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Extractive spectrophotometric estimation of omeprazole and pantoprazole sodium using tropaeoline OO dye

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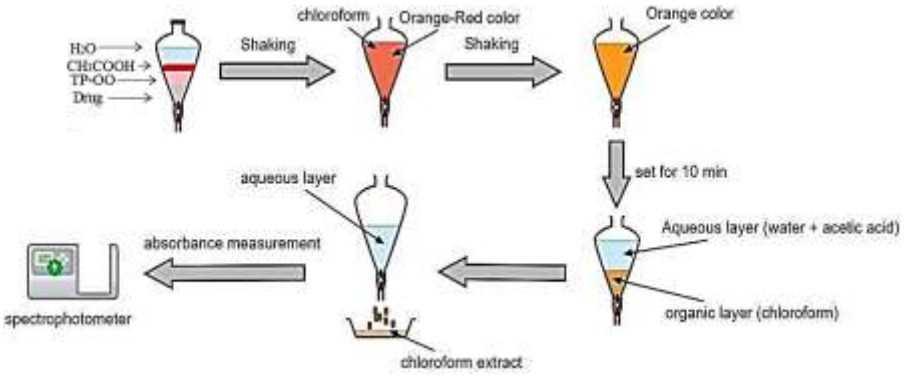
Abstract

A spectrophotometric method has been proposed to determine the proton pump inhibitors omeprazole and pantoprazole sodium in both pure and pharmacological forms, such as injections, capsules, and tablets. The method relied on the reaction of the above drugs with tropaeoline OO dye, forming ion association complexes, which are measured at 410 nm after extraction by chloroform. The method followed Beer's law over the concentration range of 0.5-14 and 0.5–13 µg/mL and with molar absorptivity values of $1.72x10^{-5}$ and $1.83x10^{-5}$ L mol^{-1} cm^{-1} for omeprazole and pantoprazole sodium, respectively. The method had good accuracy and precision, with the recovery % ranging between 98.84 and 101.02% and the relative standard deviation less than 0.66%. The method was successfully applied to pharmaceutical preparations of the studied drug compounds from different origins, and its results were in good agreement with the original content of the pharmaceutical preparations and free from interferences by excipients.



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2. tropaeoline OO dye;
2. drugs;
3. spectrophotometry.

Section Editors

Paulo Clairmont Feitosa Lima **Gomes**

Highlights

- A spectrophotometric method for the determination of Omeprazole and Pantoprazole.
- The reaction of the drugs with tropaeoline OO dye forms ion association complexes.
- The method is sensitive, accurate, and precise.
- It has been applied to determine drugs in its pharmaceutical formulations.

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1. Introduction

Both omeprazole (OPZ) and pantoprazole (PPZ) are proton pump inhibitors (PPIs) that reduce the production of gastric acid by permanently inhibiting the H+/K+ ATPase enzyme in the parietal cells of the stomach. Because of this, they work well for conditions including GERD, peptic ulcer disease, and Zollinger-Ellison syndrome that are linked to acid reflux (Strand *et al.*, 2017). They are the mainstay treatment for disorders related to abnormal excessive secretion of acids within the stomach (Malfertheiner *et al.*, 2017). These medications effectively treat digestive disorders (Chomisteková *et al.*, 2017). OPZ inhibits CYP2C19, reducing the activation of drugs like clopidogrel, which can impair antiplatelet efficacy, whereas PPZ has minimal CYP inhibition, posing a lower risk of drug interactions (Furuta *et al.*, 2010). They have recently been used as an anti-inflammatory agent to protect the gastric mucosa (Alkahtania *et al.*, 2018). OPZ is chemically called 5-Methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl) methyl] sulfonyl]-1H-benzimidazole (**Fig. 1a**). It is in the form of a white powder that is slightly soluble in water. PPZ is chemically called sodium 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl] sulfinyl] 1H-benzimidazole sesquihydrate (**Fig. 1b**). It is a white powder, highly soluble in water and ethanol (British Pharmacopoeia, 2013).

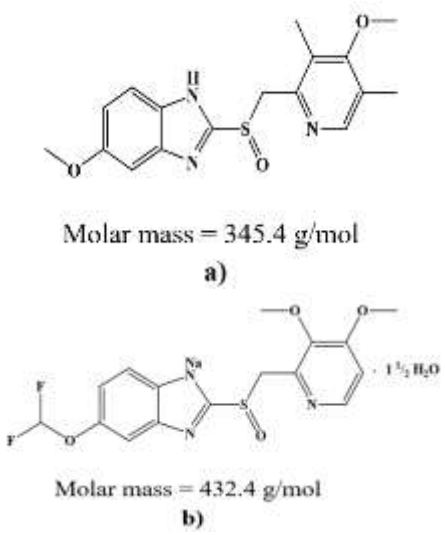

Figure 1. Chemical structure of **(a)** Omeprazole and **(b)** Pantoprazole sodium sesquihydrate.
Source: Elaborated by the authors.

Different analytical techniques were described for determining OPZ and PPZ, including fluorometry (Elmansi *et al.*, 2024; Othman and Al-Sabha, 2022), chromatography (Ahmad *et al.*, 2022; Gawad *et al.*, 2022; Joshi and Nerkar, 2020; Noubarani *et al.*, 2021), voltammetry (Khashaba *et al.*, 2019; Nigović and Hocevar, 2013; Shahrokhian *et al.*, 2015), and flow injection analysis (Al-Momani and Rababah, 2017).

Various methods and different reagents have been described for the spectrophotometric determination of OPZ and PPZ. These include potassium iodate as an oxidizing agent (Nassar *et al.*, 2017), 9-fluorenylmethyl chloroform (Alamin and Elbashir, 2019), 1,10-phenanthroline (Ayesha, 2021), bromothymol blue, methyl orange, and picric acid (Ali *et al.*, 2017), and wool fast blue (Swamy, 2018), which were applied for the determination of OPZ. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and iodine (Moustafa, 2000), iron (III) (Salama *et al.*, 2003), sodium hydroxide (Madhukara *et al.*, 2015), cerium IV in the presence of ferrous and thiocyanate ions (Devi *et al.*, 2011), and bromocresol green (Reddy *et al.*, 2014) reagents were used for the determination of PPZ. However, most of these methods are either insufficiently sensitive, tedious or needed of highly sophisticated instruments.

1.1. Analytical applications of tropaeoline OO dye

Tropaeoline OO dye, also called acid orange 5, is a monosodium salt, an acidic azo dye with an orange color (**Fig. 2**), (Pach *et al.*, 2022):

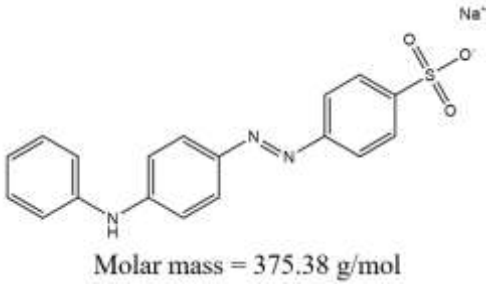

Figure 2. Chemical structure of tropaeoline OO.
Source: Elaborated by the authors.

It was used in the spectrophotometric estimation of some pharmaceutical compounds based on the formation of ion pairs, such as bromhexine (Rao *et al.*, 2005), lansoprazole (Aydoğmuş, 2006), trimethoprim (Alarfaj *et al.*, 2007), and tiapridal (Alarfaj *et al.*, 2012).

Given the importance of OMP and PPZ drugs from a therapeutic and pharmaceutical point of view. However, ion pair extractive spectrophotometry has drawn much interest in quantitatively determining several pharmaceutical compounds because extractive spectrophotometric approaches are well-liked for their sensitivity, selectivity, and cost-effectiveness in drug determination. Therefore, the proposed study aims to expand the application of tropaeoline OO dye in estimating the above pharmaceutical compounds, depending on the extraction of ion-pair complexes.

1.2. Study objective

Ion pair extractive spectrophotometry has drawn much interest in quantitatively determining several pharmaceutical compounds because extractive spectrophotometric approaches are well-liked for their sensitivity, selectivity, and cost-effectiveness in drug determination. Therefore, the proposed study aims to expand the application of tropaeoline OO dye in estimating the above pharmaceutical compounds, depending on the extraction of ion-pair complexes.

2. Materials and methods

2.1. Devices

Measurements were carried out and absorption spectra obtained using a Shimadzu UV-1800 PC double-beam spectrometer, supplied with 1 cm thick glass cells. Weighing was carried out using a KERN ABS-Germany sensitive balance. Heating was carried out using a BS-11 water bath from Lab Companion-Korea. The pH was measured using a Jenway 3510 PH meter connected to an electrode supplied by the same company. Dissolution operations were performed using a Power Sonic 405 Ultrasonic Cleaner instrument from Lab Tech-Korea.

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2.2. Materials

All chemicals of high purity were used, provided by Erba Lachewa TEDIA and Fluka companies, and drugs were supplied by SDI. OPZ and PPZ sodium solutions with a 100 µg/mL concentration were prepared by dissolving 0.01 g of each drug in its pure form in 100 mL of distilled water. The volumetric flasks were subjected to an ultrasonic shaking apparatus for five minutes to fully achieve dissolution. The solutions were stable when kept in the refrigerator. An acetic acid solution was prepared at a concentration of 2.0 mol/L by diluting 11.3 mL of concentrated acid (17.7 mol/L) with distilled water in a 100 mL volumetric flask. A 100 µg/mL concentration of tropaeoline OO dye (TP-OO) solution was prepared by dissolving 0.01 g of dye in 100 mL of distilled water and was stored in an opaque container in a refrigerator.

2.3. Recommended procedure

Into two series of 50 mL separating funnels, 1.5 mL of 100 µg/mL TP-OO dye was added, followed by the addition of 1.0 and 1.5 mL of acetic acid solution (2 mol/L), and increasing amounts (mL) of 100 µg/mL of OPZ and PPZ solution individually to cover the concentration ranges of 0.5-14 µg/mL and 0.5-13 µg/mL, respectively. The volume was made to 10 mL with distilled water. Then, 7 mL of chloroform, as an extract solvent, was added and left for 10 min to complete the extraction. The chloroform layers were measured at 410 nm against a chloroform blank for both drugs.

2.4. Analysis of injection, capsules and tablets formulations

The powder contents of three vials of OPZ and PPZ (each vial containing 40 µg of pure drug), five capsules of OPZ (each capsule containing 40 µg of pure drug), and five tablets of PPZ (each tablet containing 40 µg of pure drug) were mixed well, then carefully weighed for the equivalent of one vial, one capsule, and one tablet; after that, the contents were dissolved in distilled water, the volume was completed to 100 mL in a volumetric flask, and shaken in an ultrasonic shaker to complete dissolution. The solutions were filtered to obtain 400 µg/mL of the above drugs. Then, a solution of 100 µg/mL for each was prepared by dilution, and different volumes containing 3, 5, and 12 µg/mL for OPZ and 3, 5, and 10 µg/mL for PPZ were treated according to the recommended procedure.

3. Results and discussion

3.1. Preliminary study and absorption spectrum

In an acidic medium OPZ, and PPZ combine with TP-OO dye to produce chloroform-soluble ion association complexes. Absorption maxima for both complexes are 410 nm (Fig. 3).

3.2. Optimization of conditions

To obtain the highest sensitivity of the proposed method, all parameters were fixed, and adjusting each one separately, the effects of several factors, including acid and buffer solution, extraction solvent, dye concentration, temperature, and time, were examined and adjusted, using 10 mL volumetric flasks and a concentration of 10 µg/mL of each of OMP and PPZ.

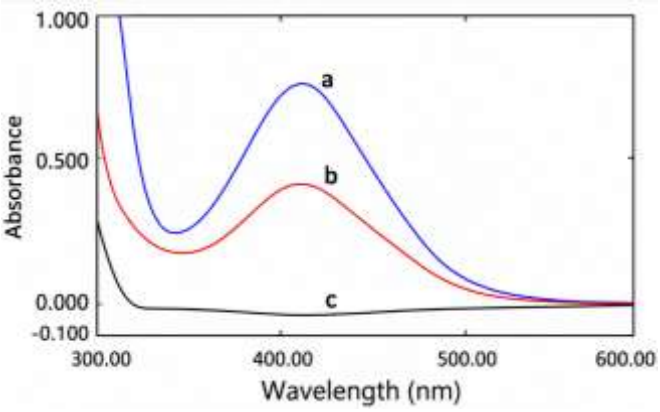

Figure 3. Absorption of the TP-OO complexes with 10µg/mL for each of **(a)** OPZ and **(b)** PPZ versus reagent blank, and **(c)** blank versus chloroform in an acidic medium.
Source: Elaborated by the authors.

3.2.1. Effect of acid and buffer solutions

It was observed that the formation of ion-pair complexes through the interaction of the studied drugs with the TP-OO dye, but the sensitivity of these complexes increased in the presence of acid. Therefore, the effect of different acids on the method sensitivity was studied (Fig. 4). It was found that acetic acid at a concentration of 2 mol/L and a volume of 1 mL and 1.5 mL for OPZ and PPZ, respectively, gave high sensitivity. However, buffer solutions including acetate and phthalate buffers, at pH 2.5, 2.8, and 3, were examined and found decreasing in their absorbance, so they were excluded.

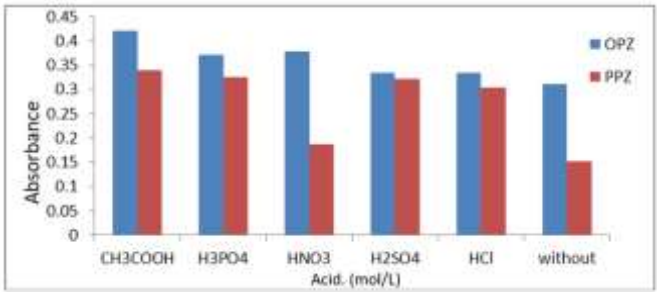

Figure 4. Effect of acid on the absorbance of OPZ and PPZ.
Source: Elaborated by the authors.

3.2.2. Effect of the extraction solvent

Among the several organic solvents examined (dichloromethane, chloroform, diethyl ether, carbon tetrachloride), chloroform was chosen for this experiment due to its ability to extract the dye-drug ion-pair complexes from the aqueous phase selectively and quantitatively (Fig. 5). Different volumes of chloroform were studied for the extraction of the complexes, and it was found that 7 mL was the optimal amount for quantitative extraction of the complexes. Shaking time ranging from 1 to 5 min did not alter the absorbance; hence, 2 min were chosen. The effect of extraction standing time was studied, and it was found that 10 min is the optimal period.

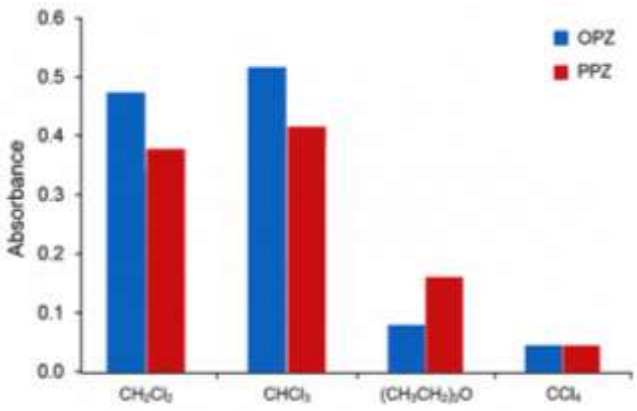

Figure 5. Effect of extraction solvent on complex adsorption.
Source: Elaborated by the authors.

3.2.3. Effect of TP-OO dye concentration

The effects of adding increasing amounts (0.5-2 mL) of TP-OO dye, at a concentration of 100 µg/mL, on the absorption of the ion-pair complexes formed were studied. It was found that the volume of 1.5 mL of dye was optimal and was recommended in this method (**Fig. 6**).

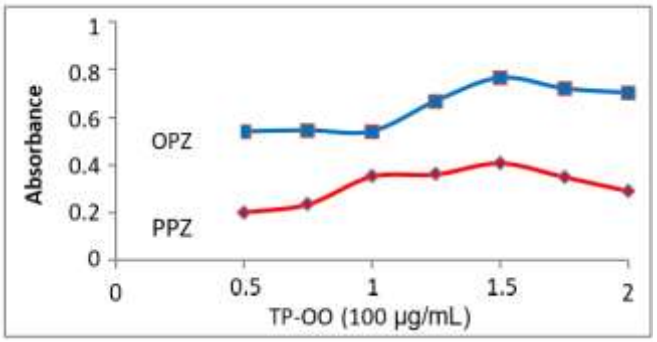

Figure 6. Effect of TP-OO concentration on the absorbance of complexes.
Source: Elaborated by the authors.

3.2.4. Effect of temperature, time, and stability of ion-pair complexes

To obtain the optimal temperature and time at which the drug-TP-OO complexes gave high sensitivity, different temperatures (23, 30, and 40 °C) and different periods were examined. It was found that the laboratory temperature (23 °C) was the best, as it gave the maximum absorption of the complexes after 10 min and remained stable for at least 2 h (**Fig. 7**). In contrast, a higher temperature reduces absorbance due, maybe, to their destruction.

3.2.5. Effect of the additional sequences

Different additional sequences for selecting the most suitable one for maximum absorbance have been examined. As seen in **Fig. 8**, the sequence (TP-OO + CH_3COOH + Drug) was the optimal one, and any change in the addition sequence negatively affects absorption.

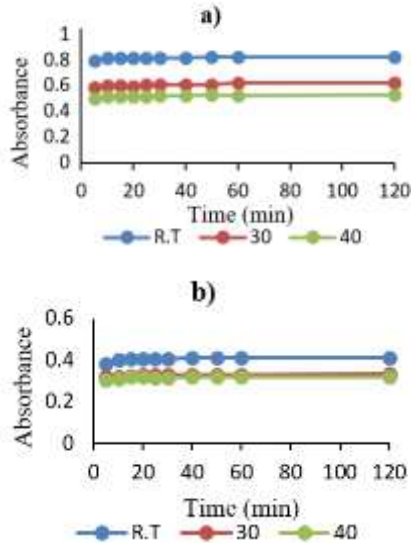

Figure 7. Effect of temperature, time and stability of OPZ **(a)** and PPZ **(b)** complexes with TP-OO dye.
Source: Elaborated by the authors.

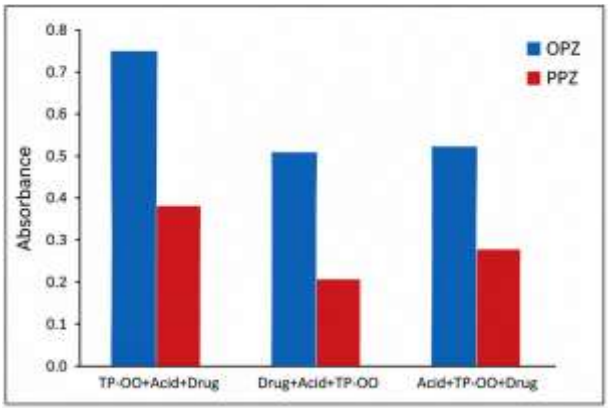

Figure 8. Effect of the addition sequence.
Source: Elaborated by the authors.

3.3. Calibration graphs and linearity

Calibration graphs were created by plotting the absorbance against various drug concentrations under the experimental conditions described in the recommended procedure, (**Fig. 9**). As the results cited in **Table 1** show, the method obeyed Beer's law in the ranges of 0.5-14 and 0.5-13 µg/mL for OMP and PPZ, respectively, with high determination coefficients. The molar absorptivity values indicate that the method is sensitive. The accuracy (average recovery %) and relative standard deviation (RSD) for analyzing three replicates of varying concentrations for each medication demonstrate that the procedure is accurate and precise. The detection limit (LOD) and quantitation limit (LOQ) (Valcarcel, 2000) were determined using **Eqs. 1** and **2**:

$$LOD = 3.3\sigma/s \quad (1)$$

$$LOQ = 10\,\sigma/s \quad (2)$$

where s is the calibration curve's slope and σ is the standard deviation of the absorption of the lowest concentration on the calibration graph.

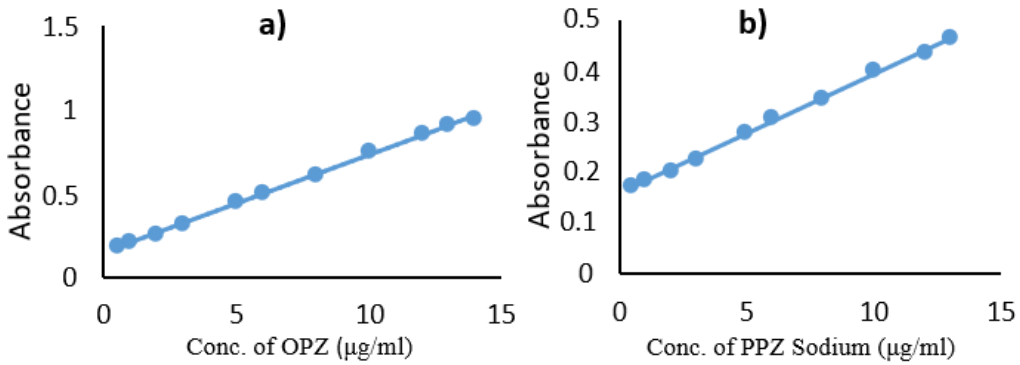

Figure 9. Calibration plot of **(a)** OPZ and **(b)** PPZ.
Source: Elaborated by the authors.

Table 1. Analytical parameters for the proposed method.

Parameter	OPZ	PPZ
Linearity range (µg/mL)	0.5 - 14	0.5 - 13
Molar absorptivity (L mol^{-1} cm^{-1})	2×10^4	1×10^4
Sandell' sensitivity (ng/cm^2)	0.017	0.043
LOD (µg/mL)	0.032	0.021
LOQ (µg/mL)	0.097	0.063
Intercept	0.1551	0.1613
Slope	0.0581	0.0234
Correlation coefficient (R^2)	0.9982	0.9982

Source: Elaborated by the authors.

3.4. Effect of excipients

To prove the efficiency of the proposed method and its success in estimating pharmaceutical compounds and to ensure that they are free from the interference of additives and excipients, the standard addition method was applied to estimate drugs in their pharmaceutical preparations. The results shown in **Figs. 10** and **11**, and **Table 2** (see subitem 3.7) indicate that the method is free from interference of excipients added to pharmaceutical preparations.

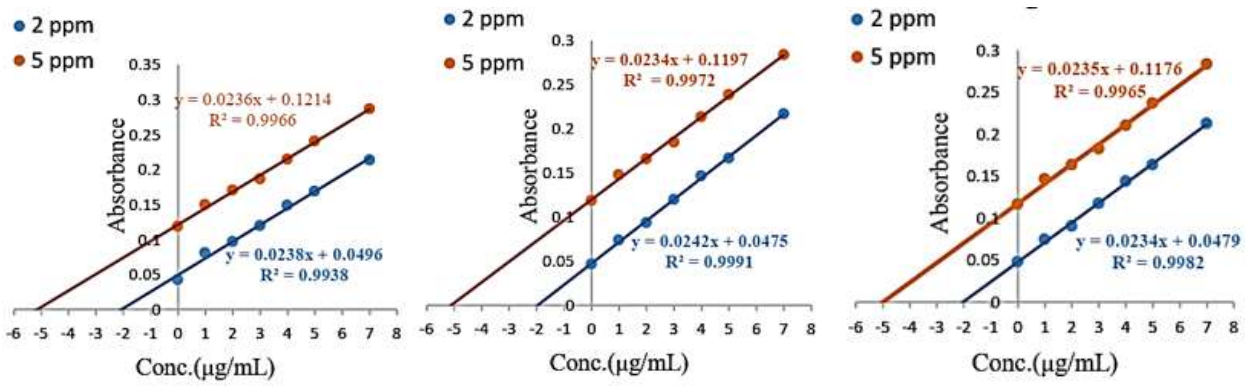

Figure 10. Standard addition plots for OPZ in its pharmaceutical preparations: **(a)** German origin, **(b)** Swiss origin, **(c)** Indian origin.
Source: Elaborated by the authors.

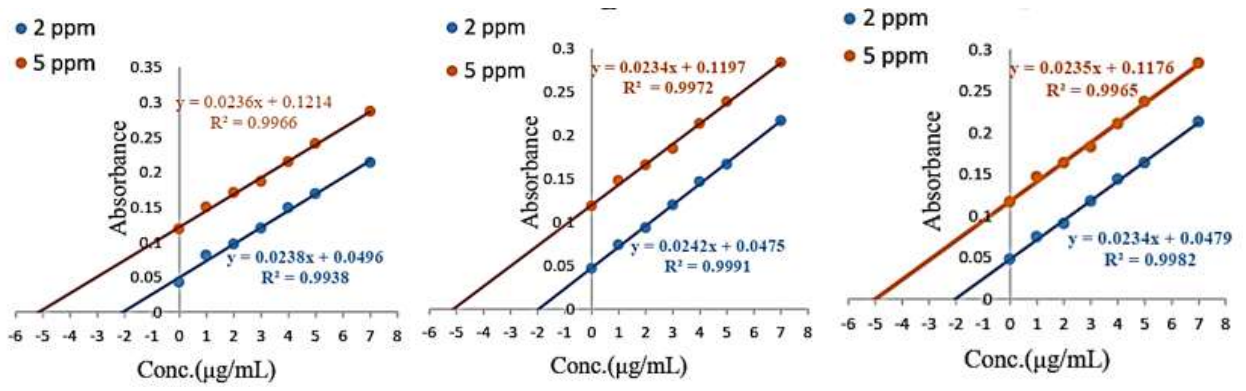

Figure 11. Standard addition plots for PPZ in its pharmaceutical preparations: **(a)** Romani. origin, **(b)** Canadian origin, **(c)** Jordanian origin.
Source: Elaborated by the authors.

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3.5. Stoichiometry and stability constant of the ion-pair complexes

The composition and stability constants of the drug-TP OO complexes were determined by applying Job's continuous variation and mole ratio methods (Valcarcel, 2000). For both methods, the results demonstrated that the ion-pair complexes are formed in a 1:1 (drug:TP-OO) ratio (**Fig. 12**).

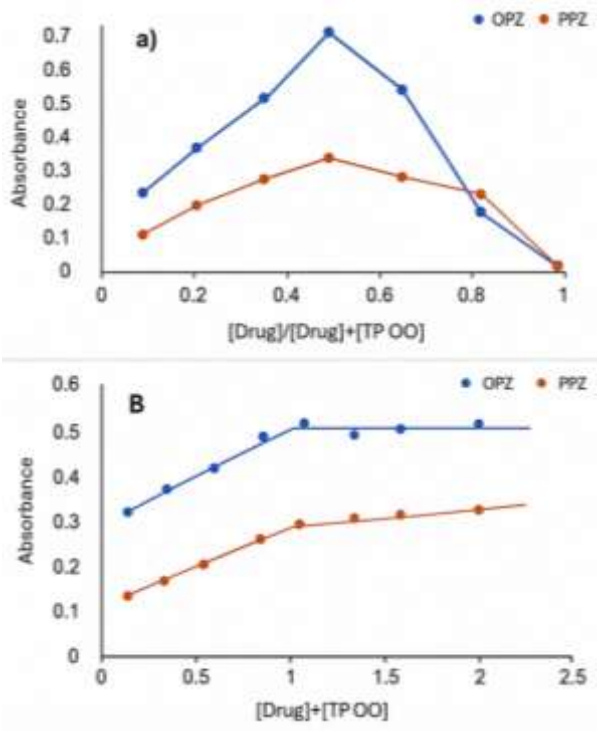


Figure 12. Continuous variations **(a)** and mole ratio **(b)** methods for OPZ and PPZ complexes with TP-OO dye.
Source: Elaborated by the authors.

The stability constant values of these complexes were calculated according to **Eq. 3**.

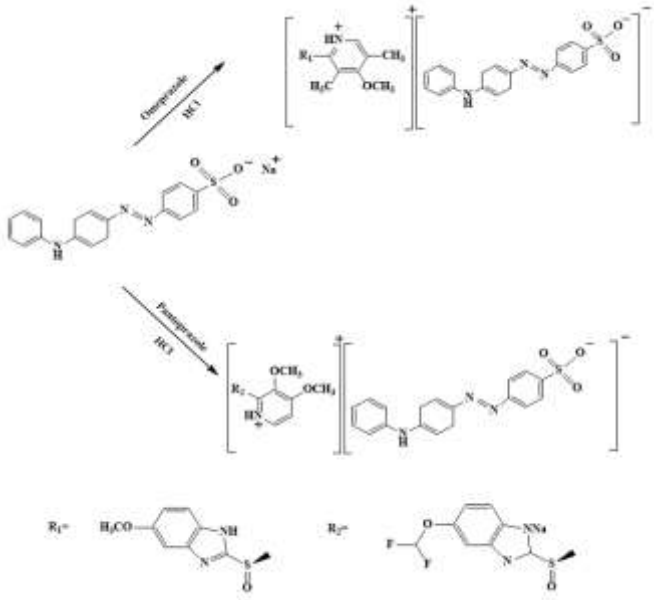
$$K_{st}=\frac{1-\alpha}{\alpha^2 C} \quad (3)$$

where K_{st} is the stability constant, α is the degree of dissociation, and c is the concentration of complex.

The K_{st} values were found to be 2.19×10^6 and 3.19×10^6 L mol^{-1} for OPZ and PPZ, respectively, indicating the high stability of the complexes.

3.6. Suggested mechanism

The suggested method is based on the formation of an extractable ion-pair complexes between TP-OO and the medications under study. These complexes may be formed by an electrostatic attraction between the sulfite anion of the dye and the most basic core in drug molecules (the amino group) in an acidic medium (Walash *et al.*, 2011). By applying Job's and mole ratio methods, it was found that the complexes were formed in a1:1 ratio (TP-OO: medication). **Scheme 1** illustrates the suggested reaction mechanism.



Scheme 1. Proposed mechanism for the reaction of OPZ and PPZ with TP-OO dye.
Source: Elaborated by the authors.

3.7. Analysis of OPZ and PPZ in pharmaceutical formulations

The proposed method was successfully applied in estimating the studied drugs in their pharmaceutical preparations as injections, capsules, and tablets, manufactured from different origins. The results obtained agreed with the original content in all commercial preparations (**Table 2**). The student t-test revealed the method is accurate.

3.8. Comparison of the proposed method with literature

The proposed method for determining OPZ and PPZ medications has been compared to previously disclosed spectrophotometric methods in the literature. The new method was distinguished by its greater sensitivity than some spectrophotometric methods indicated in **Table 3**. This procedure is easy and applicable to different pharmaceutical preparations.

Table 2. Application of the proposed method to pharmaceutical preparations.

Pharmaceutical preparation	Certified value	Amount present (µg/mL)	Amount found (µg/mL)	Recovery* (%)	Average Recovery (%)	Average amount found (mg)	t-test**	Standard addition procedure (mg)
				OPZ				
Gasec capsules (Switzerland)	40 mg	3	2.99	99.66	101.72	40.69	0.93	40.53
		5	5.07	101.4				
		10	10.41	104.1				
Omeprazole capsules (India)	40 mg	3	2.98	96.33	99.28	39.71	2.75	40.00
		5	4.90	98				
		10	10.35	103.5				
Omeprazole stada Vial (Germany)	40 mg	3	2.99	99.66	100.62	40.25	2.05	40.39
		5	4.90	98				
		10	10.42	104.2				
				PPZ				
Panzol coted/tablets (Canada)	40 mg	3	2.98	96.33	99.58	39.98	0.61	40.09
		5	5.02	100.4				
		10	10.2	102				
Pantop coted/tablets (Jordan)	40 mg	3	2.98	96.33	99.31	39.72	1.05	40.49
		5	4.98	99.6				
		10	10.2	102				
Pantorom Vial (Romania)	40 mg	3	3.02	100.66	101.89	40.75	1.04	41.41
		5	5.11	102.2				
		10	10.28	102.8				

Note: *Average of four determinations; **Theoretical value = 3.62
Source: Elaborated by the authors.

Table 3. Comparison between the proposed and literature methods.

Analytical parameters	OPZ			PPZ		
Reference	Present method	Alamin and Elbashir (2019)	Ali *et al.*, (2017)	Present method	Salama *et al.*, (2003)	Reddy *et al.*, (2014)
Reagent	TP-OO	FmCl*	Picric acid	TP-OO	iron (III)	BCG**
Methodology	ion association	derivatization	Charge transfer complex	ion association	Metal chelate	ion association
λ max (nm)	410	217	373	410	455	420
Temp. (C°)	R.T	60	R.T	23	60	R.T
Linearity (µg/mL)	0.5-14	2-12	10-80	0.5 -13	30-300	5-25
Molar absorptivity (L mol^{-1} cm^{-1})	2.01×10^4	2.889×10^4	4.033×10^3	1.93×10^4	–	–
LOD	0.032	0.364	0.107	0.021	–	–
LOQ	0.097	1.214	0.324	0.063	12.17	–
Recovery (%)	100.06	96.4	99.8-101.6	100.4	100.6	99.9-100.2
RSD	≤ 0.40	≤ 2.86	≤ 1.91	≤0.55	1.52	< 2
Application	capsules, vial	Tablet	Tablet	Tablets, vial	–	Tablet

Note: *9-Fluorenylmethyl chloroformate; **Bromocresol green.
Source: Elaborated by the authors.

4. Conclusions

A simple, sensitive, accurate, and precise extractive spectrophotometric method has been proposed to estimate OPZ and PPZ in their pure and pharmaceutical forms. The method depends on the ion-pair complex formation reaction between the drugs and TP-OO dye. The standard addition method was applied and proved to be free of interference from excipients present in pharmaceutical formulations. The method can be used in routine control analysis.

Authors' contribution

Conceptualization: Theia'a Najim Al-Sabha; **Data curation:** Zaid Abdul kareem Alsherefe; **Formal Analysis:** Theia'a Najim Al-Sabha; **Funding acquisition:** Not applicable; **Investigation:** Theia'a Najim Al-Sabha; **Methodology:** Theia'a Najim Al-Sabha; **Project administration:** Zaid Abdul kareem Alsherefe; **Resources:** Not applicable**; Software:** Not applicable; **Supervision:** Theia'a Najim Al-Sabha; **Validation:** Theia'a Najim Al-Sabha; **Visualization:** Theia'a Najim Al-Sabha; **Writing – original draft**: Zaid Abdul kareem Alsherefe; **Writing – review & editing:** Theia'a Najim Al-Sabha.

Conflict of interest

The authors declare that there is no conflict of interest.

Data availability statement

All data sets were generated or analyzed in the current study.

Artificial Intelligence usage statement

The authors declare that they did not use Artificial Intelligence tools at any stage of the preparation, correction, or evaluation of this work, including graphical abstract preparation.

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