kareem R.F., Ramzy S. *J. AOAC Int.*, 2023, **106**:490 [Crossref], [Google Scholar], [Publisher]

[34]. Yoneyama T., Teshima K., Jinno F., Kondo T., Asahi S. *J. Chromatogr. B*, 2016, **1015**:42 [Crossref], [Google Scholar], [Publisher]
[35]. Luo Z., Liu A., Liu Y., Wang G., Chen X., Wang H., Li M., Zhang H., Qiu Y., Zhai H. *J. Pharm. Biomed. Anal.*, 2018, **149**:133 [Crossref], [Google Scholar], [Publisher]
[36]. Jiang Q., Liu W., Li X., Zhang T., Wang Y., Liu X. *J. Sep. Sci.*, 2016, **39**:350 [Crossref], [Google Scholar], [Publisher]
[37]. Al-Qahtani S.D., Al-nami S.Y. *Arab. J. Chem.*, 2021, **14**:103254 [Crossref], [Google Scholar], [Publisher]
[38]. Recommendations of the SEC (Gastroenterology & Hepatology) **2022** [Publisher]
[39]. Songjun L., Huaming L.F.M., Xiaoyan Z.Q.L., Gangqiang L.L.L.W. Preparation method of Vonoprazan. *chinese patent* CN109232537B **2021**. [Publisher]
[40]. Shaoyi K., Niangen C., Lin Z.L.Y.X.C. The preparation method of Vonoprazan fumarate. *chinese patent* CN105130955B **2015**. [Publisher]
[41]. Shen C.Y., Yao X., Yuncheng. The preparation technology of Vonoprazan fumarate. *chinese patent* CN105294653B **2015**. [Publisher]
[42]. Yansun N., Maocong B.Y., Qingshuang M., Xiaoguang W. The preparation method of Vonoprazan fumarate. *chinese patent* CN106366071B **2016**. [Publisher]
[43]. Lixin W., Zhengquan Z., Tao P., Juan W. A kind of preparation method of Vonoprazan fumarate. *chinese patent* CN108503621A **2017**. [Publisher]
[44]. Rui Y., Yu C., Kai Y. Preparation method of vonoprazan fumarate. *chinese patent* CN110452222B **2019**. [Publisher]
[45]. Clinical trials of vonoprazan [Publisher]
[46]. Salman S., Ahmed M.R. *Chem. Methodol.*, 2022, **6**:997 [Crossref], [Publisher]
[47]. Najdsepas H., Rahimzadeh N., haghighikian M., Maddahali M., Milani Fard M. *Eurasian J. Sci. Technol.*, 2022, **2**:176 [Crossref], [Publisher]
[48]. Mohammed A.Y., Ahamed L.S. *Chem. Methodol.*, 2022, **6**:813 [Crossref], [Publisher]
[49]. Salehi Sardoei A. *Int. J. Adv. Biol. Biomed. Res*, 2022, **10**:44 [Crossref], [Google Scholar], [Publisher]
[50]. Gharayagh-Zandi D., Makouee S. *IJASHSS*, 2022, **11**:11 [Crossref], [Google Scholar], [Publisher]

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