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Spectrophotometric investigation of famotidine-Pd(II) complex and its analytical application in drug analysis

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Abstract: By using different spectrophotometric methods, it was found that famotidine and palladium(II) ions form a complex, Pd(II) : famotidine = 1:1, which has an absorption maximum at 345 nm. The formation of the complex between famotidine and palladium(II) chloride in Britton–Robinson buffer solution in the pH range 2.23–8.50 was studied. The conditional stability constant of the complex at the optimum pH 2.62 and ionic strength 0.5 M was found to be $\log K' = 3.742 \pm 0.025$. The Beer's law was verified over the famotidine concentration range from $5\times10^{-5} - 6\times10^{-4}$ M. The proposed method was found to be suitable for accurate and sensitive analysis of famotidine both as the substance (*RSD* = 1.02–1.80 %) and its dosage forms (*RSD* = 1.75–1.83 %).

Keywords: famotidine, palladium(II) chloride, complexometry, spectrophotometry, drug determination.

INTRODUCTION

Famotidine, (*N'*-[aminosulfonyl]-3-[(2-[diaminomethyleneamino]-4-thiazolyl)methylthio]-propanamidine), is an antagonist of histamine at H_2-receptor sites and an effective inhibitor of gastric acid secretion introduced for the treatment of peptic ulcers and related disorders. Numerous analytical methods have been developed for the quantitative assay of famotidine, including spectrophotometry,[1–6] liquid chromatography,[7–10] and polarography.[11]

In previous investigations, a potentiometric method for the determination of famotidine in aqueous solutions and pharmaceutical dosage forms was developed.[12] Famotidine is titrated with a solution of palladium(II) chloride in Britton–Robinson buffer at pH 3.60, using a silver indicator electrode. A significant potential jump appears when the stoichiometric ratio of palladium(II) to famotidine is 1:1.

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Pd(II) and Pt(II) derivatives of famotidine have been synthesized and studied structurally. It was shown that the palladium complex is a monomer while the platinum complex forms a dimer.[13]

The present work is part of investigations of the complex formation of famotidine with palladium(II) ions and on its application to the assay of famotidine in pharmaceutical formulations.

EXPERIMENTAL

Apparatus

Spectrophotometric measurements were performed on a GBS (Australia), UV-VIS, model Cintra 20 double-beam spectrophotometer using matched 10 mm quartz cells. A radiometer PHM 62 standard pH meter, calibrated with standard buffer solutions, was used for pH-measurements.

Reagents

Famotidine standard substance (Alkaloid, Skopje) p.a. and palladium(II) chloride (p.a., Merck) were used. Famosan® tablets (Alkaloid, Skopje): 40 mg of famotidine/tablet. Lecidil® tablets (Zdravlje, Leskovac): 20 mg of famotidine/tablet. All other chemicals were of analytical-grade purity (Merck). Double-distilled water was used.

Solutions

A standard palladium(II) chloride solution (2.08×10^{-2} M) was prepared as described previously,[12] and then standardized gravimetrically.[14]

Britton–Robinson buffer solutions[15] covering the pH range 2.23–8.50 were prepared by mixing 0.04 M phosphoric, boric and acetic acid with the appropriate volume of 0.2 M sodium hydroxide and sufficient 2 M potassium chloride to bring the ionic strength to 0.2 M.

A standard solution of famotidine (5×10^{-3} M) was obtained by dissolving the corresponding amount of pure substance in 10^{-2} M NaOH.

Procedure for calibration curve

Palladium(II) chloride standard solution (0.50 ml) and potassium chloride (2.50 ml) were pipetted into a 10 ml volumetric flask and an aliquot (0.10–1.20 ml) of 5×10^{-3} M famotidine was added. The pH was adjusted by adding 5.00 ml of Britton–Robinson buffer pH 2.62 and the solution was diluted to volume with water. The absorbance at 345 nm was measured after 5 min against a reagent blank. All measurements were made at room temperature (25.0 ± 0.5 ºC).

Procedure for the determination of famotidine in pharmaceutical formulations

Twenty tablets were weighed and powdered.[16] The amount containing approximately as much as required for the preparation of 5×10^{-3} M of famotidine was weighed and dissolved in 5 ml 10^{-2} M NaOH. The thus prepared solution was filtered and the filtrate was made up to 50 ml with water. An aliquot (0.7 ml) of this solution was treated by the same procedure as described for the calibration curve.

RESULTS AND DISCUSSION

The properties of the complex

The reaction of famotidine (FAM) with palladium(II) chloride in the presence of potassium chloride was investigated over the pH range 2.23–8.50 in Britton–Robinson buffer solutions. The absorption spectra were recorded over the wavelength range 300–450 nm. It was found that famotidine with palladium(II) chloride formed a yel-

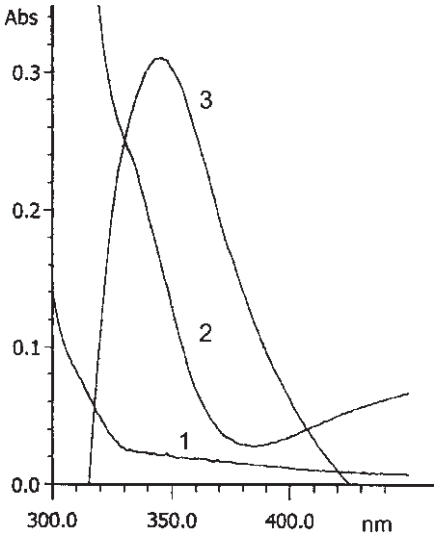

Fig. 1. Absorption spectra of famotidine (curve 1); palladium(II) chloride (curve 2); and complex (curve 3). c(FAM) = 4×10^{-4}; $c(PdCl_2)$ = 8×10^{-4} M; pH 2.62; μ = 0.50 M.

low, water-soluble complex. The complex gave an absorption peak at 345 nm (Fig. 1, curve 3), which was used for the analytical determination. Under the same conditions, famotidine does not absorb significantly over the investigation wavelength range (Fig. 1, curve 1). However, since palladium(II) chloride does absorb at the wavelength of maximum absorbance of the complex (Fig. 1, curve 2), all measurements were performed against a reagent blank with a correction for the cell blank as appropriate.

TABLE I. Conditional stability constant of the famotidine-palladium(II) complex*

Sommer's method			
log K'	SD	$S\bar{x}$	RSD/%
3.767 (N = 3)	0.0396	0.0228	1.05
Asmus's method			
log K'	A_{ext}	A_k	
3.717	0.105	0.095	

*Conditions: pH 2.62 ± 0.05; μ = 0.50 M; temperature = 25 ± 0.5 °C; SD = standard deviation; RSD = relative standard deviation

The pH of the reaction mixture had a considerable influence on the absorbance of the complex, except in the pH range 2.23–4.50, where the absorbance stays constant (Fig. 2); this fact indicates that in this pH range one type of complex is formed. With further increase of the pH, the solution becomes turbid.

An ivestigation of the effects of the palladium(II) chloride concentration on the formation of the famotidine-Pd(II) complex showed that least a two-fold mole ratio of reagent to analyte is necessary for maximum complex formation. The ionic strength (0.10–0.90 M) has little influence on the course of the reaction. Full color development

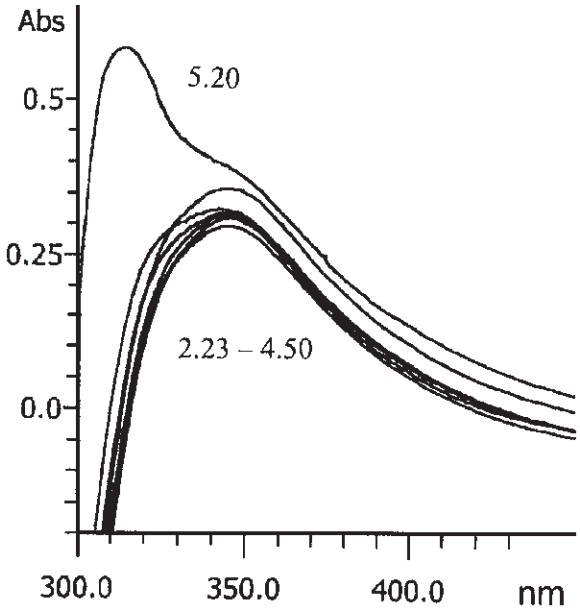

Fig. 2. The effect of pH on complex formation. c(FAM) = 4×10^{-4} M; c($PdCl_2$) = 8×10^{-4} M; μ = 0.50 M.

was observed after five minutes and the absorbance remained unchanged for up to 60 minutes.

The composition of the complex and conditional stability constant

The stoichiometric ratio of famotidine to palladium(II) chloride in the complex was determined by the Job method of equimolar solutions.[17,18] The curve displayed a maximum at a molar fraction of X_{max} = 0.5, which indicated the formation of a 1 : 1 complex (Fig. 3). By using the mole ratio method,[19] at constant famotidine concentra-

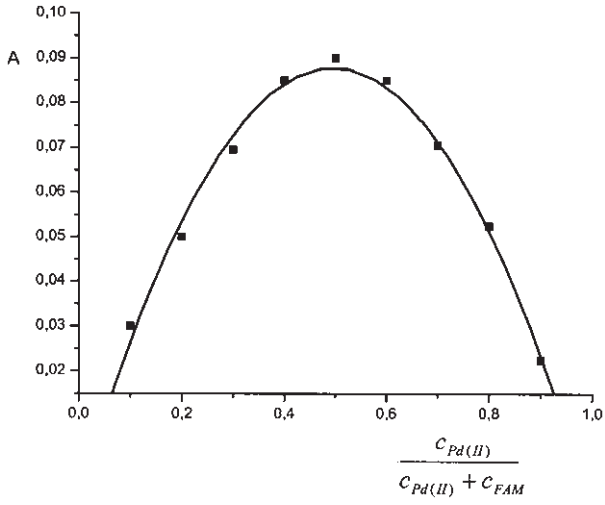

Fig. 3. Job's curve of equimolar solutions at 345 nm. c(Pd(II)) + c(FAM) = 3×10^{-4} M; pH 2.62; μ = 0.50 M.

tion (2.5×10^{-4} M) and varying palladium(II) concentration $6.25\times10^{-5} – 7.5\times10^{-4}$ M, a sharp band was observed at the mole ratio famotidine : Pd(II) = 1 : 1 (Fig. 4). The results obtained by this method confirmed that the mole ratio famotidine : Pd(II) in the complex was 1 : 1.

By applying Sommer's[20] and Asmus's[21] methods, on the basis of data obtained with Job's curve of equimolar solutions (Fig. 3), the conditional stability constant has been determined (Table I). The mean values of log *K'* obtained by two different methods (log *K'* = 3.742 ± 0.025) are in good agreement.

Quantification and application to dosage forms

A linear relationship between the absorbance and the concentration of famotidine was obtained over the range $5\times10^{-5} – 6\times10^{-4}$ M. The regression equation was $y = 0.20832x – 0.00288$ and the correlation coefficient $r = 0.999$ ($n = 7$), indicating good linearity. The detection limit of the method was found to be 3.37 μg ml^{-1}.

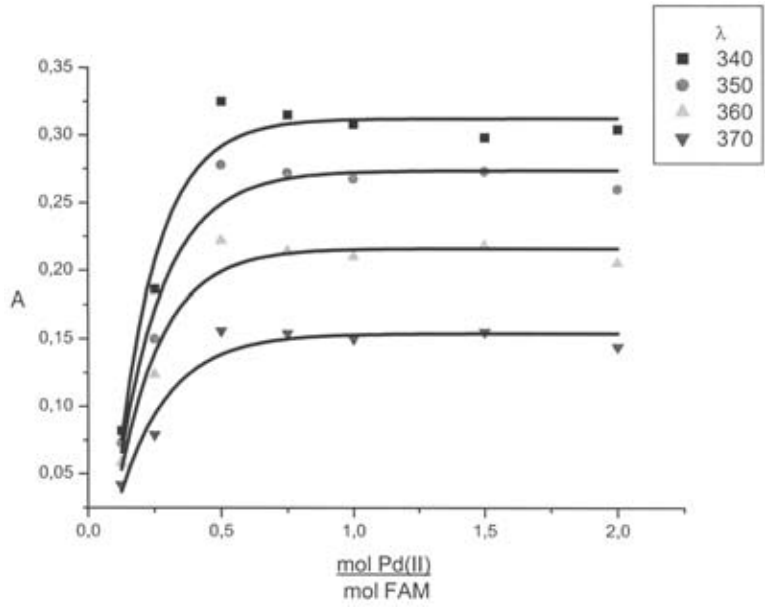

Fig. 4. Mole ratio method. c(FAM) = 2.5×10^{-4} M; c(Pd(II)) = $6.25\times10^{-5} – 7.5\times10^{-4}$ M.

The reliability of the method was checked at three different concentrations and the results are summarized in Table II. The relative standard deviation varied from 1.02 to 1.80 % for concentrations of famotidine 0.506–1.181 mg.

Analysis of pharmaceuticals

When the proposed method was applied to the determination of famotidine in Famosan® and Lecidil® tablets (Table II), the relative standard deviation varied from 1.75–1.83 %, which indicates the applicability of the assay to dosage form. The values

of the *RSD* were in almost the same range as for the pure substance showing that excipients in the tablets did not interfere with the absorbance values even if present in large excess.

TABLE II. Spectrophotometric determination of famotidine in the pure form and in tablets

Taken/mg	Found/mg	*SD*	$S\bar{x}$	*RSD*/%
0.506	0.506	0.0093	0.0035	1.80
0.844	0.845	0.0092	0.0035	1.09
1.181	1.181	0.0121	0.0045	1.02
Lecidil®; 20 mg/tabl	19.75	0.3624	0.137	1.83
Famosan®; 40 mg/tabl	39.76	0.6986	0.264	1.75

($N = 7$)

It is evident that the proposed spectrophotometric method, which uses palladium(II) chloride as the analytical reagent, is rapid and simple as well as accurate and sensitive, and can be successfully applied to the determination of famotidine both as the substance and its dosage forms.

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ИЗВОД

СПЕКТРОФОТОМЕТРИЈСКО ИСПИТИВАЊЕ ФАМОТИДИН-Pd(II) КОМПЛЕКСА И ЊЕГОВА ПРИМЕНА У АНАЛИЗИ ЛЕКОВА

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Применом различитих спектрофотометријских метода нађено је да фамотидин са паладијум(II) јоном гради комплекс састава 1 : 1, са максимумом апсорбанције на 345 нм. Реакција фамотидина и паладијум(II) јона испитивана је у Britton–Robinson-овим пуферима, у pH области 2,23–8,50. Одређена је релативна константа стабилности комплекса која на pH 2,62 и јонској сили 0,50 M и на собној температури износи log K' = 3,742 ± 0,025. Концентрација фамотидина од $5 \times 10^{-5} - 6 \times 10^{-4}$ M следи Beer-ов закон. Предложена метода је погодна за брзо и тачно одређивање фамотидина у чистој супстанци (*RSD* = 1,02 – 1,80 %) и у дозираним облицима (*RSD* = 1,75 – 1,83 %).

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