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RESEARCH ARTICLE

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Spectroscopic study of in situ-formed metallocomplexes of proton pump inhibitors in water

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Abstract

Proton pump inhibitors, such as omeprazole, pantoprazole and lansoprazole, are an important group of clinically used drugs. Generally, they are considered safe without direct toxicity. Nevertheless, their long-term use can be associated with a higher risk of some serious pathological states (e.g. amnesia and oncological and neurodegenerative states). It is well known that dysregulation of the metabolism of transition metals (especially iron ions) plays a significant role in these pathological states and that the above drugs can form complexes with metal ions. However, to the best of our knowledge, this phenomenon has not yet been described in water systems. Therefore, we studied the interaction between these drugs and transition metal ions in the surrounding water environment (water/DMSO, 99:1, v/v) by absorption spectroscopy. In the presence of Fe(III), a strong redshift was observed, and more importantly, the affinities of the drugs (represented as binding constants) were strong enough, especially in the case of omeprazole, so that the formation of a metallocomplex cannot be excluded during the explanation of their side effects.

KEYWORDS
complexation study, drug interactions, iron metal complexes, proton pump inhibitor, transition metals

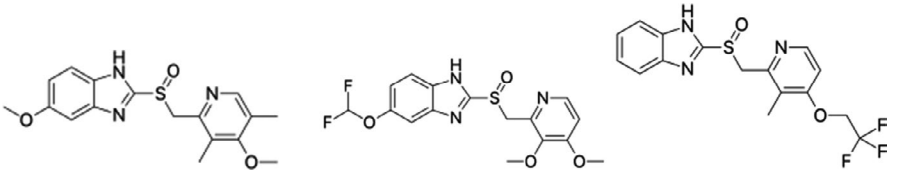

FIGURE 1 Structures of tested drugs (omeprazole, pantoprazole and lansoprazole)

1 | INTRODUCTION

Proton pump inhibitors such as omeprazole, pantoprazole and lansoprazole are extensively used for the treatment of gastrointestinal disorders (e.g. dyspepsia, peptic ulcers, *Helicobacter pylori* infection, gastroesophageal reflux disease, gastrointestinal complications and Zollinger–Ellison syndrome) (Robinson & Horn, 2003). Their physiological effect is based on the suppression of gastric acid secretion by blocking the gastric acid pump, H(+)/K(+)-adenosine triphosphatase (ATPase). They are known as safe without direct toxicity. Nevertheless, their long-term use can be associated with an increased risk of developing gastric cancer (omeprazole and pantoprazole) (Abbas, Zaidi, Robert, Thiha, & Malik, 2019), neurological adverse events such as dementia (omeprazole, pantoprazole and lansoprazole) (Novotny, Klimova, & Valis, 2019), iron deficiency anaemia (omeprazole) (Imai, Higuchi, Morimoto, Koyamada, & Okada, 2018) and cardiovascular events (pantoprazole, lansoprazole and especially omeprazole) (Sun et al., 2017). Therefore, a precise determination and evaluation of their biological functions have been highly requested. This fact can also be complicated by their interactions with biologically important molecules such as some transition metals (e.g. iron and aluminium).

Iron is the most abundant transition metal species in the human body, and the majority of iron in the body is complexed with haem and is used for oxygen transport in red blood cells and mitochondrial respiration (Galaris, Barbouti, & Pantopoulos, 2019; Kasai, Mimura, Ozaki, & Itoh, 2018). In addition, iron serves as the active centre of redox-relevant enzymes such as cytochrome P450s and DNA repair enzymes (Munro, McLean, Grant, & Makris, 2018; Puig, Ramos-Alonso, Romero, & Martínez-Pastor, 2017). High levels of iron can lead to serious diseases including cancers, neurodegenerative diseases such as Alzheimer's disease, diabetes mellitus, and mesothelioma (Belaidi & Bush, 2016; Petronek, Spitz, Buettner, & Allen, 2019; Zhu et al., 2019).

Due to the abundance of transition metals, especially iron, in the human body, the possibility of their interaction with drugs can influence the pharmacodynamic and pharmacokinetic properties of the drugs. Currently, a large number of commonly used drugs that can form stable complexes with iron are known (Campbell & Hasinoff, 1991). This phenomenon can cause significant decreases in the bioavailability of a number of various drug types (e.g. tetracyclines, penicillamine, methyldopa and ciprofloxacin). It can also be assumed that there are many other undescribed iron-drug interactions that can cause complex formation; therefore, some patients may receive inadequate therapy.

Few authors have shown that this phenomenon could have a non-negligible influence on the therapeutic effectiveness of some proton pump inhibitors. For example, Zhang et al. found that the binding constant of omeprazole in complex with serum albumin can significantly increase in the presence of Cu(II) and Fe(III) ions (Zhang, Shi, Liu, Chen, & Peng, 2011). In the case of pantoprazole, the addition of Fe(III) ions increases its binding affinity; nevertheless, the application of Cu(II) ions leads to a decrease in binding affinity. Additionally, omeprazole therapeutic effectiveness can be substantially changed by the interaction with transition metal ions. In the field, Russo et al. found that omeprazole complexed with Co(II) ions displayed higher cytotoxicity against *H. pylori* than the drug alone (Russoa et al., 2014).

These facts strongly imply that studying the interaction of proton pump inhibitors with metal ions can be a very important topic in medicinal research. Currently, the formation of omeprazole complexes with transition metal ions, such as Co(II), Cu(II) and Fe(III), or lansoprazole with Fe(III) and Zn(II) ions, has been described. (Mohamed, Nour El-Dien, Khalil, & Mohammad, 2009; Rahman & Kashif, 2010; Russoa et al., 2014) However, the tested solutions were prepared in organic solvents such as methanol or in a mixture of ethanol with water at high temperature (60°C). These experiments can give interesting information about metal affinity of above drugs, but their usability can be limited. Water unlike organic solvents can repress their interaction by decreasing host–guest electrostatic attractive interactions (Bistri & Reinaud, 2015). On the other hand, in this organic hydrophobic receptors can support their complexation by enchantment of hydrophobic interactions between them. Nevertheless, the interaction between metal ions in water systems without significant supplementation of organic solvents has not yet been studied and quantified to the best of our knowledge. Therefore, we decided to study the interactions of omeprazole, pantoprazole and lansoprazole (see Figure 1) in water.

2 | EXPERIMENTAL SECTION

2.1 | Drugs and metal salts

The studied drugs (omeprazole, pantoprazole and lansoprazole) and used salts nitrates in this case of Al(III), Co(II), Cu(II), Fe(III), Mn(II), Ni(II), Cd(II) Pb(II), Cr(III), Hg(II)

Zn(II), Mg(II), Ca(II), K(I) and Na(I) and perchlorate in the case of Fe(II) ion were acquired from Sigma-Aldrich (Czech Republic, Prague).

2.2 | Spectroscopic studies of the interactions of omeprazole, pantoprazole and lansoprazole with metal ions

For the UV-Vis 'on-off' study, 35 mg of each drug was dissolved in DMSO (dimethylsulfoxide) to a concentration of 0.01 M in a 10-ml volumetric flask. One millilitre of the drug solution was taken into a 1000-mL volumetric flask, and water was added to a final volume of 1,000 ml. The final drug concentration in the stock solution was 10 μM.

Calculated amounts of the metal salts (nitrates, and in this case the of Fe(II) ion, perchlorates) were dissolved in water/DMSO, 99:1, v/v, or drug solution (prepared according to the above method) in a 100-mL volumetric flask for a final concentration of the metal cation of 10 μM.

UV-Vis spectra of the drugs were measured by Cary 400 (Varian) in the presence and absence of the studied cations. Data were collected in the range 220–900 nm with 1-nm data spacing in a 1-cm quartz cell at a scan rate of 300 nm/min.

2.3 | Determination of conditional binding constants and the complex stoichiometry of omeprazole, pantoprazole and lansoprazole with Fe(III), Fe(II) and Al(III) ions

The drug association with Fe(III), Fe(II) and Al(III) ions was studied using UV-Vis spectroscopy in aqueous solution (water/DMSO, 99:1, v/v) in the same way that was used to study the interactions of the organic hosts with metal ions in water (Jakubek, Kejík, Antonyová, et al., 2019; Jakubek, Kejík, Kaplánek, et al., 2019; Jakubek et al., 2017, 2018). Because the solvent significantly affects the binding constants, all titrations were performed in the same environment, and the ratio of DMSO to water was held constant. Conditional constants (K values) were calculated from the absorbance changes (ΔA) of omeprazole at its spectral maximum and the spectral maximum of their complexes with Fe(III), Fe(II) and Al(III) ions by regression analysis with Letagrop Spefo 2005 software. The computational model was described and discussed in detail elsewhere (Dyrssen, Ingri, & Sillén, 1961). Assumed Ks were defined by following equation

$$K_{pq} = \frac{\left[\text{Drug}^p \text{Metal ion}^q\right]}{\left[\text{Drug}\right]^p \left[\text{Metal ion}\right]^q}$$

Because concentrations used drugs and metal ions and their expected complexes were low, activities in previous equation were expressed as concentrations. In absorbance-data analysis, the Lambert–Beer law and the law of absorbance additivity are assumed to hold. Data $A = f(c_{drug}, c_{metal})$ were evaluated using a general least-squares procedure of Letagrop Spefo, minimizing the U (sum of squares of residuals),

$$U = \sum_{j=1}^{n_\lambda} \sum_{i=1}^{n_p} \left(A_{\text{exp}} - A_{cal}\right)^2 = min$$

where A_{exp} and A_{cal} represent experimental and calculated values of absorbances, respectively. Summation is taken over all N_λ numbers of wavelengths and N_p experimental points. The models with lowest values of U were classified as the most correct. The A_{jk} (absorbance of jth solution measured at the kth wavelength) can be expressed as function of concentration and ε (extinction coefficient) of drug, metal and assumed complexes.

$$A = \sum_{j=1}^{n_c} \varepsilon_{w,j} c_j = \sum_{j-1}^{n_c} \left(\varepsilon_{pq,w} K_{pq} \text{drug}^p \text{metal}^q\right)_j$$

where c and w represented number of analysed species (drug, metal ion and expected complexes) and used wavelength, respectively.

The drug concentration was 10 μM. The concentration of Fe(III), Fe(II) and Al(III) ions varied in the range of 0–0.5 mM. UV-Vis spectra were measured from 220 to 900 nm with 1-nm data spacing in a 1-cm quartz cell at a scan rate of 600 nm/min.

3 | RESULTS AND DISCUSSION

Drug interactions with tested metal ions were studied by UV-Vis absorption spectroscopy. This study was conducted in an aqueous environment (water/DMSO, 99:1, v/v) at a 10 μM drug concentration and a 100 μM concentration of the appropriate metal cation.

Omeprazole exhibited an absorption peak at 300 nm. Upon the addition of Fe(III) into the omeprazole solution, a significant change in the absorption, such as the appearance of new absorption peaks (λ_{max} = 256 and 360 nm), appeared (Figure 2). Al(III) was observed to only extend the absorption peak and shift its absorption maxima from 300 nm to 293 nm. On the other hand, upon the addition of other metal ions, such as Co(II), Cu(II), Fe(II), Mn(II), Ni(II), Cd(II) Pb(II), Cr(III), Hg(II) Zn(II), Mg(II), Ca(II), K(I) and Na(I), no or only slight spectral changes were observed for omeprazole.

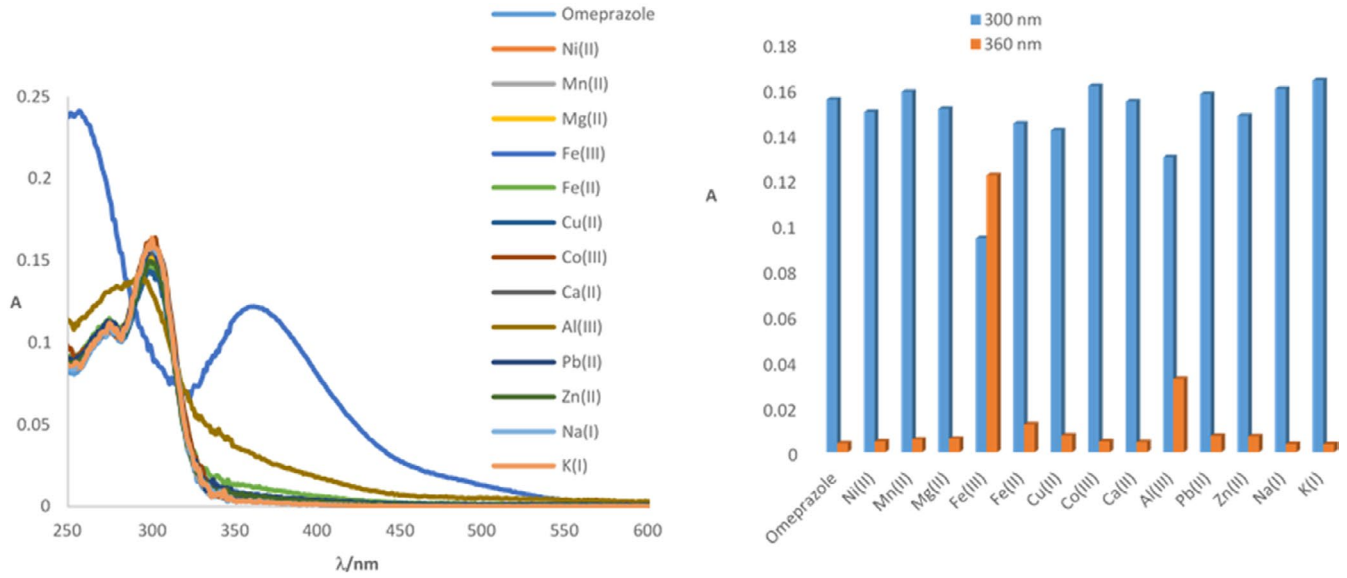

FIGURE 2 UV-Vis spectra of omeprazole (10 μM) without and with metal ions in water (water/DMSO, 99:1, v/v) [Colour figure can be viewed at wileyonlinelibrary.com]

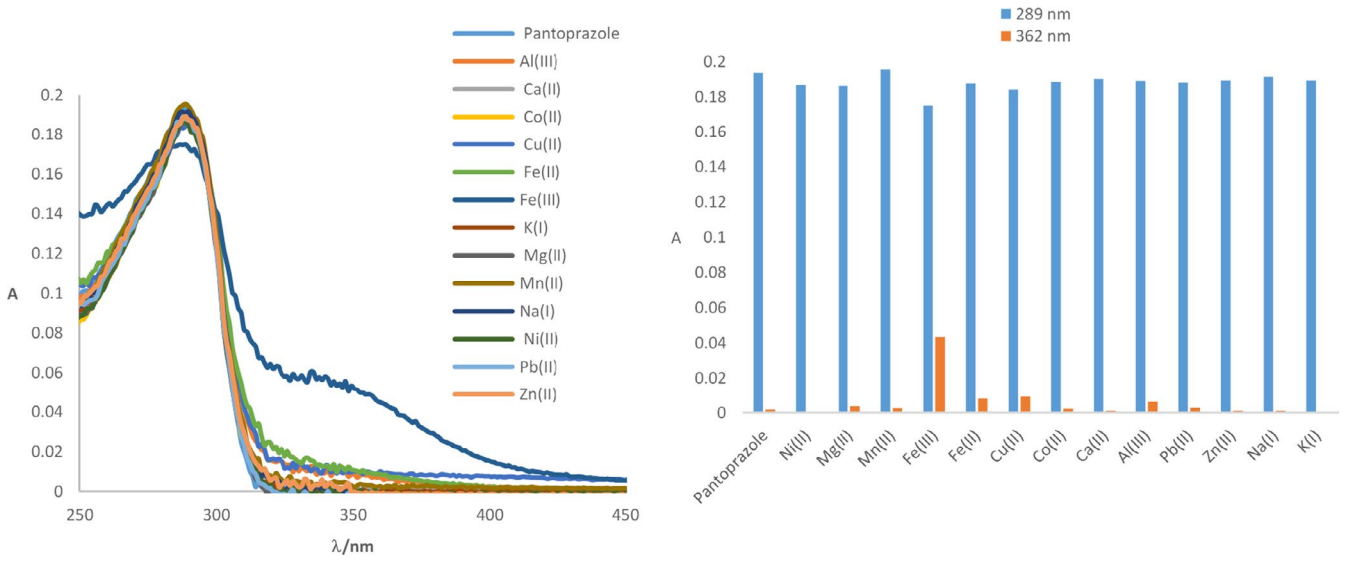

FIGURE 3 UV-Vis spectra of pantoprazole (10 μM) without and with metal ions in water (water/DMSO, 99:1, v/v) [Colour figure can be viewed at wileyonlinelibrary.com]

In contrast, pantoprazole displayed a strong spectral change only in the presence of Fe(III) ions (Figure 3). During their interaction, the pantoprazole absorption band shifted from 289 to 362 nm with decreasing intensity. In the presence of the other tested metal ions, no significant spectral changes were observed, with only a slight decrease or increase in the intensities at 289 and 362 nm, respectively.

In the case of lansoprazole, significant changes in its absorption spectra were caused by Fe(III), Al(II) and Fe(II) ions (Figure 4). In the presence of Fe(III), its spectral maximum shifted from 284 to 360 nm. After the addition of other metal ions (except Fe(II) and Al(III)), this phenomenon was not observed, as only a slight spectral change was observed. The application of Fe(II) and Al(III) ions significantly increased and decreased lansoprazole absorbance at 284 and 360 nm, respectively. However, the intensities of these phenomena were sometimes smaller than in the case of Fe(III) ions.

To determine the omeprazole complexation with Fe(III) and Al(III) ions, a titration experiment was performed (Figure 5). In the presence of Fe(III) ions, two new absorption peaks (λ_{max} = 256 and 360 nm) appeared. As the concentration of Fe(III) ion gradually increased, the absorbance at the original spectral maximum at 271 nm decreased until the concentration of Fe(III) reached 3 equivalents. Then, further addition of Fe(III) ions leads to a slow decrease in the absorbance. In the case of the new absorption peaks, Fe(III)

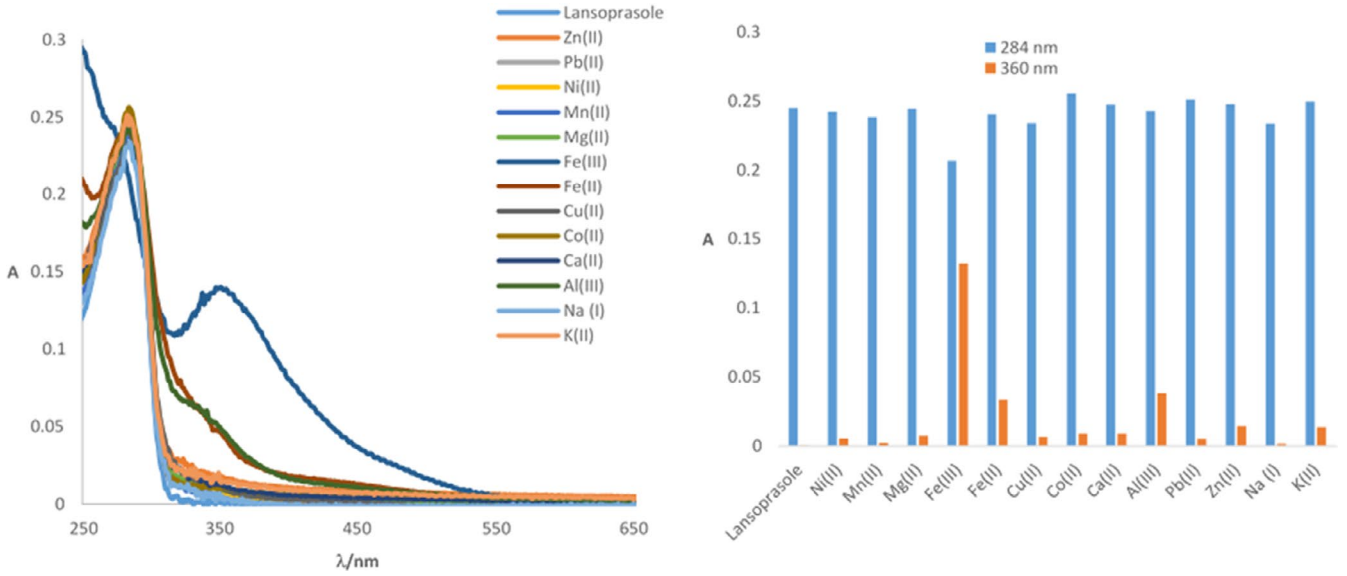

FIGURE 4 UV-Vis spectra of lansoprazole (10 μM) without and with metal ions in water (water/DMSO, 99:1, v/v) [Colour figure can be viewed at wileyonlinelibrary.com]

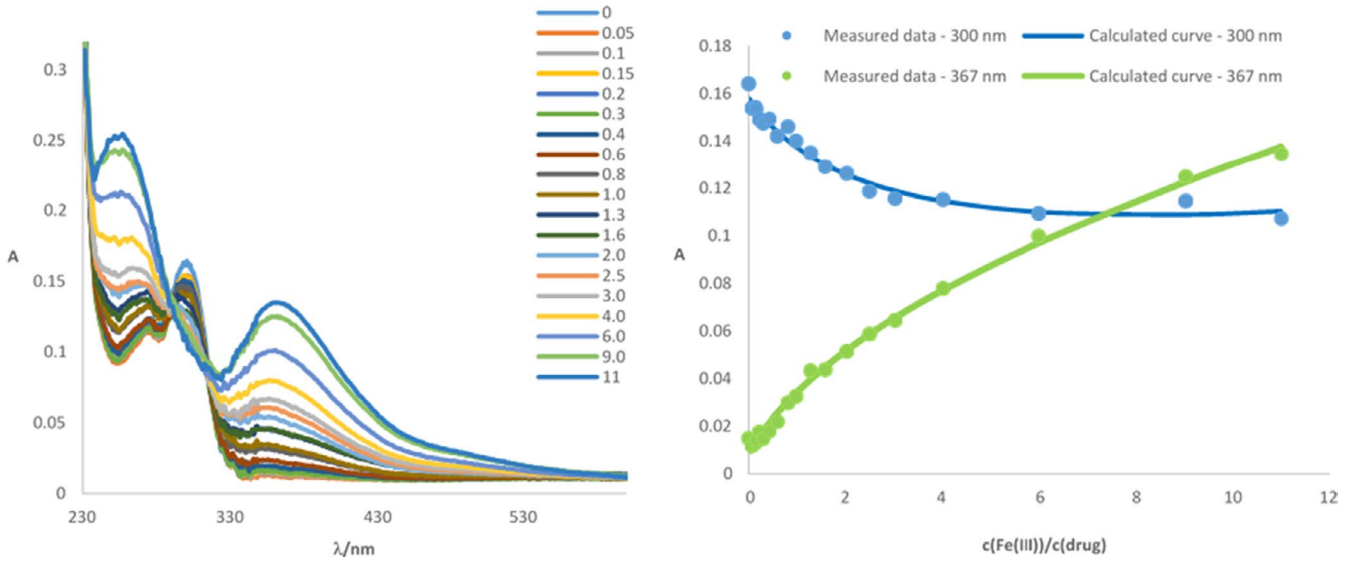

FIGURE 5 Titration and titration curve of omeprazole (10 μM) with $Fe(NO_3)_3$ in water (water/DMSO, 99:1, v/v) [Colour figure can be viewed at wileyonlinelibrary.com]

ion supplementation (3 equivalents, or less) was observed to strongly increase the absorbance. Specifically, in the presence of 3 equivalents of Fe(III) ions, the absorbance at 360 nm increased more than fivefold (from 0.12 to 0.64) with respect to the value in the absence of Fe(III). Further additions of Fe(III) lead to a slower increase in absorbance. The highest value of absorbance (0.13) was observed when 11 equivalents of Fe(III) ions were added to the studied solution.

The omeprazole interaction with Al(III) was coupled with only a blueshift of the omeprazole absorption peak and a decrease of its absorbance (Figure 6.). For example, in the presence of 5 equivalents of Al(III) ions, the value of the absorbance decreased from 0.15 to 0.13. Supplementation with additional Al(III) ions did not cause a significant change in the absorbance value.

Different interaction modes of pantoprazole with Fe(III) ions were found. In the presence of a small amount of added Fe(III) ions (approximately 0.5 equivalents or less), only negligible spectral changes were observed (Figure 7). As the concentration of Fe(III) ion gradually increased (interval between 0.5 and 2 equivalents), a strong increase in absorbance was observed, corresponding to a new absorption peak (λ_{max} = 362 nm). Specifically, in the presence of 2 equivalents of Fe(III) ions, the absorbance at 362 nm rose more than fivefold (from 0.005 to 0.025) with respect to the value in the absence of Fe(III). Increasing additions of Fe(III) lead

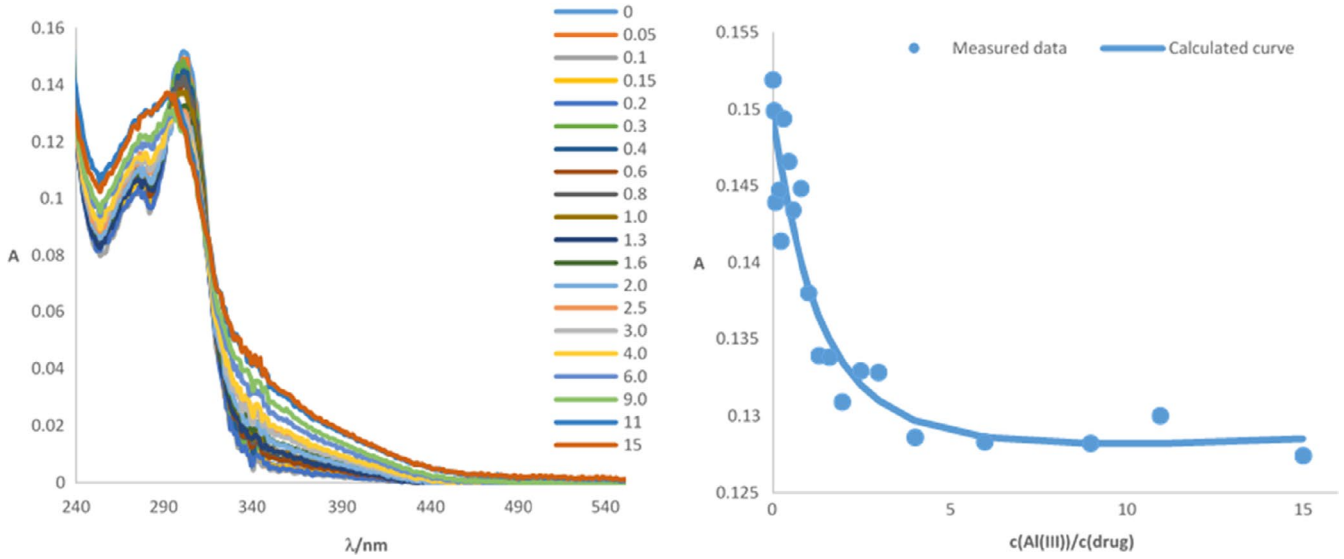

FIGURE 6 Titration and titration curve of omeprazole (10 μM) with $Al(NO_3)_3$ in water (water/DMSO, 99:1, v/v) [Colour figure can be viewed at wileyonlinelibrary.com]

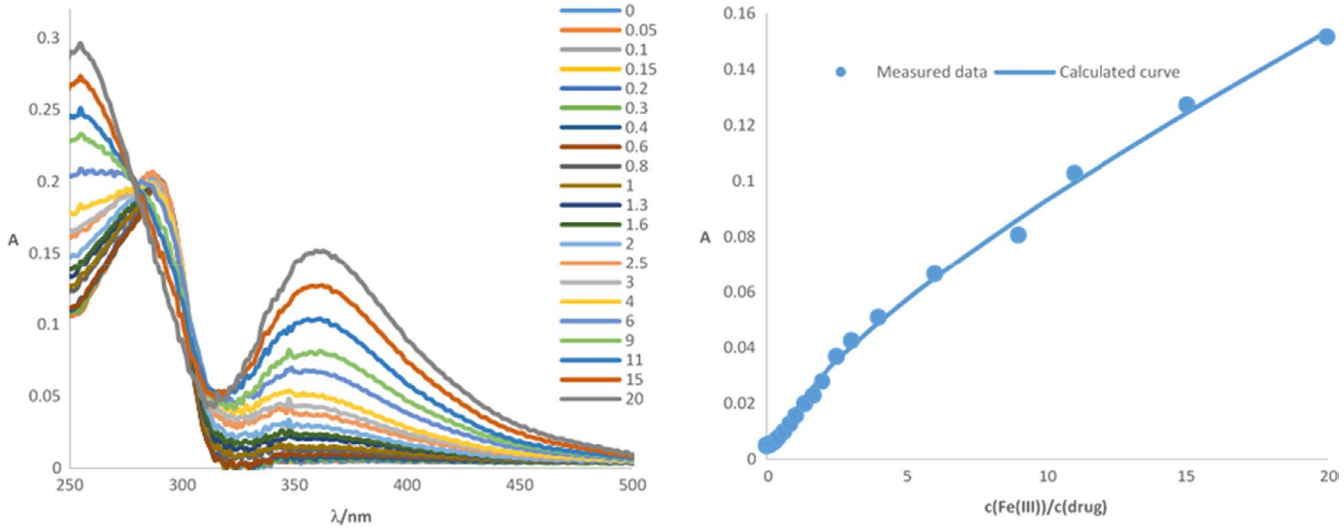

FIGURE 7 Titration and titration curve of pantoprazole (10 μM) with $Fe(NO_3)_3$ in water (water/DMSO, 99:1, v/v) [Colour figure can be viewed at wileyonlinelibrary.com]

to a significant but smaller increase in absorbance at 362 nm than for previous supplements. The absorbance of the original spectral maximum at 289 nm decreased after the addition of more than 0.5 equivalents of Fe(III) ions.

For lansoprazole, a strong increase in absorbance at 362 nm was observed after the addition of a small amount of Fe(III) ions (Figure 8). The absorbance value in the presence of two equivalents of Fe(III) ions was 0.06, while this value without the addition of Fe(III) was 0.01. Additional supplementation of Fe(III) led to only a moderate increase in the absorbance. In addition, the formation of a new absorption band also occurred and caused a decrease in the absorbance value of the original lansoprazole spectral band.

In the case of the lansoprazole complexes with Al(III) and Fe(II), only a blueshift of the omeprazole absorption peak was observed, coupled with a moderate decrease in its absorbance (Figures 9 and 10). For example, in the presence of 13 equivalents of Al(III) and Fe(II) ions, the value of lansoprazole absorbance decreased from 0.25 to 0.22 and 0.24, respectively. With supplementation of other Al(III) or Fe(II), significant changes in the lansoprazole absorption spectra were not observed.

The K values of the drug complexes with transition metal ions (Fe(III) and Al(III)) were calculated by Letagrop Spefo 2005. The values of their stability constants for the drug complexes with metal ions are shown in Table 1. The highest

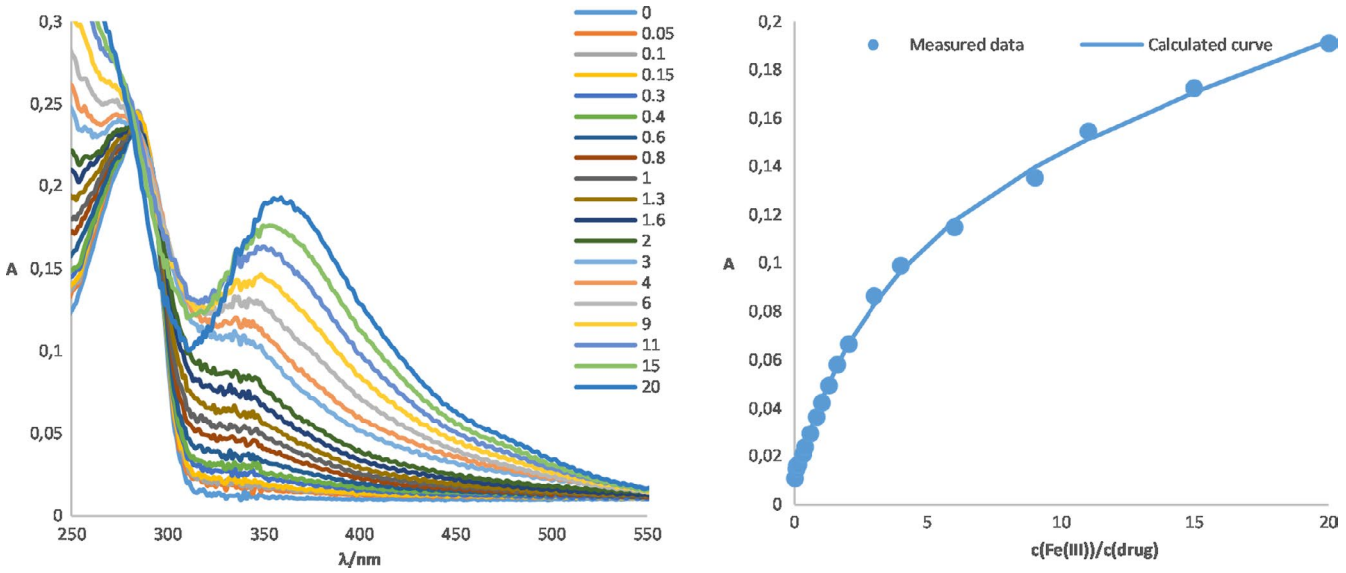

FIGURE 8 Titration and titration curve of lansoprazole (10 μM) with $Fe(NO_3)_3$ in water (water/DMSO, 99:1, v/v) [Colour figure can be viewed at wileyonlinelibrary.com]

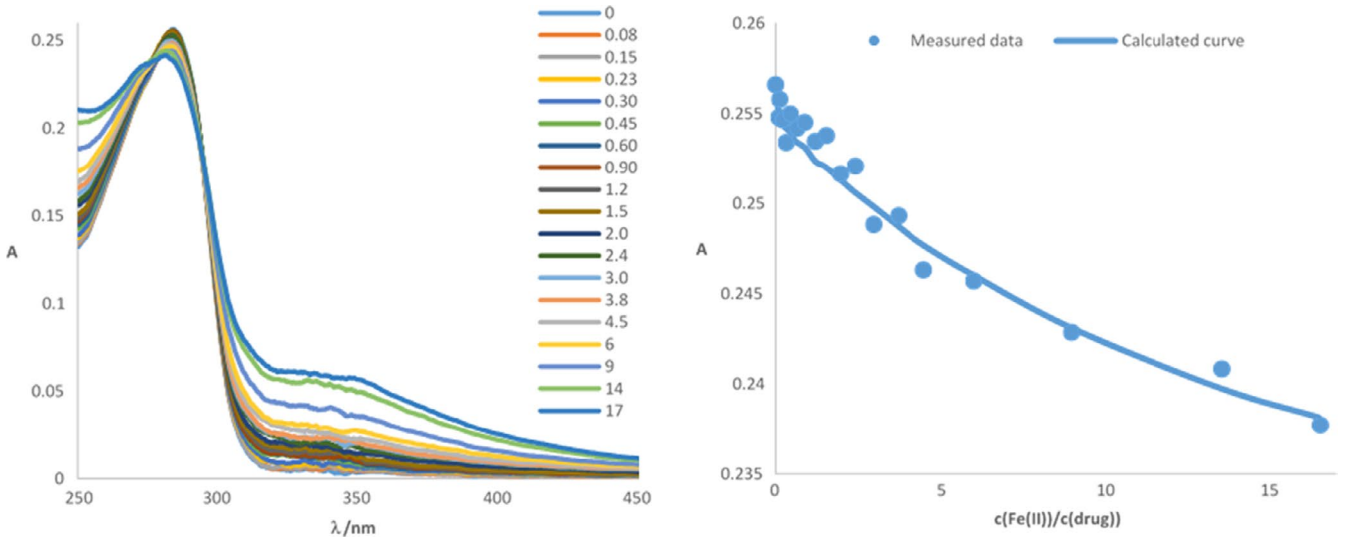

FIGURE 9 Titration and titration curve of lansoprazole (10 μM) with $Fe(ClO_4)_2$ in water (water/DMSO, 99:1, v/v) [Colour figure can be viewed at wileyonlinelibrary.com]

affinities (representing the binding constant) for Fe(III) and Al(III) ions were observed for omeprazole.

The above data show that the tested drugs can form strong complexes with transition metals, especially Fe(III) ions. Values of their affinities for transition metals (represented by K) are comparable with values of other chelated drugs such as ciprofloxacin ($K = 10^9\ M^{-2}$, 1:2, Fe(III): drug) (Siddiqi, 2010). Recommendations for its application shall state that ciprofloxacin should not be taken with supplements containing metals such as iron. The question is whether the tested drugs can be influenced by its interaction with iron ions, mainly Fe(III), and how much this interaction influences the therapeutic action and side effects. In this case, we can usually expect that this phenomenon can cause a lower bioabsorption of iron and probably the drugs alone (Campbell & Hasinoff, 1991). On the other hand, the use of proton pump inhibitors, such as omeprazole, pantoprazole and lansoprazole, can lead to the lower secretion of gastric acid and thereby significantly lower the iron intake from food, subsequently causing anaemia (Sarzynski, 2011).

In addition, there are other serious reasons to study iron interactions with proton pump inhibitors. It is well known that higher levels of iron ions can play an important role in a number of pathological states, such as oncological, metabolomic and neurodegenerative diseases (Fernandez-Real, McClain, & Manco, 2015; Petronek et al., 2019;

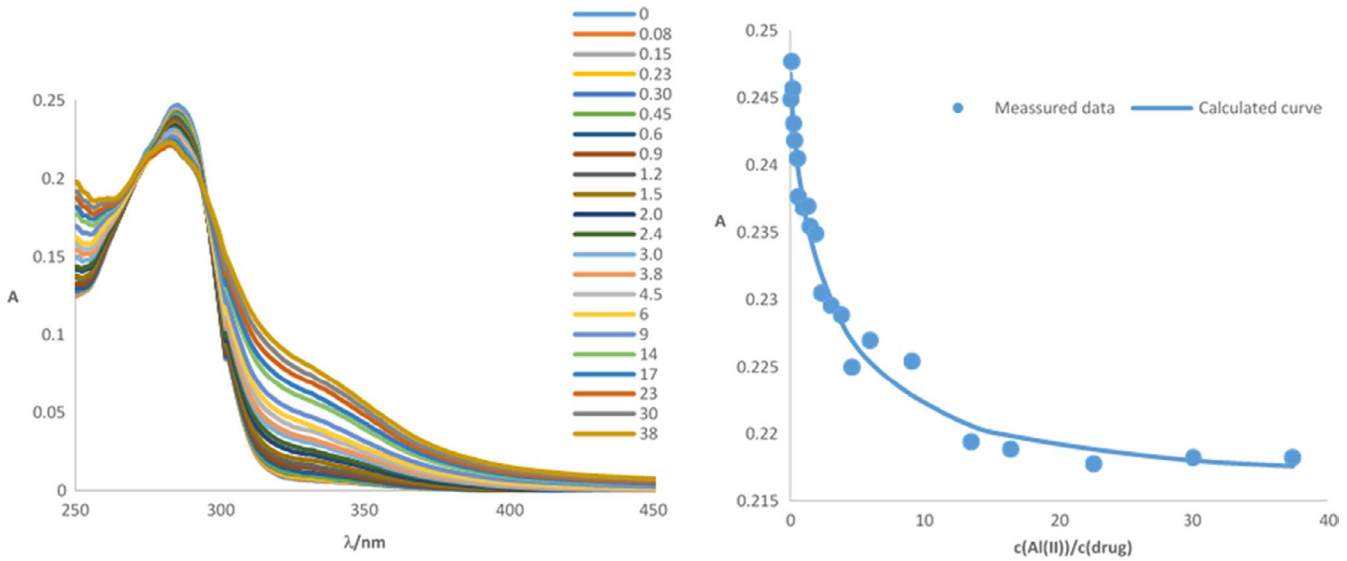

FIGURE 10 Titration and titration curve of lansoprazole (10 μM) with $Al(NO_3)_3$ in water (water/DMSO, 99:1, v/v) [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 K values and stoichiometry of the drugs in complex with transition metals in water (water/DMSO, 99:1, v/v)

Drug	Ion	Log (K)	Stoichiometry (metal ion: drug)
Omeprazole	Fe(III)	6.7	1:1
	Al(III)	12.1	1:2
Pantoprazole	Fe(III)	5.0	1:1
		11.5	1:2
Lansoprazole	Fe(III)	4.5	1:1
	Al(III)	9.3	1:2
	Fe(II)	8.1	1:2

Schneider, Zorzi, & Nardocci, 2013). Some of these pathological states are seriously associated with long-term use of the above tested drugs (Abbas et al., 2019; Novotny et al., 2019). It has been published that the metallocomplexes containing these drugs can display significantly higher therapeutic efficacy than original drugs (e.g. omeprazole in complex with Co(II) against *H. pylori*) (Russoa et al., 2014). However, it cannot be excluded that some of their side effects can also be caused by the chelation to transition metal ions.

In addition, iron supplements are among the most frequently prescribed and used drugs (Fuentes, Pineda, & Venkata, 2018), and therefore, their interaction with proton pump inhibitors cannot be excluded. On the other hand, protein pump inhibitors, such as pantoprazole, have started to be tested in clinical studies for their combined applications with an iron chelator to target iron metabolism (e.g. reduction in serum ferritin level) for patients with thalassaemia (Eghbali, Khalilpour, Taherahmadi, & Bagheri, 2019).

The above implies the number of points of contact between iron metabolism and the therapeutic properties of proton pump inhibitors. Our study shows that these drugs form iron complexes in the aqueous environment. It has been postulated that the studied drugs could display chelation abilities in vivo, and this phenomenon could, in part, explain some of their side effects. Nevertheless, a number of further studies are necessary for confirmation or refutation of this phenomenon.

4 | CONCLUSION

The interactions of proton pump inhibitors (omeprazole, pantoprazole and lansoprazole) with metal ions were observed by UV-Vis spectroscopy in water (water/DMSO, 99:1, v/v). In the presence of Fe(III), significant changes in their UV-Vis spectra were observed leading to a clear conclusion of the metal complex formation. The highest affinity was observed for omeprazole; in the case of the other drugs tested, the affinities were significantly smaller but still significant. This implies that the formation of iron complexes with proton pump inhibitors should not be neglected in studying the mechanisms of their side effects.

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