International Journal of Pharmaceutics, 102 (1994) 271–274

© 1994 Elsevier Science Publishers B.V. All rights reserved 0378-5173/94/$07.00

IJP 03382

Reversed-phase high-performance liquid chromatographic and derivative UV spectrophotometric determination of famotidine in pharmaceutical preparations

G. Carlucci [a], P. Mazzeo [a], C. Vetuschi [b] and E. Di Giuseppe [a]

[a] *Dipartimento di Chimica, Ingegneria Chimica e Materiali dell'Università dell'Aquila, Via Assergi 6, 67100 L'Aquila (Italy) and* [b] *Dipartimento Farmaco-Chimico, Università di Bari, Via E. Orabona 4, 70126 Bari (Italy)*

(Received 23 June 1993)
(Accepted 21 July 1993)

Key words: Famotidine; Pharmaceutical form; Reversed-phase HPLC; Derivative UV spectrophotometry

Summary

A method for the determination of famotidine in tablets and vials is described. The procedure is based on the use of the reversed-phase high-performance liquid chromatography, and of the second-derivative ultraviolet spectra, by utilizing the linear relationship between drug concentration and derivative peak amplitude. The minimum concentration detectable by derivative spectrophotometry was 0.5 μg/ml, and by HPLC 0.1 μg/ml. The relative standard deviations observed were approx. 1.5% for derivative spectrophotometry, and 1.2% for HPLC. The proposed methods, which give thoroughly comparable data, are simple and rapid, and allow one to obtain precise and accurate results.

Famotidine is a specific histamine H_2-receptor antagonist, which has been proved to be highly effective and useful in the treatment of peptic ulcer (Ryan, 1984; Campoli-Richards et al., 1986). Its chemical name is 3-[[[2-[(aminoiminomethyl) amino]-4-thiazolyl]methyl]thio]-*N*-(aminosulphonyl)propanimidamide (structure shown in Scheme 1).

Several high-performance liquid chromatographic (HPLC) procedures have been reported for the determination of famotidine in biological fluids (Vincek et al., 1985; Carlucci et al., 1988; Rahman and Hoffman, 1988; Cvitkovic et al., 1991;; Wanwimolruk et al., 1991) and in pharmaceutical formulations (Biffar et al., 1986; Ficarra et al., 1987). Also, two spectrophotometric methods have been described for the analysis of the drug in pharmaceutical forms (Fawzy, 1992; Kamath et al., 1992).

This paper reports a simple and fast method for the determination of famotidine in pharmaceutical formulations by derivative UV spectrophotometry and HPLC.

Famotidine was kindly supplied by Merck Sharp & Dohme Italia (Rome, Italy). HPLC grade acetonitrile and methanol were obtained from Farmitalia-Carlo Erba (Milan, Italy). All other chemicals (analytical grade) were purchased from Fluka Chemie (Buchs, Switzerland). Water was purified and deionized using a Milli-Q ion ex-

Correspondence to: G. Carlucci, Dipartimento di Chimica, Ingegneria Chimica e Materiali dell'Università dell'Aquila, Via Assergi 6, 67100 L'Aquila, Italy.

change filtration system (Millipore, Bedford, MA, U.S.A.).

Water was filtered through WCN 0.45 μm filters, while acetonitrile was filtered through WTP 0.5 μm filters (Whatman, Maidstone, U.K.).

The chromatographic apparatus (Waters Associates, Milford, MA, U.S.A.) consisted of a model 510 solvent delivery system, and a model 484 spectrophotometric detector connected to a model HP-3396-II integrator (Hewlett-Packard, Rome, Italy). A model 7125 sample injector (Rheodyne, Cotati, CA, U.S.A.) equipped with a 20 μl loop was used.

Separation was performed on a reversed-phase Viosfer LC-RP-18 (250 × 4.6 mm, 5 μm particle size) column (Violet, Rome, Italy). The mobile phase consisted of a mixture of 1% (v/v) orthophosphoric acid-acetonitrile (10:90 v/v). The mobile phase was prepared daily, filtered, sonicated before use, and delivered at a flow rate of 1.5 ml min^{-1}. The detector wavelength was set at 268 nm.

A Perkin-Elmer model Lambda 5 UV-Vis spectrophotometer was used. Derivative conditions were as follows: scan speed, 60 nm min^{-1}; spectral slit width, 2 nm; $\Delta\lambda$, 6 nm.

A stock solution of famotidine (1.0 mg ml^{-1}) was prepared in methanol, kept at −20°C and brought to room temperature when required.

Famotidine was found to be stable in methanol for at least 1 week at −20°C.

Standard solutions for HPLC were prepared with methanol by varying the concentration of famotidine in the range 0.2–10 μg ml^{-1}, and maintaining the concentration of methyl-4-hydroxybenzoate (internal standard) at a constant level of 2 μg ml^{-1}. Standard solutions for derivative spectrophotometry were prepared in methanol with concentrations of the drug in the range 1–20 μg ml^{-1}.

The calibration curve for HPLC analysis was constructed by plotting the peak area ratio of the drug to internal standard against the drug concentration. The calibration curve for derivative spectrophotometry was obtained by plotting vs the drug concentration the peak-trough amplitude in the second-derivative UV spectrum between 268 and 290 nm.

The equations, obtained through regressional analysis of data for the above standard solutions (each datum average of a minimum number of five determinations), were:
(a) For HPLC

$$y = 0.01x + 0.0015 \ (r = 0.999)$$

where y is the peak area ratio in the arbitrary units of the HP-3396-II system used and x denotes the drug concentration (μg ml^{-1});
(b) For derivative spectrophotometry

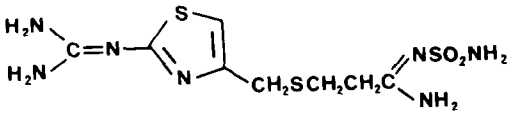
$$y = 0.1x + 0.00999 \ (r = 0.9999)$$

where y is the peak-trough amplitude between 268 and 290 nm in the second-derivative spectrum, measured on the scale ± 2.0 and x denotes the drug concentration (μg ml^{-1}).

Five tablets were crushed and combined. An amount of material was accurately weighed, added with methanol, sonicated for 5 min, filtered, transferred in a 100 ml calibrated flask, and completed to volume with methanol. The solution obtained was diluted with methanol so as to obtain a concentration of famotidine in the range of linearity previously determined, and analyzed by derivative spectrophotometry by using the above calibration equation. HPLC analysis was carried out on an analogous solution, added with the internal standard (2 μg ml^{-1}), by using the corresponding calibration curve.

The contents of five vials were combined. A volume of solution was accurately measured, diluted with methanol, filtered, transferred in a 100 ml calibrated flask, and completed to volume with methanol. The solution obtained was diluted with methanol so as to obtain a concentration of famotidine in the range of linearity previously determined, and analysed by derivative spectrophotometry by using the above calibration equation. HPLC analysis was carried out on an analogous solution added with internal standard (2 μg ml^{-1}), by using the corresponding calibration curve.

Fig. 2 shows an example of derivative ultraviolet spectra of the examined pharmaceutical forms. Fig. 3 shows a typical HPLC chromatogram of the



Scheme. 1. Chemical structure of famotidine.

two pharmaceutical formulations analysed; the retention times (min) were 3.2 (famotidine) and 4.5 (internal standard).

The lower detection limit of the drug, defined as 3-times the level of the baseline noise, was 0.1 μg ml^{-1} for HPLC analysis, and 0.5 μg ml^{-1} for

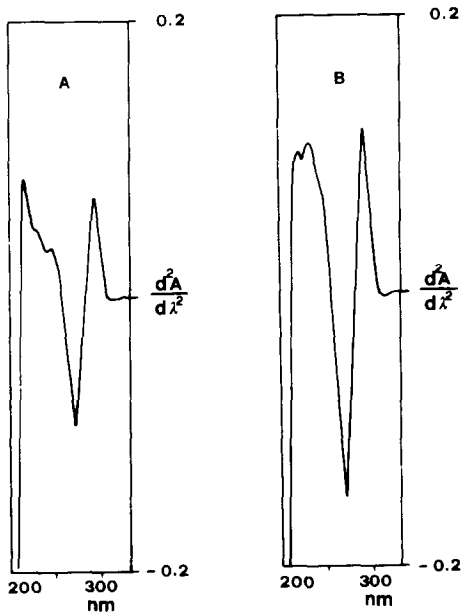


Fig. 2. Second-derivative ultraviolet spectra of: (A) tablets; (B) vials.

TABLE 1

Results obtained in the analysis of famotidine in pharmaceutical forms

Sample	Nominal (mg)	Found (DS) (mg)	Found (HPLC) (mg)
Tablets	40	39.6	39.8
Vials	20	19.8	20

DS, derivative spectrophotometry. The data are the average of five determinations for each sample. Relative standard deviations: approx. 1.5% for derivative spectrophotometry and 1.2% for HPLC.

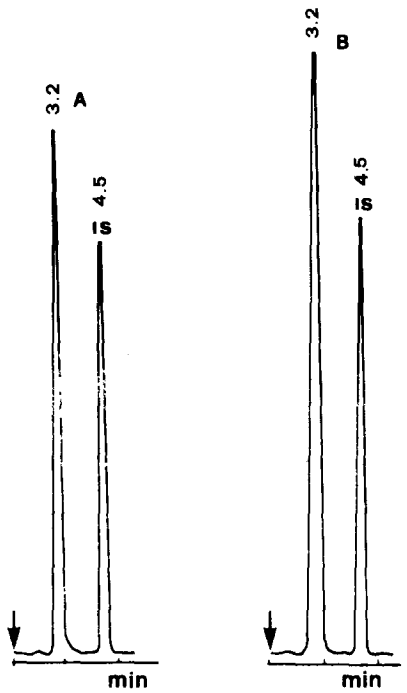


Fig. 3. HPLC chromatograms of: (A) tablets; (B) vials.

the spectrophotometric procedure.

The relative standard deviation observed was approx. 1.2% for HPLC analysis and 1.5% for the derivative spectrophotometric method.

In Table 1 the results obtained in the analysis of the two pharmaceutical forms are summarized.

The reported methods for the determination of famotidine in pharmaceutical formulations are very simple and rapid, and give accurate and precise results. The data obtained by both procedures are throughly comparable.

Acknowledgements

This research was supported by a grant from the Ministero della Università e della Ricerca Scientifica e Tecnologica (quota 40%) and the Consiglio Nazionale delle Ricerche.

References

Biffar, S.E. and Mazzo, D.J., Reversed-phase determination of famotidine, potential degradates, and preservatives in

pharmaceutical formulations by high-performance liquid chromatography using silica as a stationary phase. *J. Chromatogr.*, 363 (1986) 243–249.

Campoli-Richards, D.M. and Clissold, S.P., Famotidine – Pharmacodynamic and pharmacokinetic properties and a preliminary review of its therapeutic use in peptic ulcer disease and Zollinger-Ellison syndrome. *Drugs*, 32 (1986) 197–221.

Carlucci, G., Biordi, L., Napolitano, T. and Bologna, M., Determination of famotidine in plasma, urine and gastric juice by high-performance liquid chromatography using disposable solid-phase extraction columns. *J. Pharm. Biomed. Anal.*, 6 (1988) 515–519.

Cvitkovic, L., Zupancic-Kralj, L. and Marsel. J., Determination of famotidine in human plasma and urine by high-performance liquid chromatography. *J. Pharm. Biomed. Anal.*, 9 (1991)207–210.

Fawzy, A.E.-Y., Second-derivative spectrophotometric determination of famotidine. *Spectrosc. Lett.*, 25 (1992) 1011–1021.

Ficarra, R., Ficarra, P. and Calabrò, M.L., Cromatografia liquida nell'analisi farmaceutica: determinazione nelle compresse della famotidina, nuovo H_2-antagonista. *Il Farm. Ed. Pr.*, 42 (1987) 307–312.

Kamath, B.V., Shivram, K. and Vangani, S., Spectrophotometric determination of famotidine by charge-transfer complexation. *Anal. Lett.*, 25 (1992) 2239–47.

Rahman, A. and Hoffman, N.E., High-performance liquid chromatographic determination of famotidine in urine. *J. Chromatogr.*, 428 (1988) 395–401.

Ryan, R., Clinical pharmacology of famotidine: summary of data from the United States. *Ital. J. Gastroenterol.*, 16 (1984) 171–174.

Vincek, W.C., Constanzer., M.L., Hessey, G.A. and Bayne, W.F., Analytical method for the quantification of famotidine, an H_2-receptor blocker, in plasma and urine. *J. Chromatogr.*, 338 (1985) 438–443.

Wanwimolruk, S., Zoest, A.R., Wanwimolruk. S.Z. and Hung, C.T., Sensitive high-performance liquid chromatographic determination of famotidine in plasma. Application to pharmacokinetic study. *J. Chromatogr.*, 572 (1991) 227–238.