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Short Communication

High-performance liquid chromatography of ranitidine in pharmaceuticals

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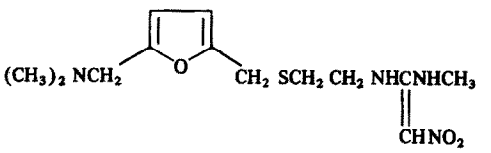
Introduction

The H_2-receptor antagonists such as metiamide and cimetidine are structurally based on the imidazole nucleus of histamine, and have been shown to be potent inhibitors of gastric acid secretion, and to provide symptomatic relief and healing of peptic ulcers [1]. Ranitidine (Glaxo–Duncan) (**1**), which differs structurally from earlier H_2-receptor antagonists in having a furanyl nucleus, inhibits nocturnal gastric acid secretion and is four times more potent than cimetidine in inhibiting pentagastrin-stimulated gastric acid secretion in humans [2].



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A high-performance liquid chromatographic (HPLC) method for ranitidine determination in plasma and urine was sensitive and free from interference by endogenous plasma constituents and metabolites [3]. This report describes a rapid HPLC method for the determination of ranitidine in pharmaceuticals.

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Experimental

Instrumentation

Assays were carried out using a constant-flow high-performance liquid chromatograph consisting of a solvent delivery system (Perkin–Elmer series 3B), and injector (Rheodyne Inc., model 7105), a column oven (Perkin–Elmer model LC-100), a variable-wavelength UV absorbance detector (Perkin–Elmer LC-75 with autocontrol), operating at 221 nm, and an integrator fitted with a printer–plotter (Perkin–Elmer Sigma 10B Chromatography Data Station). The column (25 cm long × 0.26 cm i.d., Perkin–Elmer) contained 10 μm HC-ODS SIL-Xl as the stationary phase.

Reagents and chemicals

Powdered samples of ranitidine hydrochloride, benzocaine (Farmitalia — Carlo Erba Spa, Milan, Italy) and ethyl-*p*-aminobenzoate were used in the analytical procedure and in the preparation of standard curves. These and all other chemicals and solvents (E.G. Merck, Darmstadt, Federal Republic of Germany) were analytical reagent grade. The mobile phase, consisting of methanol-distilled water (90:10 v/v) was prepared daily. The internal standard was a solution of 8.25 mg/100 ml ethyl-*p*-aminobenzoate in methanol.

Solution standards for calibration curve

A stock solution of ranitidine was prepared in methanol (15.5 mg/100 ml). Aliquots of 5, 10, 15, 20 and 25 ml of the stock solution were placed in 100 ml volumetric flasks. Five millilitres of the internal standard stock solution in methanol was pipetted into each flask, and the solution brought to volume with methanol. The five concentrations of drug were subjected to a linear regression analysis, and the slope and intercept were calculated.

Solution standard

A solution of ranitidine (62 mg/100 ml) was prepared in methanol, 5 ml of the internal standard stock solution in methanol was pipetted into a flask, and the solution was brought to volume with methanol.

All stock solutions and sample preparations were made and used within 24 h. When the solutions were stored overnight, they were kept at 4°C in the dark.

Conditions for chromatographic separation and quantification

The mobile phase was pumped through the ODS column at a flow rate of 2 ml/min (2000 psig) at 50°C until a stable baseline was obtained. For the standard solutions and analysis of ranitidine in pharmaceuticals, replicate 1 μl injections of each solution were made using a 10 μl Hamilton syringe. Solute concentrations were measured by digital integration of the peak area.

Injectable formulation assay

Exactly 2, 3, 4 and 5 ml of ranitidine injections (A. Menarini, Firenze) were transferred to four 100 ml volumetric flasks and, after addition of 5 ml of internal standard solution, brought to volume with distilled water.

Tablet formulation assay

Five tablets (A. Menarini, Firenze; 150 mg/tablet of ranitidine base) were triturated to a fine powder. Accurately weighed aliquots equivalent to 33, 66, 89, 130 and 220 mg

were transferred to 50 ml volumetric flasks. Following addition of methanol (35 ml) the flasks were shaken for 30 min and the resulting suspensions were centrifuged at 3000 rpm. These suspensions were filtered through a 0.25 μm Millipore filter and the residues were washed with three 5 ml portions of water. The filtrates and washings were collected in five 100 ml volumetric flasks each containing 5 ml of the internal standard solution. The flasks were brought to volume with methanol and a 1 μl aliquot was injected into the liquid chromatograph.

When the ratio of the ranitidine peak height and the internal standard peak height was constant the standard and test samples were injected.

Table 1
HPLC analysis of ranitidine (pure drug)

Sample	Calculated (mg)	Found (mg)	Recovery (%)
1	15.50	15.48	99.9
2	31.00	31.30	100.9
3	62.00	61.97	99.9
4	77.50	77.35	99.8
5	108.50	108.26	99.7

Mean recovery, 100.04; standard deviation, 0.488; RSD %, 0.49.

Results

Preliminary studies showed that the best separation was achieved on an ODS column by a 90:10 v/v mixture of methanol-distilled water. A flow rate of 2 ml/min allowed an analysis in less than 3 min. The UV detector, operating at 221 nm, provided maximum sensitivity for low concentrations of ranitidine (Fig. 1).

A response factor of 1.92 for ranitidine versus benzocaine was calculated by injecting mixed solutions in various concentration ratios. Test solution concentrations were thus calculated from the equation:

$$C = \frac{A}{A_{IS}} \cdot C_{IS} \cdot 1.92$$

where $\frac{A}{A_{IS}}$ was the ratio between the peak area of the test substance and the internal standard peak area and C_{IS} the standard concentration. The calibration curve for the determination of ranitidine was found by calculating the ratio of each peak area to the area of the internal standard. The regression line of these data at five drug concentrations gave a slope, intercept and correlation coefficient of 1.26, −0.0035 and 0.9999 respectively.

Five solutions of ranitidine, prepared in the same way as the standards, and with concentrations 15.5–108.5 mg/100 ml were tested. Table 1 shows the excellent recoveries obtained.

Tables 2 and 3 show results for the assays of ranitidine after extraction from tablets, and after dilution of the injectable formulations. It is clear that the proposed HPLC method for tablet and injectable formulations is simple, rapid and precise.

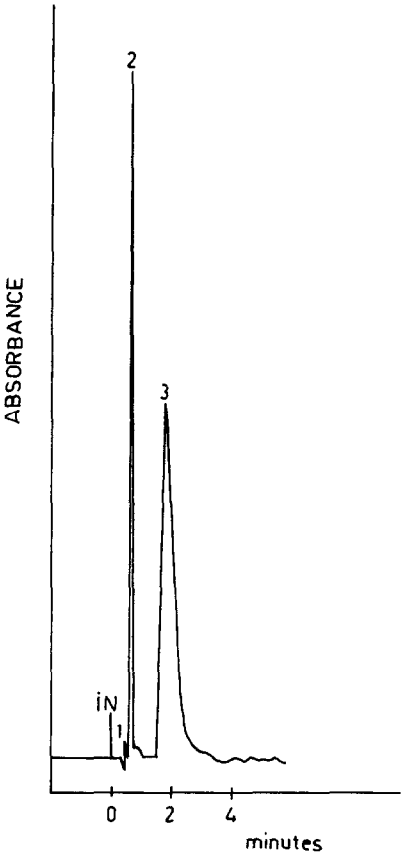

Figure 1
Chromatogram of ranitidine on ODS column with 90:10 v/v methanol–water. 1, solvent; 2, benzocaine; 3, ranitidine.

Table 2
HPLC analysis of ranitidine tablets

Sample	Calculated (mg)	Found (mg)	Recovery (%)
1	15.81	16.20	102.4
2	31.62	32.08	101.4
3	42.65	42.61	99.9
4	62.30	63.23	101.5
5	110.22	109.20	99.09

Mean, 100.8; standard deviation, 1.33; RSD %, 1.3.

Table 3
Results of HPLC analysis of ranitidine injectable formulations*

Sample	Calculated (mg)	Found (mg)	Recovery (%)
1	20.00	19.94	99.7
2	35.00	34.76	99.3
3	45.00	44.98	99.9
4	50.00	49.72	99.4

Mean, 99.57; standard deviation, 0.236; RSD %, 0.23.
*10 mg/ml ranitidine base.

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References

[1] W. L. Burland and M. A. Simkins, Cimetidine, in *Proceedings of the Second International Symposium on Histamine H_2-Receptor Antagonists*, Excerpta Medica, Amsterdam (1977).
[2] N. R. Peden, D. A. Richards, J. H. B. Saunders and K. Wormslex, *Lancet* 199–200 (1979).
[3] G. W, Minhaly, O. H. Drummer, A. Marshall, R. A. Smallwood and W. J. Louis, *J. Pharm. Sci.* **69**, 1155–1157 (1980).

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