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Short communication

Extractional-spectrophotometric determination of famotidine in pharmaceutical formulations

Ali Z. Abu Zuhri [a,*], Raqi M. Shubietah [b], Ghassan M. Badah [a]

[a] *Chemistry Department, Faculty of Science, An-Najah National University, P.O. Box 707, Nablus, Palestine*
[b] *Faculty of Pharmacy, An-Najah National University, Nablus, Palestine*

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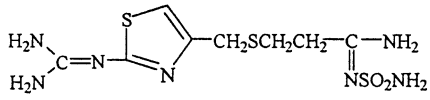
1. Introduction

Famotidine (I), propanimid amide, N1-(aminosulfonyl)-3- [[[2-[(diaminomethylene) amino-4-thiazolyl] methyl] thio] is a H_2 receptor blocker which is more potent and has a longer duration of effect than either cimitidine [1,2] or ranitidine. Campoli-Richards and Clissold [3] found that therapeutic trials have shown that 40 mg daily dose of famotidine either taken once or divided into two equal doses may be an effective alternative to standard doses of cimitidine.



(I)

A non-aqueous titration method has been reported in USPXXII for the assay of the raw material in addition to a HPLC method for determination of the drug in tablets [4]. HPLC [5–8] have been applied for the analysis of microquantities (nano-levels) of the drug in biological samples. Some of these methods involve several manipulation steps, which are not simple for routine analysis of pharmaceutical formulations and need sophisticated instruments. On the other hand, a few spectrophotometric [9–11] and polarographic [12,13] methods have been reported for famotidine determination as a drug substance or in commercial dosage forms.

This paper describes the formation of a 1:1 ion-pair complex between famotidine and each of bromocresol green (BCG) and bromothymol blue (BTB) in order to develop a new spectrophotometric method for the drug determination. These results showed that the suggested method may be suitable for the routine quality control of famotidine in pharmaceutical formulations.

* Corresponding author. Tel.: +972-923-70042; fax: +972-923-87982.
E-mail address: abuzuhri@najah.edu (A.Z. Abu Zuhri)

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2. Experimental

2.1. Apparatus

All spectral and absorbance measurements were made on a UNICAM, UV–VIS double-beam spectrophotometer (UV-2) with 10 mm matched quartz cells. The pH measurements were made by using a combined glass–calomel electrode attached to a pH-meter (Hanna HI 8424).

2.2. Reagents and solutions

All chemicals used were of analytical reagent grade and doubly distilled deionized water was used throughout. Famotidine was obtained from Jerusalem pharmaceutical company and its purity was confirmed by HPLC. Stock standard solution of famotidine (1.0×10^{-3} M) was prepared by dissolving 33.70 mg in 1–2 ml of 1.2 M HCl, diluted with water and stored in the dark under refrigeration to avoid possible decomposition. Bromocresol green, BCG, bromothymol blue, BTB and dichloromethane were obtained from Aldrich. BCG and BTB solutions (10^{-3} M) were prepared by dissolving the appropriate amounts in 2 ml of 0.1 M sodium hydroxide and 20 ml of ethanol (96%) and diluting with doubly distilled water to 100 ml. Britton–Robinson buffer solutions were prepared from phosphoric, boric and acetic acids and sodium hydroxide [14].

2.3. Procedure

An aliquot of standard solution of famotidine was transferred into a 100 ml separatory funnel. A 5 ml of buffer solution of the desired pH was followed with either 5 ml of 1.0×10^{-3} M of BCG and BTB, respectively, then with 20 ml of dichloromethane. The mixture was shaken vigorously for 1 min. The yellow dichloromethane phase was separated from the aqueous phase, dried with anhydrous sodium sulfate and completed to 25 ml with dichloromethane.

The absorbance was measured at 420 nm for BCG and BTB, against a reagent blank prepared similarly but without the addition of famotidine. A calibration plot of concentration against absorbance was constructed and used for subsequent determination.

2.4. Determination of famotidine in tablets

The content of two '10' tablets containing 20 and 40 mg famotidine were weighed, finely powdered and mixed. A portion of the powder equivalent to either 20 or 40 mg tablet was accurately weighed and dissolved in 100 ml of water. Aliquot portions of this solution were analyzed by the recommended procedure.

3. Results and discussion

3.1. Absorption Spectrum

Famotidine reacts with BCG and BTB to form an ion-pair complex. Extraction of the yellow ion-pair complex from the aqueous reaction medium with dichloromethane was investigated. The ion-pair formed was found to be quantitatively extracted into dichloromethane and its absorption spectrum (Fig. 1) displays an absorption peak at 420 nm with molar absorptivities of 5.0×10^3 and 1.2×10^4 L mol^{-1} cm^{-1} for BCG and BTB, respectively. Neither famotidine nor BCG and BTB alone exhibit any significant absorption at 420 nm under the same conditions. On the other hand, the absorbance of the repeated dichloromethane extract of the remainder of the reaction mixture and that of blank reagent were insignificant.

3.2. Effect of pH

The extraction of the drug was carried out over the pH range 2–8 in the presence of BCG or BTB. The results indicate that the quantitative extraction of famotidine is optimum at pH 3.7 and 6.2 in presence of BCG and BTB, respectively. Hence all of the extractions were carried out at these pHs. On the other hand, it was found that famotidine solution is highly stable over a wide range of pH [11,13].

To prove the quantitative extration of famotidine, a specific amount of drug is directly

measured using the recommended procedure. The extraction recovery percentage (%E) was calculated from the resulting absorbance values using the previously plotted calibration graph.

3.3. Composition and stability of complex

The composition of the famotidine-BCG or BTB ion-pair complex was determined, at the optimum pH, by applying the molar ratio and the continuos variation method. The results indicated that the components of the ion-pair complex react in a 1:1 stochiometric ratio. The effect of time on the absorption maxima at 420 nm was studied for the famotidine solution prepared as described in the general procedure. The results obtained showed that full colour development was attained instantly and the intensity of the colour stayed constant for at least 48 h after preparation of the sample.

The effect of temperature on the stability of the ion-pair complexes was studied within the temperature range 15–35°C. No detectable change in absorbance was obtained, therefore, all the measurements were done at room temperature (23 ± 1°C).

3.4. Effect of equilibration time

The equilibration time for extraction of the two complexes was varied between 15 s and 10 min. There is no adverse effect on the equilibration time up to 10 min. It was observed that absorbance remained constant, when the shaking period was 45 s or more. Therefore an equilibration time of 1 min was chosen in order to ensure the complete extraction.

3.5. Effect of reagent concentration

The effect of increasing BCG and BTB concentration, at constant famotidine concentration, shows a constant and maximum colour intensity in the presence of a 3-fold molar excess of the reagent. On the other hand, the separation of two layers takes a long time in the presence of a high dye concentration. Therefore, a 3-fold excess of BCG or BTB reagent was preferred throughout the experiment.

3.6. Choice of organic solvent

Various organic solvents were examined for extraction of the ion-pair complex. The extraction

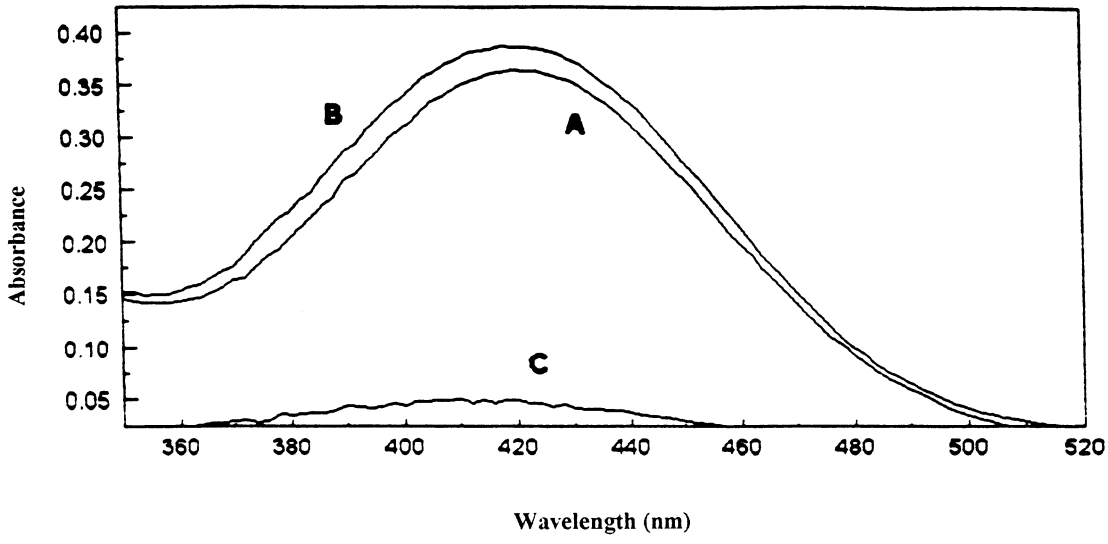

Fig. 1. Absorption spectra of (A) famotidine-BCG against a reagent blank, (B) famotidine-BTB against a reagent blank and (C) the reagent blank (containing BCG or BTB) against dichloromethane.

Table 1
Effect of solvent, famotidine = 6.74 μg

Solvent	%$E^a \pm$ S.D.	
	BCG method	BTB method
Dichloromethane	99.8 ± 1.6	99.5 ± 2.1
Chloroform	92.1 ± 2.4	90.8 ± 3.0
Toluene	30.5 ± 3.9	34.1 ± 2.8
Carbon tetrachloride	14.6 ± 5.8	18.1 ± 4.5
Benzene	52.2 ± 6.3	55.4 ± 5.2
Diethylether	12.5 ± 4.2	16.6 ± 3.1

[a] Percent of extraction.

was found to be incomplete in all the solvents except dichloromethane (Table 1).

3.7. Effect of excipients

No significant interference was observed from the excipients commonly used in the famotidine formulations, such as talc powder, starch, lactose, glucose and magnesium stearate. It was found that the above excipients at levels as high as 500-fold excess had no effect on the absorbance of the ion-pair complexes.

3.8. Calibration curve

Under the optimum experimental conditions a calibration curve was made of series of standard solutions of famotidine complexed with BCG or BTB. The absorbance was measured at 420 nm against a blank prepared similarly without the drug following the recommended procedure. A linear graph was obtained by measuring the absorbance of the solution as a function of the famotidine concentration. The points on the standard calibration curve represent the outcome of five determinations. The calibration curve was used for subsequent determination of unknown famotidine samples. Beer's law was valid over the concentration range 2.0–23.6 and 0.7–8.1 μg ml^{-1} for the BCG and BTB methods, respectively. The detection limits were found to be 2.0

Table 2
Analytical characteristic for the ion-pair formation method

Parameter	Famotidine-BCG	Famotidine-BTB
λ_{max} (nm)	420	420
Recommended optimum pH	3.7	6.2
Shaking time (s)	60	60
Concentration of dyes (M)	1.2×10^{-3}	4.0×10^{-5}
Detection limits (μg ml^{-1})	2.0	0.7
Beer's law limits (μg ml^{-1})	2.0–23.6	0.7–8.1
Molar absorptivity ε (l mol^{-1} cm^{-1})	5.0×10^3	1.2×10^4
Correlation coefficient	0.9998	0.9985
Intercept	0.012	0.046
Slope (A vs μg ml^{-1})	0.065	0.094

Table 3
Spectrophotometric determination of famotidine in pure form

Taken (μg)	Found[a] (μg)					
	BCG method	Recovery (%)	RSD (%)	BTB method	Recovery (%)	RSD (%)
3.37	3.48	103.5	4.3	3.43	101.7	2.3
6.74	6.81	101.0	2.6	6.77	100.4	1.6
13.48	13.82	102.5	1.1	[b]	[b]	[b]
20.22	20.28	100.3	2.3	[b]	[b]	[b]

[a] Average of five measurements.
[b] Out of linear range of Beer's law.

Table 4
Determination of famotidine in some pharmaceutical formulations by proposed and reference procedures

Drug (trade name)	Labelled amount (mg)	BCG method			BTB method			Official method		
		Found (mg)[a]	Recovery (%)	RSD (%)	Found (mg)[a]	Recovery (%)	RSD %	Found (mg)[a]	Recovery (%)	RSD (%)
Famodine[b]	20.0	18.9	94.7	2.5	18.6	93.1	1.8	19.7	98.4	2.2
Famodine[b]	40.0	40.0	100.0	3.4	37.9	94.8	2.2	41.2	103.0	4.3
Famo[c]	20.0	19.4	97.1	1.8	19.0	95.1	2.8	19.6	97.9	3.6
Famo[c]	40.0	39.4	98.5	1.6	39.5	98.7	3.1	37.4	93.6	2.1

[a] Average of five measurements.
[b] Jerusalem Pharmaceutical Co., Palestine.
[c] CTS, Chemical Industries Ltd, Israel.

Table 5
Comparison of the proposed method with existing spectrophotometric methods for the determination of famotidine in pharmaceutical formulations

Reagent	λ_{max} (nm)	Linear range (μg ml^{-1})	Molar absorptivity (l mol^{-1} cm^{-1})	Application	Ref.
Methanol	288	5–15	–	Drug formulations	[9]
Chloranil	458	50–500	0.67×10^3	Drug formulations	[10]
DDQ[a]	460	40–450	0.82×10^3	Drug formulations	[10]
DCNP[b]	425	10–100	3.7×10^3	Drug formulations	[10]
SNP[c]	498	50–500	5.9×10^2	Drug formulations	[11]
BCG	420	2–23.6	5.0×10^3	Drug formulations	This work
BTB	420	0.7–8.1	1.2×10^4	Drug formulations	This work

[a] DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone.
[b] DCNP = 2,4-Dichloro-6-nitrophenol.
[c] SNP = Sodium nitroprusside.

and 0.7 μg ml^{-1} for BCG and BTB, respectively. Beer's law was given by the equations $y = 0.012 + 0.065x$ and $y = 0.046 + 0.094x$ for the BCG and BTB methods, respectively. The spectral data for the reaction between famotidine and each reagent, as well as, characteristics of calibration curve are listed in Table 2. To check the reproducibility of the method, determinations were carried out at different concentrations of famotidine. The RSD% and recovery of five determinations are listed in Table 3.

3.9. Analytical applications

The applicability of the methods for the determination of famotidine in dosage forms was examined by analysing a famodine 20 and 40 (Jerusalem Pharmaceutical Co, Palestine), and famo 20 and 40 (CTS, Chemical Industries Ltd, Israel). The average recovery of five determinations was found to be 97.6, 95.4 and 98.2% for BCG, BTB and the official method, respectively. Table 4 shows that the results are accurate, reproducible, and comparable favourably with the official method. The proposed methods can be applied for the analysis of famotidine in pharmaceutical formulations.

3.10. Comparison with other spectrophotometric methods

The suggested methods for determination of famotidine in pharmaceutical formulations were compared favourably with other spectrophotometric methods (Table 5). It was found that the suggested methods have the advantages of high sensitivity ($\varepsilon = 1.2\times10^4$ l mol^{-1} cm^{-1} for the BTB method), fast response and direct application of drug samples without prior separation or treatment. On the other hand, the proposed methods are simple and reproducible (RSD = 1.1–4.3% and 1.6–3.4% for pure and dosage forms, respectively), using the BCG method. The proposed methods can analyse the famotidine in its pharmaceutical formulations without interference from excipients.

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