

Spectrophotometric and Conductometric Study of the Complexation of Ranitidine to Fe^{2+} , Fe^{3+} , Al^{3+} , Mg^{2+} , Cu^{2+} , Ni^{2+} and Pb^{2+} Metal Ions: Pharmaceutical Implications.

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Abstract:

Complexation properties of ranitidine (Ran) with Fe^{2+} , Fe^{3+} , Al^{3+} , Mg^{2+} , Cu^{2+} , Ni^{2+} and Pb^{2+} were studied using UV/VIS spectroscopy and conductometric titrations respectively. Ranitidine was found to form 1:1 complexes in methanol or aqueous buffer (pH 6.5) with all cations except magnesium. In case of Fe^{3+} complexes of the formula $[(\text{Fe}^{3+})_2\text{Ran}]$ were evident.

Key words:

Ranitidine HCl, Spectroscopy, conductometric titration, Complexation, Metal ions.

Introduction

Ranitidine (Ran) is a substituted amino-alkyl-furane derivative which competitively inhibits H_2 receptors [1]. It has been on the market since the beginning of the 80s [2]. The drug is believed to be more potent and with fewer side effects than cimetidine [2-6]. The most significant advantage of ranitidine over cimetidine appears the lower anti-androgen activity, fewer CNS side effects and no effect on hepatic drug metabolism [2,3,5]. The occurrence of these side effects may be associated with the ability of the drug to form complexes with certain metals, particularly iron [7]. It has been shown that cimetidine and to less extent Ran inhibit

cytochrome P-450 by interacting with the heme iron and ending with modifications of the pharmacokinetics of many drugs whose metabolism is dependent on P-450 [8-10]. Metals like iron, aluminum and magnesium are often given concurrently with Ran either as iron supplement or in antacids because anemia and hyperacidity are associated with gastric ulcers. Therefore studying possible interactions between Ran and such metals is important in order to predict a possible effect of such combinations on the patient. Concurrent administration of ferrous sulfate with Ran for example may lead to decrease in serum blood level if complexation occurs between Ran and iron(II).

Few reports have described the interaction of Ran with metal ions including iron [11-12], platinum and palladium [13]. Nevertheless literature is devote of complete studies regarding Ran- metal interactions. Moreover the reports are sometimes controversial; for example some reports indicate that Ran doesn't form complexes with iron [11] while our findings and other studies [12] suggest otherwise. Therefore it was of our interest to study the interaction of Ran with the different metals in buffer and methanolic solutions.

Experimental

Materials and apparatus:

Distilled water and analytical reagent grade materials were used for all experiments. Lead nitrate, copper sulfate, nickel chloride, magnesium chloride, aluminum chloride, ferrous sulfate and ferric chloride were obtained from BDH chemicals (Boole, England Ltd). Tris buffer was obtained from Sigma (Saint Louis, USA) and prepared (50 mM, pH 6.5) according to Partlow et al, [11]. HPLC grade methanol, diethyl amine and ethylacetate were obtained from Labscan Ltd. (Stillorgan Ind Park, Co. Dublin, Ireland). Ranitidine hydrochloride was a kind gift from The Arab Pharmaceutical Manufacturer, Salt, Jordan. All spectroscopic measurements were made

on a Cary E-1 UV/visible spectrophotometer with 1-cm quartz cuvetts. Conductivity was measured using F530 conductivity-meter (WTW, 8120, Weiheim, OB, Germany).

Spectroscopic titrations:

For Fe^{2+} , Fe^{3+} , Al^{3+} , Mg^{2+} and Pb^{2+} spectroscopic titrations were carried out by preparing solutions containing fixed amount of ranitidine HCl ($2 \times 10^{-4}\text{M}$). Increasing amounts of the metal to be examined were added to each of the Ran solutions so that the final molar ratio of the metal to Ran lies in the range 0-4 is obtained. After 20 minutes electronic spectra of each solution was recorded against a proper blank containing the same amount of iron at each point but without Ran. The resulting spectra (for Ran) were examined.

For copper and nickel metal ions titrations were carried out by preparing solutions containing fixed amount of the metal (0.01M) and increasing concentrations of Ran so that the final molar ratio of the metal to Ran lies in the range (0-4). The visible spectra for each solutions were recorded against the solvent (methanol or Bis Tris buffer pH 6.5) and compared to that of the metal alone.

Conductometric titrations:

For all metals conductometric titrations were carried out by measuring the conductivity of each solution that was prepared for spectroscopic titrations. The obtained values for conductivity were plotted against the molar ratio of the metal to Ran.

Results and discussion

Spectroscopic titration of Ran with Fe^{+3} showed that the absorbance at 227 nm decreases (hypochromic shift) together with a gradual shift to longer wavelength (bathochromic shift) as

the molar ratio increases in both water and methanol (Fig. 1). These spectroscopic changes indicate clearly that interaction between Ran and Fe^{+3} does take place in water as well as in methanol. Both bathochromic shift and hypochromicity are typical of complex formation and could be used to characterize the complexation process.

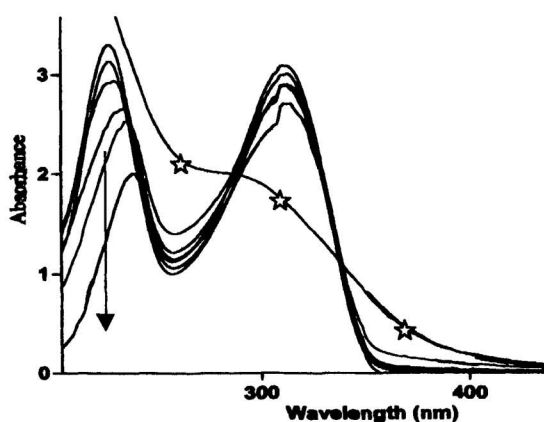


Fig. 1: Overlaid UV spectra of Ranitidine solutions in methanol ($2.166 \times 10^{-4}\text{M}$) with increasing concentration of ferric chloride (arrow shows the direction of increasing iron concentration). The spectrum with (☆) is due to ferric chloride solution alone.

As the bathochromic shift is not dependent on the absolute concentration of the complex it was found to give more reproducible plots and thus was used in this paper to obtain a binding isotherm (Fig. 2). The plot in Figure 2 shows that λ_{max} changes continuously with increasing the molar ratio of the metal to the drug in both solvents methanol and water until it plateaus at a molar ratio of about 2:1. However there seems to be a significant difference in the binding behavior of Ran in the two solvents. In water the binding seems to be cooperative in the sense that the binding of the first Fe^{+3} atom is slow and once the ratio of the metal starts to exceed 1:1; the complexation to second Fe^{+3} becomes easier.

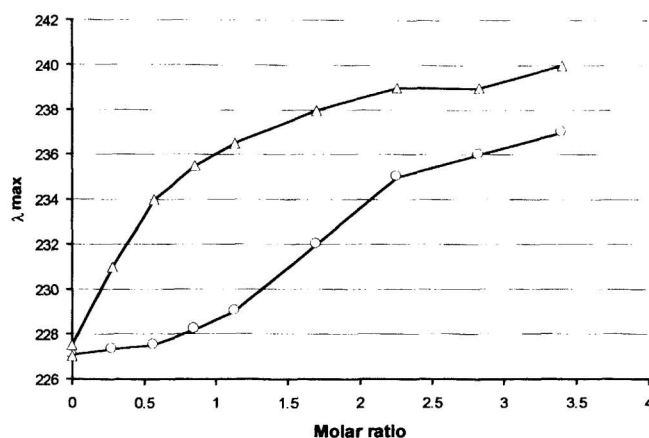


Fig. 2: Plot of λ_{max} of Ran solutions (2.166×10^{-4} M) in methanol (triangle) and Bis Tris buffer (circle) against the molar ratio of Fe^{3+} :Ran.

Further evidence on complexation came from the conductometric titration. The plot of conductivity against molar ratio (Fig. 3) of Ran solutions in Bis Tris buffer showed a break in linearity at a metal to Ran molar ratio of about 2:1 as compared to the blank of Fe^{3+} . Thus conductometric and spectroscopic titration were in good agreement.

For the metals Fe^{2+} , Al^{3+} , Pb^{2+} and Mg^{2+} no clear changes in the UV spectra were obtained when methanolic or buffered solutions (pH 6.5) of Ran were titrated with each metal. Typical spectra of the titration of Ran with ferrous sulfate in methanol are shown in Figure 4. However this may not necessarily indicate that Ran does not form complexes with these metal ions. Instead, complexes may form but without inducing UV spectral changes. Thus UV titrations were not considered conclusive in answering whether Ran interacts with these metals or not.

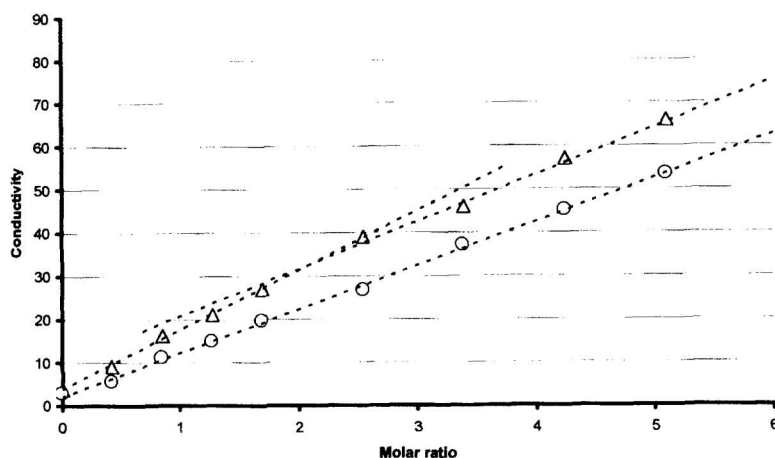


Fig.3: Plot of the conductivity of Ran solutions (in Bis Tris buffer) containing increasing concentrations of Ferric chloride (triangle) as compared to blank which are solutions containing increasing concentrations of ferric chloride alone(circle).

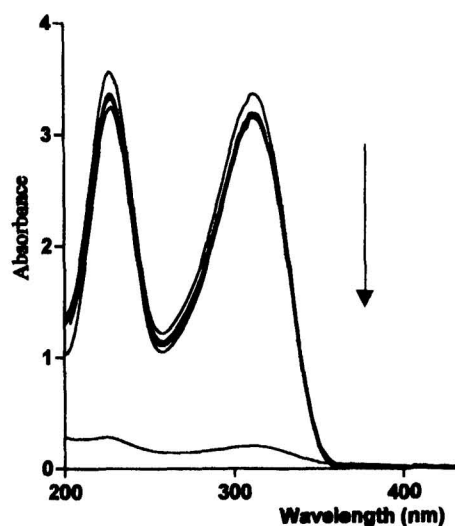


Fig. 4: Overlaid UV spectra of Ran solutions titrated with increasing concentrations of ferrous sulfate. The spectrum at the bottom is due to ferrous sulfate solution (blank). The arrow indicates the direction of increasing iron concentration.

The conductivity of Ran solutions (in Bis Tris buffer) with increasing concentrations of Fe^{2+} , Al^{3+} and Pb^{2+} was measured and plotted against the molar ratio of the metal to Ran (Fig. 5). The conductometric titration plots for Fe^{2+} and Pb^{2+} are shown in plate A and separate from the plots of Al^{3+} and Mg^{2+} (plate B) for clarity. Conductometric titrations provided a clear evidence of the complexation between Ran and each of Fe^{2+} , Al^{3+} and Pb^{2+} . The break point in each titration curve suggests a binding ratio of 1:1 in each case (Fig. 5). Interestingly, no indication of binding was evident in the case of magnesium. The suggested complex formation between aluminum and Ran may explain previous reports that Ran may affect the bioavailability of aluminum [15].

In the case of copper and nickel the complexation was investigated spectroscopically by monitoring the visible absorbance at the λ_{max} of the metals i.e. 800 nm. Ran has no absorption at 800 nm which made the detection of the complexation process easier. Titration of Ran solutions with copper sulfate and nickel chloride showed that the addition of Ran to the metal solution leads to a progressive hyperchromic shift at the λ_{max} of the metal (Fig. 6). This behavior which can also be noticed visually as a progressive change in the blue color is typical of complex formation more. Hyperchromic shift was observed in both methanol and aqueous buffer solutions for both copper and nickel although less marked with the latter.

For both metals methanol produced greater maximum change in the absorptivity at 800 nm, which suggest that methanol, is a preferred solvent for complexation. Binding isotherms for both metals in methanol and water were obtained by plotting the absorbance for each metal against the molar ratio of Ran to metal (Fig. 7).

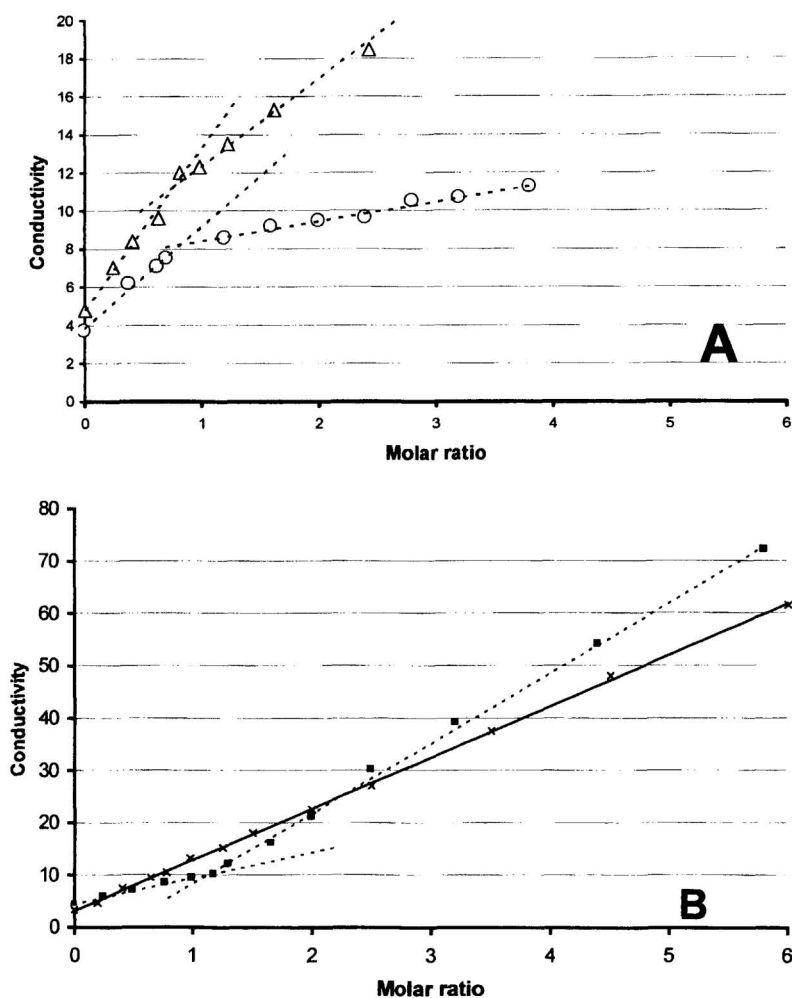


Fig.5: Plots of the conductivity of Ran solutions (in Bis Tris buffer) containing increasing concentrations of the metals against the molar ratio of metal to Ran. In A; Fe^{2+} (triangle), Pb^{2+} (circle) and in B Al^{3+} (square) and Mg^{2+} (cross).

The isotherms suggest the formation of 1:1 complexes between the metals and Ran. Binding of copper and nickel to Ran may have clinical significance in cases where copper sulfate is given as a drug [16-18] or when copper is in excess e.g. Wilson's disease [19].

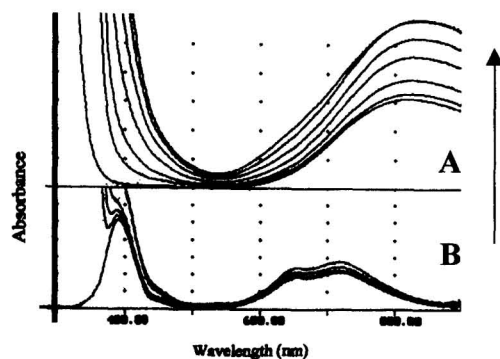


Fig. 6: Overlaid absorption spectra of copper sulfate (A) and nickel chloride (B) solutions titrated with Ran in methanol. Arrow indicates direction of increasing Ran concentration.

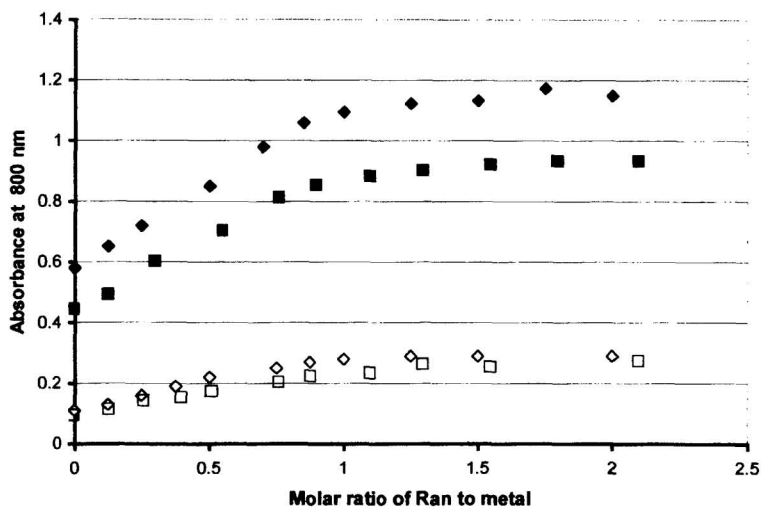


Fig. 7: Plot of absorbance at 800 nm for copper sulfate (diamond) and nickel chloride (square) solutions titrated with Ran in methanol (black) and in Tris buffer (empty). Note the linearity in the initial part of the curve.

Conclusion

Ran can form complexes with Fe^{2+} , Fe^{3+} , Al^{3+} , Cu^{2+} , Ni^{2+} and Pb^{2+} Metal Ions. Of potential practical clinical significance is the interaction of Ran with iron, aluminum and copper. Both ferrous sulfate and aluminum hydroxide are often prescribed to patients concomitantly with Ran to treat associated anemia or hyperacidity. In both cases interaction of Ran with the metals may results in the reduction of the effect of either medicaments. This may explain the frequent incidence of anemia developed in patients taking Ran for long time. The interaction of Ran with aluminum may explain the suggested decrease in bioavailability of Ran as a result of co-administration with aluminum containing antacids.

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