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UV-Visible Spectrophotometric Determination of Vonoprazan Fumarate in Pharmaceutical Formulation Through Complex Formation with Cu(II) and Fe(II) Ions †

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Abstract

A simple, sensitive and reproducible spectrophotometric method is developed for the determination of Vonoprazan(VPZ) in pharmaceutical formulation. The developed method involved the formation of colored binary Complexes I and Complex II between the VPZ and Copper (II) and Iron (II) ions, respectively. The maximum absorbance values for Complex I and Complex II were at wavelengths of 265 nm and 360 nm, respectively. The stoichiometry of the reaction between the VPZ and Copper (II) is found to be 5:5, while for Vonoprazan and Iron (II) was found to be 7:3. The Calibration curve obtained by Beer's law, has a linear domain in the concentration ranges of 0.001 M to 0.01 M for both metals. The validity of the proposed method was assessed. Statistical analysis of the results has been carried out, revealing high accuracy and good precision. The proposed methods for the determination of VPZ in pharmaceutical formulation are rapid, simple, sensitive, and can be comparable with other sophisticated techniques for quality control applications.

Keywords: vonoprazan fumarate; job's stoichiometry; UV-visible spectroscopy; complexation

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1. Introduction

Half of the world's population, meaning more than four billion people, have been identified to be infected by Helicobacter pylori *(H. pylori*). Consequently, the World Health Organization (WHO) classifies it in group 1 (carcinogenic to humans) and considers this infection a global concern [1,2]. In 1990s, the first eradications of *H. pylori* using dual therapy with proton pump inhibitors (PPIs) was reported, although the cure rate was initially unsatisfactory [3,4]. In contrast to the treatment based on PPIs, considered the first-line treatment of this infection, based on binding to the hydrogen-potassium ATPase

pump irreversibly, [5,6] the tablets containing Vonoprazan fumarate (VPZ) are useful for reducing acidity [7]. In comparison to traditional PPIs, Vonoprazan fumarate (VPZ), a potassium-competitive acid blocker (PCAB), has more strong and longer-lasting effects on controlling acid production in the stomach [8,9] and was launched in 2015 [10]. The VPZ is a pyrroles derivative namely [1-[5-(2-fluorophenyl)-1-pyridin-3-ylsulfonylpyrrol-3-yl]-N-methylmethanamine] currently being developed by the Takeda Pharmaceutical Company [11,12], and other pharmaceutical companies. For Example, in Japan, VPZ has been licensed for the treatment of gastric and duodenal ulcers, the healing of reflux esophagitis and protection from relapse, for the additional avoidance of non-steroidal anti-inflammatory medication (NSAID) or low-dose aspirin-induced gastric mucosal damage, and for first and second line Therapy for eliminating *H. pylori* [11]. The main consequence of the aforementioned gastrointestinal disorders is gastric cancer with H. pylori [13,14], therefore research towards the creation of new acid-suppressive drugs in an effort to get around PPI restrictions [15], has been intensified.

The US Food and Drug Administration (FDA) has warned against the prolonged use of PPIs alone or in combination with prescription drugs due to many adverse effects, including achlrorhydria, which is the primary cause of atrophic gastritis causing gastric cancer. Unfortunately, this is because PPIs work by activating the proton pump. Additionally, PPI-based treatments for H. pylori are no Longer as effective, and the treatment rate has lately decreased [16]. Because stomach acid activation is no longer necessary, VPZ is rapidly absorbed and achieves its maximal plasma concentration after being administered orally. Thus, the elimination of *H. pylori* and the treatment of gastro duodenal ulcers are approved uses of VPZ [17].

As secondary effects, the literature has reported the development of white globe appearance (WGA) lesions in the noncancerous stomach, which were associated with the removal of *H. pylori* by treatment with VZP over three years [18]. Preventing gastrointestinal (GI) bleeding is crucial when receiving therapy with VPZ [19,20]. Moreover, individuals who used treatments with PPIs had significantly higher chances of having positive COVID -19 when compared to those who did not use PPIs drugs [21]. Consequently, VPZ has been shown to effectively affect both active and resting pumps, in contrast to PPIs, which need drug accumulation and acid activation. Additionally, due to VPZ's prolonged retention in the secretory glands and parietal cells, it can reduce the impact of freshly generated pumps [22]. People with the history of drug allergies have weight loss during an eradication therapy, which included 20 mg of Vonoprazan fumarate [23].

According to the literature, only a few techniques for evaluating VPZ alone or in combination with other medications have been reported. These strategies include HPLC [24],electrochemical, [25] and fluorometric [26] methods. To the best of our knowledge, only recently were reported a few spectrophotometric method for VPZ determination [21,27]. The UV-Vis method is simple, low-cost, and widely available in quality control laboratories, but it is not yet official in any of the Pharmacopeias for applications, although this purpose is in accordance with the new Green Analytical Procedure Index (GAPI) [28,29].

The aim of the study was to develop and validate, for the first time according to the best of our knowledge, a spectrophotometric method to determine VPZ in pharmaceutical formulations via a complexation reaction with Cu(II) or Fe(II) ions, which form a colored Complex I or Complex II, respectively.

2. Experimental

2.1. Reagents

Vonoprazan Fumarate IUPAC- (1- [5-(2-fluorophenyl)-1-pyridin-3-ylsulfonylpyrrol-3-yl]-N-methylmethanamine) $C_{21}H_{20}FN_3O_6S$, structure presented in the inset of Figure 1) with a purity of 99.6% was gifted by Managing Director of Agha Jee Medicos distributors. Dimethyl sulfoxide, ortho-phosphoric acid, ammonia, NH_4Cl, NH_4OH, boric acid, sodium hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate, acetic acid, hydrochloric acid, Ammonium ferrous sulfate hexa-hydrate, Ammonium iron(II) sulfate (Mohr's salt) and copper chloride were acquired from Sigma Aldrich were of analytical reagent grade purity and used without further purification. Distilled water was used to prepare the solutions.

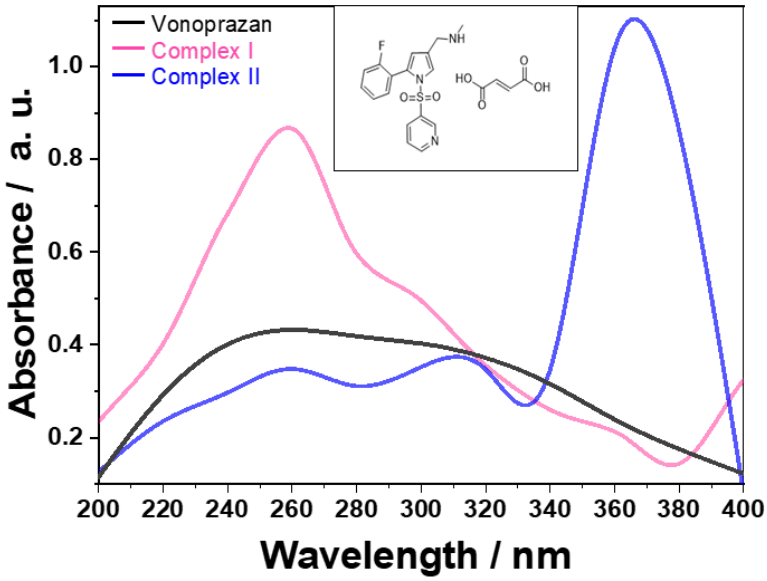

Figure 1. UV-Vis spectra of VPZ (black line), Complex I (magenta line) and Complex II (blue line).

The DMSO was diluted in distilled water (i.e., 50:50 *v*/*v*) ratio and was used in all preparations throughout the experiments. The VPZ standard solution was prepared by dissolving 0.445 g of VPZ in 100 mL of DMSO, and then diluted up to 1000 mL with distilled water, obtaining a 0.000445 g/mL (445 µg/mL) or 0.001289 M (or 1.29 mmol/L). Complex I and Complex II were obtained by mixing 1.29 mM VZP with different volumes of 1.3445 mM $CuCl_2$ or 3.9214 mM $(NH_4)_2Fe(SO_4)_2 \times 6H_2O$. The 1.3445 mM $CuCl_2$ and 3.9214 mM $(NH_4)_2Fe(SO_4)_2 \times 6H_2O$ solution were prepared in different buffers, such as: borate, ammonia, acetate, Robinson and phosphate buffers

Vocinti (20 mg, produced by Takeda Pharmaceuticals), Vonaspaire (20 mg, produced by Martin Dow Marker Ltd.), Vonseca (20 mg, produced by Zeta Pharma) and Vonica (10 mg, produced by Hilton Pharma), Vonozan TM (20 mg, generic name Vonoprazan, manufactured by Gets Pharma Co., Abbottabad, Pakistan) was purchased from a local pharmacy. The solution was prepared as in the case of the VPZ standard solution, by dissolving in DMSO and diluting to the appropriate concentration with distilled water.

2.2. Instruments

A high-performance double beam spectrophotometer (type T80) available with a fixed (1 nm) or spectral bandwidth, which has a spectral range of 190–900 nm, provided by PG Instruments (UK) was used for the spectrophotometric measurements. In the wavelengths range of 200–400 nm, the absorption spectra of different prepared sample solutions were monitored and recorded against a blank.

3. Result and Discussion

3.1. Spectrophotometric Behaviour of Cu(II)-VPZ and Fe(II)-VPZ Complexes

The advantages of UV-Visible spectrophotometric analysis are its accessibility, high sensitivity and resolution [21]. The wavelength at which a substance has its strongest photon absorption (λmax) is often used to indicate the nature of the transition in a particular compound and can then be used as a quantitative parameter for calculation.

Using this technique, VPZ (structure presented in the inset of Figure 1) and the colored Complexes I or II formed between VPZ with Cu(II) or Fe(II) ions, respectively, via a complexation reaction following reactions (1)–(2), were investigated.

$$C_{17}H_{16}FN_3O_2S + Cu^{2+} \xrightarrow{DMSO} [C_{17}H_{16}FN_3O_2S - Cu]^{2+} \quad (1)$$

(VPZ) (Cu(II)-VPZ or Complex I)

$$C_{17}H_{16}FN_3O_2S + Fe^{2+} \xrightarrow{DMSO} [C_{17}H_{16}FN_3O_2S - Fe]^{2+} \quad (2)$$

(VPZ) (Fe(II)-VPZ, or Complex II)

The complexation reaction was conducted in a buffered solution, under controlled temperature, pH of the buffer and reaction time.

For the VPZ, Complex I and Complex II, the wavelength range between 200–400 nm was investigated. As shown in Figure 1, the UV-Vis spectra show maximum absorbance at λmax of VZP, Complex I and Complex II at 260 nm, 265 nm and 360 nm, respectively. Compared to VPZ, Complex I and Complex II showed a shift to greater λmax, indicating the formation of both complexes. Both, Complex I and Complex II are formed due to the shifting of electrons from the electronegative group of VPZ to the metal ion.

3.2. Optimization of the Experimental Parameters for the Complexation Reaction of the Cu(II)-VPZ and Fe(II)-VPZ

In order to optimize the Cu(II)-VPZ and Fe(II)-VPZ complexes formation, several experimental parameters were studied such as: the nature of the buffer solution, its volume, the pH of buffer, the reaction temperature, the heating time, and the concentration of VPZ in the reaction mixture.

The effects of buffer concentrations on complex formation reactions were studied in 0.01 M of borate, ammonia, acetate, Robinson and phosphate buffers. As seen in Figure 2A, the maximum absorbance value was for Complex I formed in acetate buffer and Complex II formed in Robinson buffer, respectively. These two buffer solutions were used for further investigations. The influence of the volume of buffer in the reaction mixture was investigated in the range of 1–7 mL.

The Figure 2B shows that the maximum absorbance is obtained when 5 mL of acetate is used for obtaining Complex I and 4 mL of Robinson buffer when Complex II is obtained. While other factors influencing the complexation reaction, like temperature and heating time, were maintained unchanged, the buffer's pH influence on the maximum absorbance of the obtained Complex I and Complex II was studied. In the studied pH range (i.e., 2–12), both Complexes formed at pH 8 exhibited a maximum of the absorbance value (Figure 2C). The complexation reaction was conducted in thermostated condition, ranging from values of 10 to 100 °C. A temperature maintained at 40 °C in the case of Complex I and 70 °C in the case of Complex II, gives rise to maximum absorbance values (Figure 2D). The reaction mixture was kept reacting between 1 to 10 min. A maximum of absorbance values was obtained when the reaction time was 4 min in the case of Complex I, and 7 min in the case of Complex II, respectively (Figure 2E). For both complex I and Complex II, a

VZP concentration of 0.8 mM led to obtaining the maximum of absorbance values (Figure 2F).

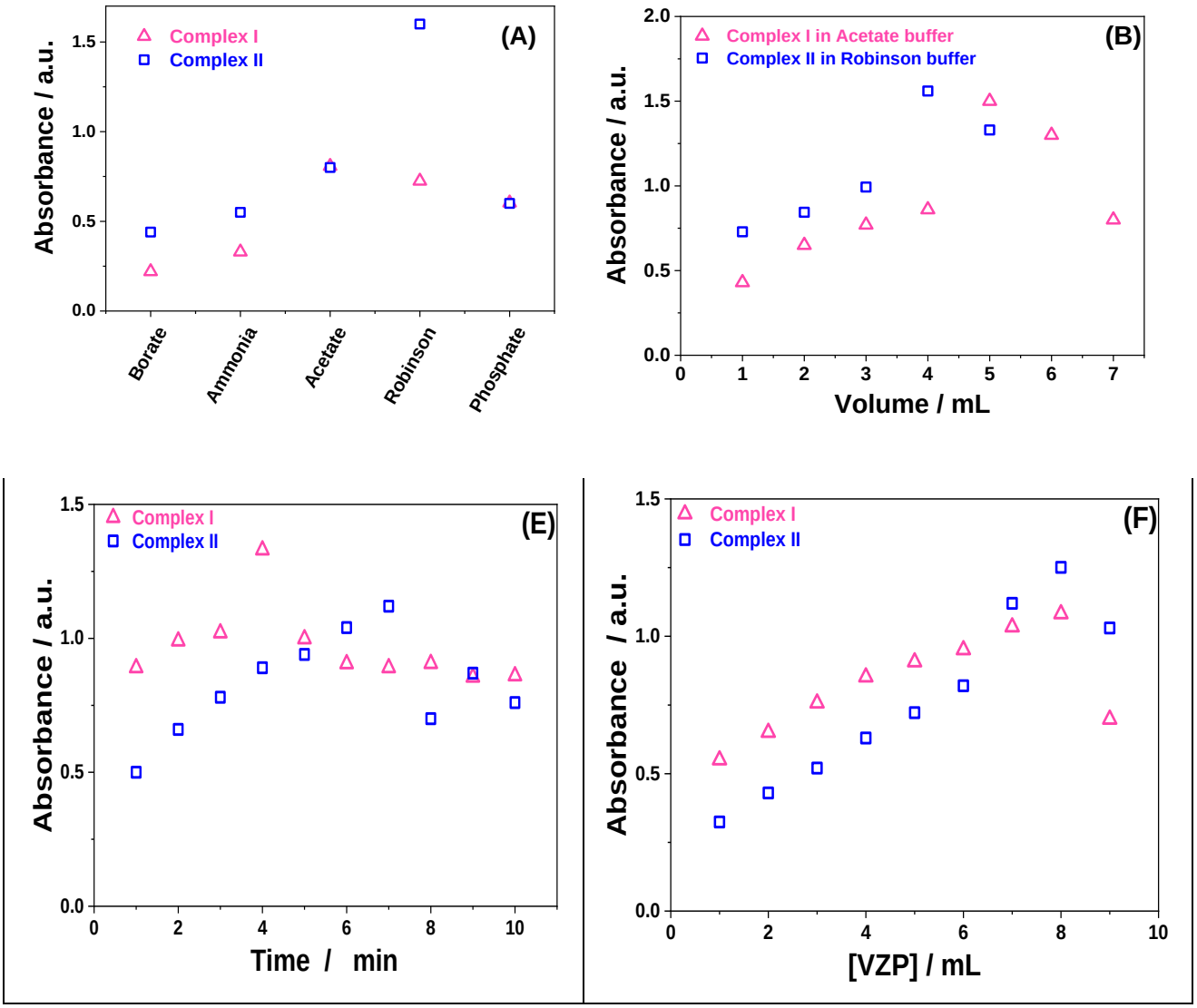

Figure 2. Optimisation of the nature of the buffer solution (**A**), volume of buffer (**B**), the pH of buffer (**C**), the reaction temperature (**D**), the heating time (**E**), and the concentration of VPZ in the reaction mixture (**F**) for the reaction of complexation between VZP and Cu(II)) (Δ, magenta) and Fe(II) (□, blue).

3.3. Determination of Stoichiometry of Complex I and II Synthesis Reaction

Generally, a chemical synthesis reaction can be written as follows: a VZP + b Salt = p Complex; where a, b and p are the stoichiometric coefficients. In order to estimate the stoichiometry in the complexation reaction of obtaining the two complexes (i.e., Complex I, and Complex II), Job's method could be applied. In this method, the molar concentration of the reactants is kept constant, but they are mixed in different volume ratios (molar fraction) while keeping the total volume constant [30]. Knowing that the maximum mole fraction (x_{max}), is given by the equation x_{max} = b/(a + b), the stoichiometric ratio could be estimated as $b/a = x_{max}/(1 - x_{max})$.

Thus, VZP, $CuCl_2$ and $(NH_4)_2Fe(SO_4)_2 \times 6H_2O$ solutions were prepared in equal concentration of 0.01 M, and their volume ratio was changed, in order to have a 0.1–0.9 molar fraction range of VZP in the reaction mixture. As seen from Figure 3, the maximum mole

fraction (x_{max}) is 1.72 a.u. for Complex I and 1.82 a.u. for Complex II. Thus b/a = 1 (i.e., 5/5) for Complex I, and 2.3 (i.e., 7/3) for Complex II, respectively.

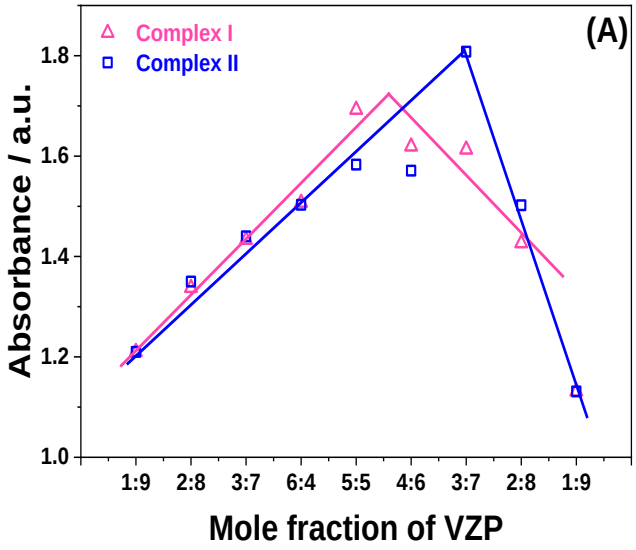

Figure 3. Job's plots illustrating the effect of the standard VZP concentration in the reactant mixtures (**A**), and the effect of various drugs (Δ, Vocinti, black), (□, Vonica, red), (☆, Vonaspaire, green) (o, Vonseca, blue) in the Complex I (**B**) or complex II (**C**) formation.

3.4. Analytical Parameters for Vonoprazan Determination via Complex I and II

Complex I and Complex II of different concentrations were prepared starting from the standard VZP solution, and the maximum absorbance at λ_{max} in the wavelength range between 200–400 nm was measured. The following calibration curves were obtained in the linear domain of VZP concentration ranging between 0.001 to 0.009 mM (Figure 4):

for Complex I

$$A/a.u. = (0.029 \pm 4.54427 \times 10^{-4}) + (3.21667 \pm 0.08075) \times [VZP]/mM,\ R^2 = 0.9956,\ n = 9\ points \quad (4)$$

for Complex II

$$A/a.u. = (0.028 \pm 3.25537 \times 10^{-4}) + (3.21667 \pm 0.05785) \times [VZP]/mM,\ R^2 = 0.9977,\ n = 9\ points \quad (5)$$

After studying linearity, it was found that the suggested approach, with a good coefficient of determination R^2 = 0.9956 and 0.9677, respectively, obeyed Beer's law in the concentration range of 0.001 to 0.009 mM VZP.

The limit of Detection (LOD, calculated as: LOD = 3 × s_a/slope) and the limit of quantification (LOQ, calculated as LOQ = 10 × s_a/slope). The estimated values are LOD = 4.24 × 10^{-7} M and LOQ = 1.41 × 10^{-6} M for Complex I and LOD = 3.04 × 10^{-7} M and LOQ = 1.01 × 10^{-6} M for Complex II, respectively.

According to the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) criteria, the concentration range, linearity, accuracy, sensitivity, precision, stability, and robustness of the suggested VZP method of determination by complexation were evaluated in order to validate parameters of the proposed analytical procedure.

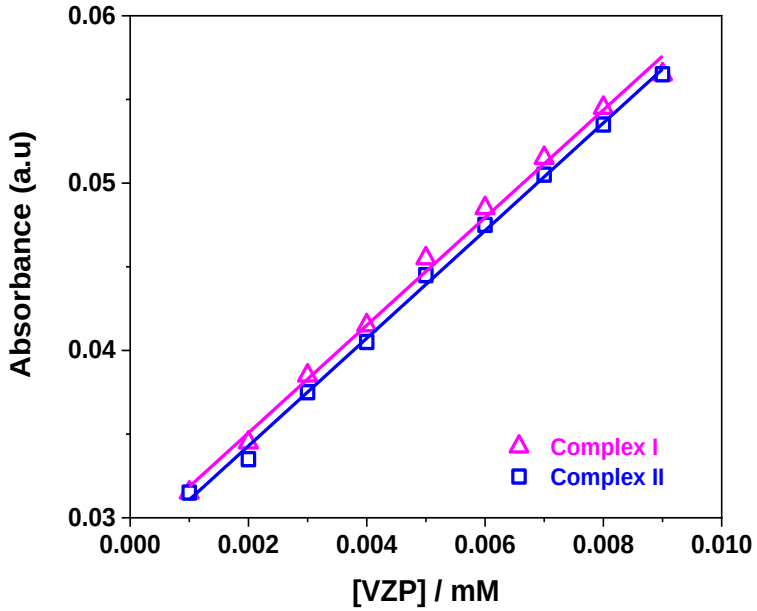

Figure 4. Effect of the Concentration of buffer on the Cu(II) (□, black) and Fe(II) (Δ, red) complexes.

Table 1. Analytical parameters and method of validation for the VPZ spectrophotometric method of determination via complexation.

S. No	Analytical Parameter	Our Results		Reported Paper 1 [21]	Reported Paper 2 [24]
		For Complex I	For Complex II	Results	Results
1.	Wavelength(λmax)	265 nm	360 nm	230 nm	
2.	Linear range	0.001 mM to 0.01 mM	0.001 Mto 0.01 M	2.00 -30.00 µg/mL	
3.	Sensibility (in a.u/mM)	3.2167	3.2167	0.0321	
4.	intercept	0.029	0.038	0.0042	
5.	Coefficient of determination (R^2)	0.9956	0.9977	0.9997	
6.	Standard Deviations (SD)	0.0042	0.0031	0.347	0.356
7.	Relative Standard Deviation	0.0894	0.00698	0.352	0.361
8.	Limit of detection M	4.24×10^{-7} M	3.04×10^{-7} M	0.24	--
9.	Limit of Quantification	1.41×10^{-6} M	1.01×10^{-6} M	0.70	---
10.	% recovery	99.08 ± 0.6	98.5 ± 0.83	98.59 ± 0.39	
11.	Molar Absorptivity L mol- cm-	5.10×10^{-5}	8.06×10^{-4}	---	
12.	Mean	0.047	0.0444	99.48	98.73
13.	Normal Distribution function (Nexp)	232.7	160.9	---	-----
13	Q-test(Qexp)	0.437	0.501	-----	-----
14	Grubb's Test (Gexp)	No Outlier	No outlier	-----	----
15	Student's t -test confidence Limit	0.391	0.293	1.29	-----
16	F-test(Fexp)	1.0017 (5.05)		7.081 (45)	---

Recovery Test for Vonoprazan in pharmaceutical preparations:

In order to validate the accuracy of the proposed complexation procedure, recovery tests were carried out. The obtained results, summarized in Table 1, show that the percentages of recovery for all drug samples were between 99.08% and 99.5%, values less than 120%, which are acceptable in the pharmaceutical industry [31] in these tables. The mean recovery percentage was found to be 99.08 ± 0.6 for Complex I and 98.5 ± 0.83 for Complex

By analysing the test samples, both intraday and interlay the new method's precision was evaluated. Thus, at λ_{max} for Complex I the mean value of the absorbance was 0.88(a.u) with an RSD of 0.0894, and for Complex II the mean value of the absorbance was 1.03(a.u)with an RSD 0.00698, respectively. Due to the fact that the RSD values, in both cases, have values very less than 2, it proves that the method by preparing Complex I and Complex II is robust enough.

No. of Test	Type of Drug	Amount Labelled/mg	Amount Found by Spectrophotometry	Percentage of Recovery/%
via Complex I				
1	Vonseca	20	18.7	98.99
2	Vociniti	20	18	99
3	Vonica	10	8	97.99
	Mean			99.08
via Complex II				
1	Vonseca	18	19.5	99.5
2	Vociniti	8	19.76	98.80
3	Vonica	10	9.879	98.79
	Vonaspaire	20	19.85	99.25
	Mean			98.5

Recovery Calculated using formula (mean = sum of no test/total tests).

Green analytical procedure index (GAPI) evaluation of the analytical method's greenness

Green analytical procedure (GAPI) scale was used to find the greenness profile of proposed method [28,29,32]. Every stage of the analytical process is assessed based on 15 factors divided into four main categories, which include the objective of the method, sample collection, transportation, preservation, preparation, compound utilize, reagent and instrumentation [33]. The results are represented with five colored pentagrams showing evidence of an analytical technique by the GAPI tool assessment, using green for the low, yellow for medium, and red colour for high environmental effect [34]. Thus, in Figure 5., (i) green colour indicates the low impact on environment. In this case, it is possible to see those aspects of the method that present a minor environmental impact, thus assuring its generally greener profile; (ii) yellow colour indicate the medium impact, which include sample preservation, reagents, and treatment of wastes; and (iii) the areas in red indicate the high impact on the environment. They correspond to the initial collection of the sample, its transport to quality control labs, and the absence of a treatment of wastes.

From Figure 5, it is possible to see that the proposed VZP determination method presents a high green profile, with no complex steps of extraction, according to Eco-Scale and GAPI recommendations for greener analytical procedure. Also, the proposed VZP determination method sample uses no very purified solvents.

Figure 5. The GAPI of the analytical method.

4. Conclusions

A new spectrophotometric method for the determination of Vonoprazan in pharmaceutical formulations has been developed. The approach is based on the formation of Vonoprazan-based Complexes I and Complex II, with copper (II) ions and iron (II) ions, respectively. The obtained colored binary complexes can be spectrophotometrically determined. The absorbance of the colored complexes was optimized at their appropriate λ_{max} against the complexation reagent blank for each complexes. The procedure is accurate and exact, with a high rate of recovery, and was validated by applying different statistically tests.

These methods are based on the use of simple compounds and attain sensitivities comparable to those obtained by complex and expensive techniques, such as HPLC and GC. As a result, as part of industrial quality control, these methods can be utilized as an option for rapid and routine determination of bulk samples and tablets.

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Informed Consent Statement:

Data Availability Statement:

Conflicts of Interest:

Abbreviations

The following abbreviations are used in this manuscript:

MDPI	Multidisciplinary Digital Publishing Institute
VZP	Vonoprazan fumarate
WHO	World Health Organization
GAPI	Green Analytical Procedure Index
GI	gastrointestinal

(NSAID non-steroidal anti-inflammatory medication
PPIs Proton Pump Inhibitors
FAD US Food and Drug Administration

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