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ANALYTICAL METHODS FOR ESTIMATION OF VONOPRAZAN IN PHARMACEUTICAL DOSAGE FORM-A REVIEW

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ABSTRACT

Vonoprazan is a novel potassium-competitive acid blocker (P-CAB) that has gained significant clinical importance due to its potent, rapid, and sustained suppression of gastric acid secretion. Unlike conventional proton pump inhibitors, vonoprazan is chemically stable in acidic environments and does not require acid activation, resulting in improved therapeutic outcomes in acid-related gastrointestinal disorders. With the increasing use of vonoprazan in pharmaceutical formulations, the development and validation of reliable analytical methods for its quantitative estimation are essential to ensure quality, safety, and efficacy. This review focuses on the physicochemical properties, pharmacological profile, and analytical techniques employed for the estimation of vonoprazan in bulk drug and pharmaceutical dosage forms. Emphasis is given to chromatographic methods such as LC–MS/MS and HPLC, as well as UV spectrophotometric techniques, highlighting their principles, advantages, and applications in quality control and pharmacokinetic studies.

KEYWORDS: Vonoprazan, Potassium-competitive acid blocker, HPLC, LC–MS/MS, UV spectrophotometry, Pharmaceutical analysis.

1. INTRODUCTION

Acid-related gastrointestinal disorders such as gastroesophageal reflux disease (GERD), peptic ulcer disease, and Helicobacter pylori infection represent a major global health burden. Proton pump inhibitors (PPIs) have long been the cornerstone of acid-suppressive therapy;

however, their delayed onset of action, variable response, and instability in acidic environments have prompted the development of alternative therapeutic agents. Vonoprazan, a potassium-competitive acid blocker (P-CAB), has emerged as a promising advancement in acid suppression therapy.

Vonoprazan directly and reversibly inhibits the gastric H^+/K^+-ATPase enzyme by competing with potassium ions, resulting in rapid and sustained suppression of gastric acid secretion. Its superior pharmacodynamic and pharmacokinetic profile, including acid stability and CYP3A4-mediated metabolism, necessitates accurate and sensitive analytical methods for routine quality control, stability testing, and pharmacokinetic evaluation. This review compiles and discusses the analytical methods reported for the estimation of vonoprazan in pharmaceutical dosage forms.

1.1 Analytical Chemistry

Analytical chemistry is the branch of chemistry concerned with the qualitative and quantitative determination of chemical components present in a sample. It involves the development, optimization, and validation of methods to identify substances, determine their concentration, and evaluate their purity. Analytical chemistry plays a vital role in pharmaceutical sciences, environmental analysis, clinical diagnostics, food analysis, and industrial quality control.

In pharmaceutical analysis, analytical chemistry ensures the identity, strength, quality, and purity of drug substances and pharmaceutical formulations. Techniques such as UV–Visible spectrophotometry, High-Performance Liquid Chromatography (HPLC), and Liquid Chromatography–Mass Spectrometry (LC–MS/MS) are widely employed for drug assay, impurity profiling, stability studies, and bioanalytical applications. These methods are selected based on parameters such as sensitivity, selectivity, accuracy, precision, and cost-effectiveness.

Analytical chemistry also encompasses method validation and regulatory compliance, guided by international standards such as ICH guidelines. Through accurate measurement and systematic evaluation, analytical chemistry supports drug development, ensures patient safety, and maintains consistency in pharmaceutical products.

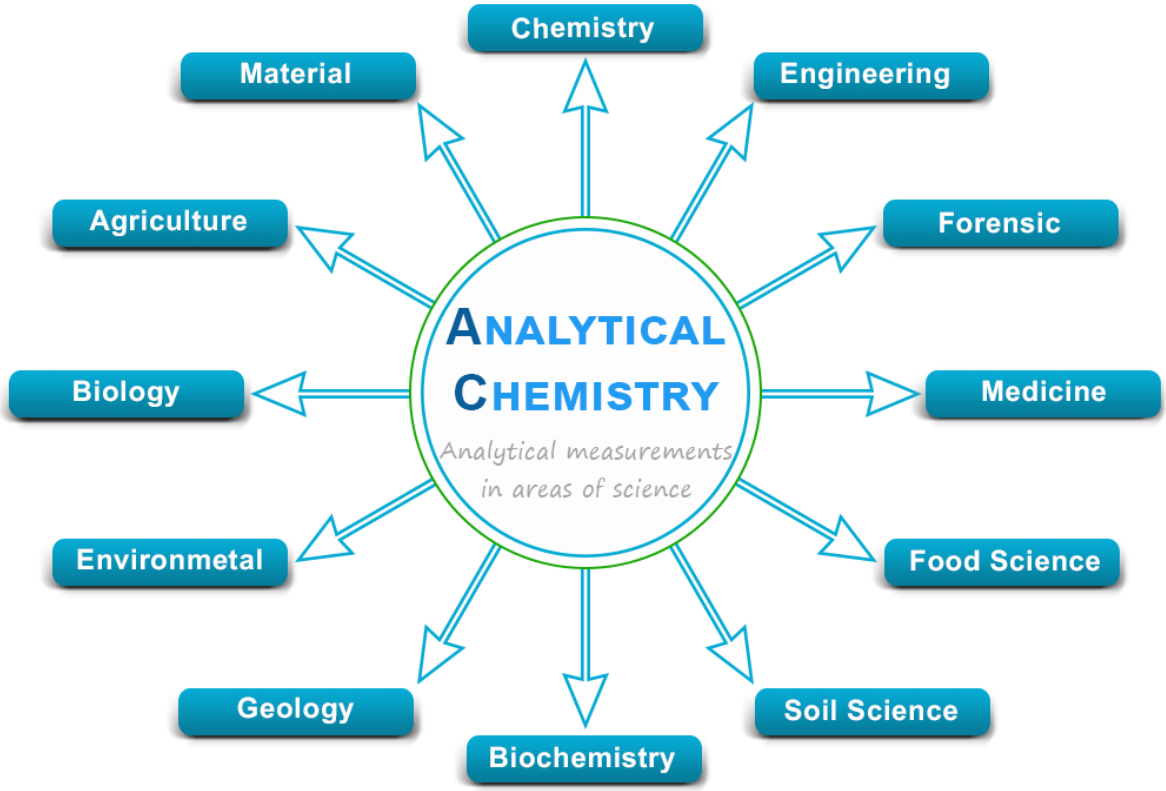

Fig. 1: Analytical Chemistry.

1.2 Liquid Chromatography–Mass Spectrometry (LC–MS/MS)

Liquid Chromatography–Mass Spectrometry (LC–MS/MS) is a highly sensitive and selective analytical technique extensively used for the quantitative estimation of pharmaceutical compounds, including vonoprazan, in both dosage forms and biological matrices. The technique integrates the separation efficiency of liquid chromatography with the detection capability of tandem mass spectrometry, enabling accurate identification and quantification based on mass-to-charge (m/z) ratios.

In LC–MS/MS analysis of vonoprazan, reverse-phase C18 columns are commonly employed with mobile phases consisting of methanol or acetonitrile combined with aqueous buffers containing formic acid. Detection is typically carried out using electrospray ionization (ESI) in positive ion mode, which enhances ionization efficiency due to the basic nature of vonoprazan. Tandem mass spectrometry improves method selectivity by monitoring specific precursor-to-product ion transitions, thereby minimizing interference from excipients, metabolites, or degradation products.

LC–MS/MS methods demonstrate excellent sensitivity, allowing detection of vonoprazan at nanogram concentration levels, making them particularly suitable for pharmacokinetic, bioavailability, and bioequivalence studies. These methods exhibit good linearity, accuracy, precision, and reproducibility over a wide concentration range. Owing to its high analytical performance, LC–MS/MS is considered the gold standard for trace-level estimation of vonoprazan in plasma and complex matrices.

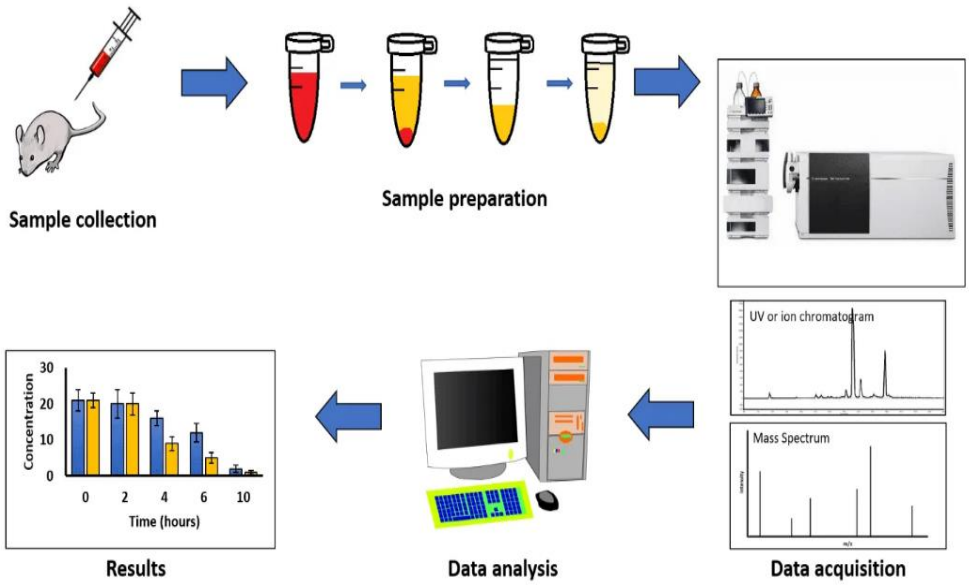

Fig: 2 Liquid Chromatography–Mass Spectrometry (LC–MS/MS).

1.3 High-Performance Liquid Chromatography (HPLC)

High-Performance Liquid Chromatography (HPLC) is one of the most widely employed analytical techniques for the quantitative estimation of vonoprazan in bulk drug substances and pharmaceutical dosage forms. Owing to its high sensitivity, accuracy, precision, and reproducibility, HPLC is extensively used in routine quality control, stability testing, and method validation studies.

Most reported HPLC methods for vonoprazan utilize reverse-phase chromatography with a C18 (octadecylsilane) column as the stationary phase. The mobile phase generally consists of a combination of aqueous buffer (such as phosphate or formate buffer with pH adjusted between 3.0 and 6.5) and organic solvents like methanol or acetonitrile. Detection is commonly performed using a UV detector at wavelengths around 254 nm, where vonoprazan shows significant absorbance.

The optimized HPLC methods provide good peak symmetry and effective separation of vonoprazan from formulation excipients and degradation products, with retention times typically around 3–4 minutes. These methods are validated according to ICH guidelines and demonstrate acceptable linearity, accuracy, precision, robustness, and specificity. Due to its reliability and suitability for routine pharmaceutical analysis, HPLC remains the method of choice for assay and stability studies of vonoprazan in pharmaceutical formulations.

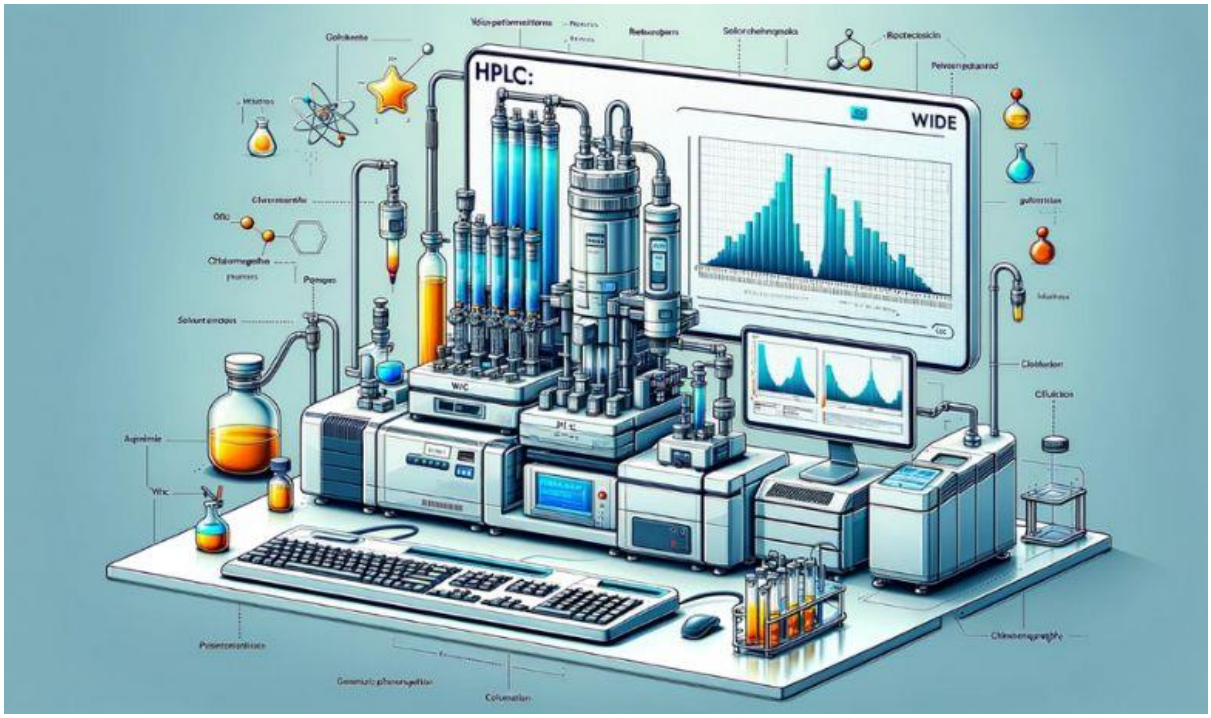

Fig. 3: High-Performance Liquid Chromatography (HPLC).

1.4 UV Spectroscopic Method

UV spectrophotometry is a simple, rapid, and cost-effective analytical technique widely used for the quantitative estimation of vonoprazan in bulk drug and pharmaceutical dosage forms. The method is based on the absorption of ultraviolet radiation by the drug molecule containing suitable chromophores, resulting in electronic transitions. According to Beer–Lambert's law, the absorbance measured at a specific wavelength is directly proportional to the concentration of the drug in solution.

Vonoprazan exhibits significant UV absorbance in the ultraviolet region, typically around 230 nm, when dissolved in solvents such as methanol or a methanol–water mixture. The UV spectroscopic method shows good linearity over a suitable concentration range, with correlation coefficients (R^2) generally greater than 0.999. The method is validated for

parameters such as accuracy, precision, repeatability, and robustness, demonstrating acceptable results for routine analysis.

Although UV spectrophotometric methods are less sensitive and selective compared to chromatographic techniques, they offer advantages such as simplicity, low operational cost, minimal sample preparation, and rapid analysis time. Therefore, UV spectroscopy is particularly suitable for routine quality control and assay determination of vonoprazan in pharmaceutical dosage forms where high sensitivity is not required.

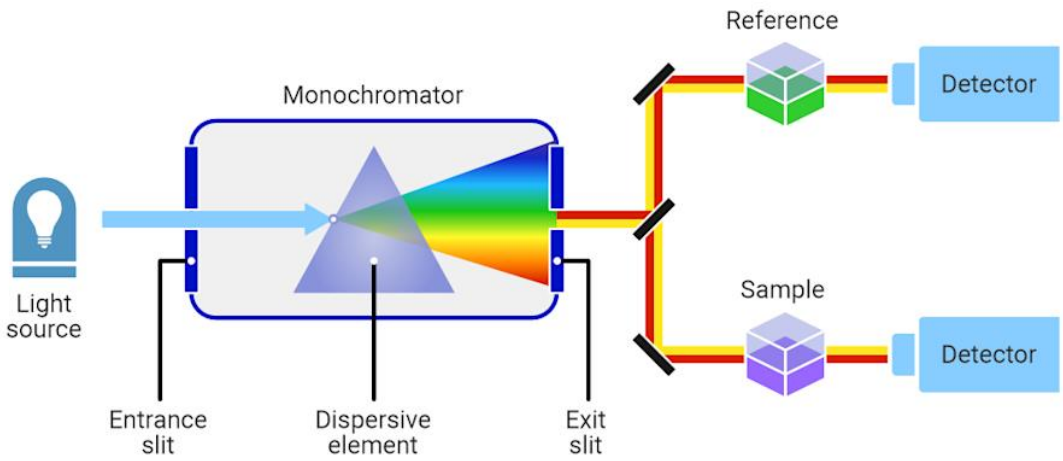

Fig. 4: UV Spectroscopic Method.

2. DRUG PROFILE

2.1 Physio – Chemical Properties

- **Generic Name:** Vonoprazan
- **Chemical Class:** Potassium-Competitive Acid Blocker (P-CAB)
- **IUPAC Name:** 1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine
- **Molecular Formula:** $C_{17}H_{16}FN_3O_2S$
- **Molecular Weight:** 345.39 g/mol
- **Monoisotopic Mass:** 345.0941 Da
- **Appearance:** White to pale yellow crystalline powder
- **Melting Point:** 174–176 °C
- **Solubility:** Freely soluble in methanol, Soluble in ethanol, Slightly soluble in water, Soluble in organic solvents such as DMSO

- **Salt Form:** Vonoprazan fumarate
- **Chemical Structure Features:** Pyrrole ring, Pyridine sulfonyl group, Fluorophenyl moiety, Weakly basic amine group
- **Stability:** Chemically stable at physiological pH More stable than proton pump inhibitors in acidic conditions

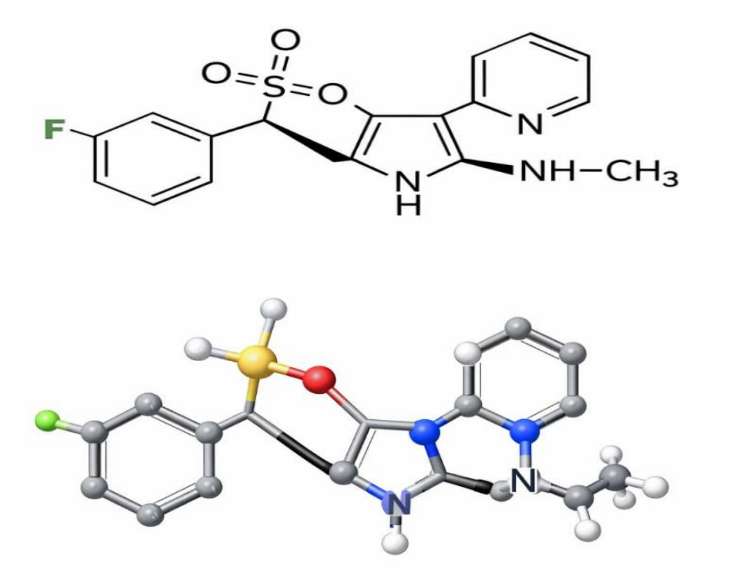

Fig. 5: Molecular Structure Of Vonoprazan.

2.2 Description

Vonoprazan is a novel acid-suppressing drug classified as a potassium-competitive acid blocker (P-CAB) used in the management of acid-related gastrointestinal disorders. It acts by reversibly inhibiting the H^+/K^+-ATPase enzyme in gastric parietal cells, thereby suppressing gastric acid secretion. Unlike proton pump inhibitors, vonoprazan does not require activation in an acidic environment and produces a rapid, strong, and sustained increase in intragastric pH. It is effective in conditions such as gastroesophageal reflux disease, peptic ulcer disease, and in combination therapy for *Helicobacter pylori* eradication. Due to its stability in acidic conditions and consistent acid suppression, vonoprazan offers improved efficacy and faster symptom relief compared to conventional proton pump inhibitors.

2,3 Drug Interactions

Vonoprazan can interact with other drugs mainly due to its potent and prolonged suppression of gastric acid and its metabolism via hepatic CYP enzymes, especially CYP3A4. By increasing gastric pH, vonoprazan may reduce the absorption of drugs that require an acidic environment for optimal bioavailability, such as ketoconazole, itraconazole, atazanavir, and

iron salts, thereby decreasing their therapeutic effectiveness. Vonoprazan is metabolized primarily by CYP3A4, so strong CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole, ritonavir) can increase vonoprazan plasma levels, while CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, St. John's wort) may reduce its efficacy. In *Helicobacter pylori* eradication regimens, vonoprazan is commonly combined with amoxicillin and clarithromycin, where it can enhance antibiotic stability and efficacy by maintaining a higher gastric pH. Overall, although vonoprazan has fewer clinically significant interactions than proton pump inhibitors, caution is required when co-administered with pH-dependent drugs or potent CYP3A4 modulators.

2.4 Mechanism of Action

Vonoprazan acts as a potassium-competitive acid blocker (P-CAB) that suppresses gastric acid secretion by directly and reversibly inhibiting the H^+/K^+-ATPase (proton pump) located on the secretory canaliculi of gastric parietal cells. It competes with potassium ions (K^+) at the binding site of the proton pump, thereby blocking the final step of acid secretion. Unlike proton pump inhibitors, vonoprazan does not require activation in an acidic environment and remains stable at low pH, resulting in a rapid onset and long-lasting acid suppression from the first dose. This strong and sustained inhibition effectively increases intragastric pH throughout the day and night, making vonoprazan highly effective in the treatment of acid-related disorders such as GERD and peptic ulcer disease.

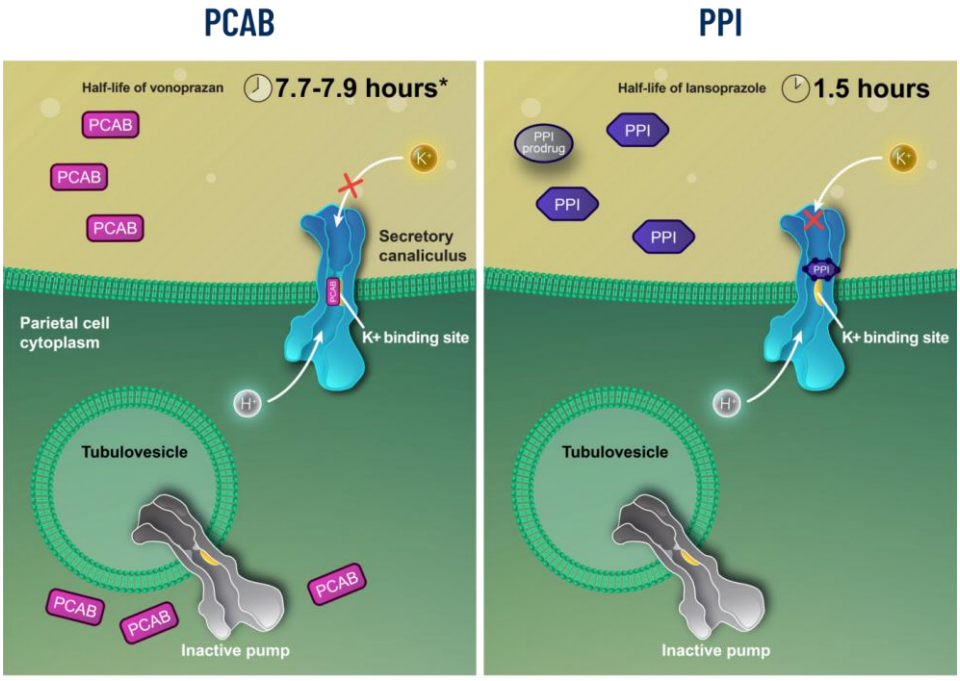

Fig. 6: Mechanism Action Of Vonoprazan.

2.5 Pharmacodynamics

Vonoprazan exhibits potent and sustained acid-suppressive pharmacodynamic effects by acting as a potassium-competitive acid blocker (P-CAB). It directly and reversibly inhibits the gastric H^+/K^+-ATPase enzyme in parietal cells, leading to a rapid reduction in gastric acid secretion. Vonoprazan produces a faster onset of action than proton pump inhibitors and maintains consistently high intragastric pH levels over 24 hours, including effective control of nocturnal acid secretion. It significantly increases the duration for which gastric pH remains above 4, which is crucial for mucosal healing and symptom relief in acid-related disorders. Additionally, vonoprazan causes a dose-dependent increase in serum gastrin levels due to prolonged acid suppression, reflecting its strong and long-lasting pharmacodynamic activity.

2.6 Pharmacokinetics

Absorption: vonoprazan absorption is characterized by rapid oral uptake, reaching peak plasma levels (Cmax) within ~2 hours, regardless of food intake, due to its acid stability, unlike traditional PPIs. Key aspects include fast absorption (tmax< 2h), a longer half-life (~7-9h), time-independent pharmacokinetics, and minor food effects, enabling once-daily dosing and differing significantly from PPIs due to its primary metabolism by CYP3A4, not CYP2C19. Analytical methods often use UV spectrophotometry or HPLC for quality control and PK studies, focusing on linearity and precision.

Volume of distribution: Vonoprazan exhibits a large volume of distribution (Vd), around 782.7 L at steady state, indicating extensive tissue distribution, despite its significant plasma protein binding (85-88%) and relatively short half-life (7-9 hrs). This large Vd, combined with its mechanism as a potassium-competitive acid blocker (PCAB), allows it to achieve prolonged and potent acid suppression by distributing widely beyond the bloodstream into gastric parietal cells.

Protein binding: Moderate plasma protein binding, typically around 85–88%, primarily to albumin.

Metabolism: Vonoprazan is primarily metabolized in the liver, mainly by the CYP3A4 enzyme, with minor contributions from other CYP isoenzymes. It is converted into inactive metabolites, which are subsequently excreted. Unlike proton pump inhibitors, its metabolism

is less affected by genetic polymorphisms of CYP2C19, leading to more consistent plasma levels across patients.

Elimination: Vonoprazan is eliminated primarily through the feces as metabolites, with a smaller fraction excreted via the urine. Only a minimal amount of the unchanged drug is detected in excreta. Its elimination, combined with a half-life of 7–9 hours, supports once-daily dosing.

Clearance: Vonoprazan exhibits moderate systemic clearance, primarily through hepatic metabolism by CYP3A4. A smaller portion of the drug is excreted unchanged via the urine and feces. Its clearance, together with a half-life of 7–9 hours, supports once-daily dosing for effective acid suppression.

Half-life: The half-life of vonoprazan, a potassium-competitive acid blocker (P-CAB), is relatively long, averaging around 7 to 7.7 hours.

2.7 Side Effects

- **Gastrointestinal:** Diarrhoea, constipation, abdominal pain, nausea, flatulence
- **Central nervous system:** Headache, dizziness
- **Laboratory findings:** Increased serum gastrin levels (hypergastrinemia)
- **Rare effects:** Rash, liver enzyme elevation

2.8 Toxicity

- **Gastrointestinal disturbances**: nausea, vomiting, diarrhoea
- **Hypergastrinemia**: prolonged acid suppression can increase gastrin levels
- **Liver effects**: rare elevation of liver enzymes

3. LITERATURE REVIEW:

3.1 Liquid Chromatography-Mass Spectroscopy (LC-MS/MS)

Itis a highly sensitive and selective analytical technique used in pharmaceutical analysis for the accurate quantification of drugs. In the assay of vonoprazan, LC–MS/MS combines efficient chromatographic separation with tandem mass spectrometric detection, enabling precise identification based on mass-to-charge (m/z) ratios. The use of MS/MS improves selectivity by monitoring specific ion transitions, reducing interference from excipients or impurities. Due to its high sensitivity, accuracy, and reliability, LC–MS/MS is widely

employed for the assay of vonoprazan in pharmaceutical formulations and biological samples.

Table 1: Liquid Chromatography-Mass Spectrometry(LC-MS/MS).

S. No	Stationary Phase/ Instrumentation	Method/Conditions	Results	Reference
1.	LC-MS/MS	Column:C18;Mobile phase:Methanol:0.1 % formic acid in water; flow rate : 0.3ml/min; Mass detection: ESI positive mode	Highly sensitive ; can detect low concentration in plasma; linear range: 1-1000 ng/ml; useful for pharmacokinetic studies	Saito et al., Biomed Chromatography, 2018

3.2 High Performance Liquid Chromatography (HPLC)

High-Performance Liquid Chromatography (HPLC) is one of the most widely used analytical techniques in pharmaceutical analysis for the quantitative determination of Vonoprazan in bulk drug and pharmaceutical dosage forms. Due to its high sensitivity, accuracy, and reproducibility, HPLC is preferred for routine quality control and stability studies of Vonoprazan. The method commonly employs a reverse-phase C18 column with UV detection, allowing effective separation of the drug from excipients and degradation products. Hence, HPLC serves as a reliable and precise method for the assay and validation of Vonoprazan in pharmaceutical analysis.

Table 2: High Performance Liquid Chromatography (HPLC).

S. No	Stationary Phase	Mobile Phase	Flow Rate, Method Of Detection Retention Time	Results	Reference
1.	C18 (octadecylsilane)	use a mixture of aqueous buffer (like phosphate or formate, pH ~3-6.5) and organic solvents such as acetonitrile or methanol	0.8 – 1.0Ml/min UV 254nm Around 3.9 mins	Able to separate Vonoprazan from degradation products; %Assay: 98–102%; Confirms stability of drug	ICH Q1A(R2) Guidelines; Takeda et al., 2017

3.3 UV Spectroscopic Method Of Vonoprazan:

UV spectroscopic method is a widely used analytical technique in pharmaceutical analysis for the quantitative estimation of drugs in bulk and dosage forms. It is based on the absorption of ultraviolet light by drug molecules containing chromophores, resulting in electronic

transitions. The absorbance measured at a selected wavelength is directly proportional to the drug concentration according to Beer–Lambert's law. Due to its simplicity, rapid analysis, low cost, and good reproducibility, UV spectrophotometry is commonly employed for routine quality control and assay of pharmaceutical compounds.

Table: 3 UV Spectroscopic Method

S. No	Stationary Phase/ Instrumentation	Mobile Phase/ Solvent	Floe Rate, Method Of Detection, Retention Time	Result	Reference
1.	**Stationary Phase** Not applicable (NA) **Instrumentation** UV–Visible spectrophotometer with quartz cuvettes (1 cm path length)	Methanol (or Methanol: Water, 50:50 v/v)	Not applicable (NA), UV absorbance, 230nm, Not applicable	The method obeys Beer–Lambert's law, shows good linearity ($R^2 > 0.999$), and is suitable for routine quantitative estimation of vonoprazan	Patel, M. R., Shah, D. A., & Patel, C. N. (2019).

4. DISCUSSION

Drug Profile and Pharmacological Characteristics: Vonoprazan is a weakly basic compound with a molecular formula of $C_{17}H_{16}FN_3O_2S$ and a molecular weight of 345.39 g/mol. It appears as a white to pale yellow crystalline powder and exhibits good solubility in organic solvents such as methanol and DMSO. The drug demonstrates high chemical stability under acidic conditions, making it distinct from proton pump inhibitors. Pharmacodynamically, vonoprazan produces rapid and long-lasting acid suppression by maintaining intragastric pH above 4 for extended periods, including nocturnal hours. Pharmacokinetic studies reveal rapid absorption, a relatively long half-life (7–9 hours), extensive tissue distribution, and predominant metabolism via CYP3A4, resulting in consistent plasma concentrations among patients.

Analytical Methods for Estimation of Vonoprazan (LC–MS/MS Methods) Liquid chromatography–tandem mass spectrometry (LC–MS/MS) is considered the most sensitive and selective technique for vonoprazan estimation, particularly in biological matrices. The use of reverse-phase C18 columns coupled with electrospray ionization in positive mode allows precise detection at low nanogram concentrations. These methods are widely applied in pharmacokinetic and bioavailability studies due to their excellent sensitivity, specificity, and accuracy.

High-Performance Liquid Chromatography (HPLC) HPLC is the most commonly employed technique for routine analysis of vonoprazan in bulk and dosage forms. Reverse-phase HPLC methods using C18 columns and UV detection at around 254 nm provide reliable separation from excipients and degradation products. These methods are validated according to ICH guidelines and are suitable for assay, stability, and quality control studies.

UV Spectrophotometric Methods UV spectrophotometry offers a simple, rapid, and cost-effective approach for the estimation of vonoprazan in pharmaceutical formulations. The drug exhibits significant absorbance around 230 nm, and the method follows Beer–Lambert's law over a wide concentration range. Although less sensitive than chromatographic methods, UV spectroscopy is suitable for routine analysis where advanced instrumentation is unavailable.

5. CONCLUSION

Vonoprazan represents a significant advancement in the management of acid-related gastrointestinal disorders due to its potent and sustained acid suppression. The increasing therapeutic use of this drug underscores the importance of developing accurate, precise, and validated analytical methods for its estimation in pharmaceutical dosage forms. Among the available techniques, LC–MS/MS offers superior sensitivity and selectivity for pharmacokinetic applications, while HPLC remains the method of choice for routine quality control and stability studies. UV spectrophotometric methods provide a simple and economical alternative for routine analysis. Collectively, these analytical approaches ensure the quality, safety, and efficacy of vonoprazan formulations and support its continued clinical application.

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