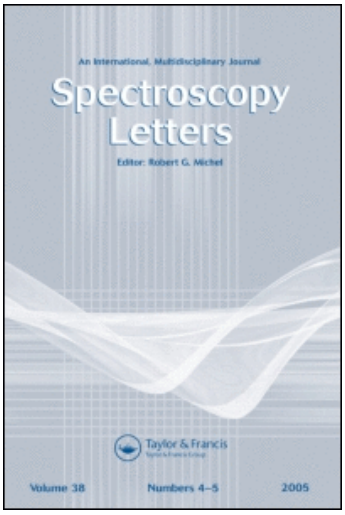

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Quantitavive Proton Magnetic Resonance Analysis of Ranitidine in Solid Dosage Forms

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QUANTITAVIVE PROTON MAGNETIC RESONANCE ANALYSIS OF RANITIDINE IN SOLID DOSAGE FORMS

Key Words : PMR Analysis, Ranitidine

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ABSTRACT

A rapid and specific proton magnetic resonance (PMR) spectroscopic method was developed for determining ranitidine hydrochloride in tablets. 2-Choloroacetophenon was used as the internal standard and DMSO-d_6 served as the PMR solvent. The concentration of drug per unit dose was calculated

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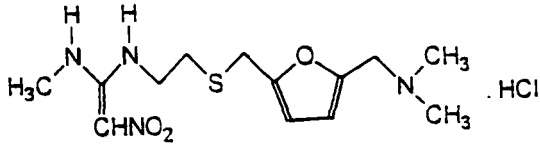
from the integration values for the resonance signals of ranitidine hydrochloride at 4.32 δ ppm and int. st. at 5.19 δ ppm. The method using commercial products gave comparable results to those obtained by the methods of UV spectroscopy and USP XXIII.

INTRODUCTION

The H_2 antagonists in clinical use are analogs of histamine that contain a bulky side chain in place of the ethylamine moiety. This ring is replaced in more recenty developed compounds by a furan (ranitidine) or a thiazole (famotidine, niyazidine)[1-2]. Ranitidine {N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine} an H_2 receptor antagonist, is a powerful inhibitor of gastric acid secretion in the treatment of peptic ulcers and related disorders[3].



N-[2-[[[5-(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl -2-nitro-1,1-ethenediamine, monohydrochloride (ranitidine hydrochloride)

Methods used for the assay of ranitidine in biological and pharmaceutical samples have included HPLC[4-6] and UV spectrophotometry[7-8]. In the USP XXIII, the assay of ranitidine hydrochloride in tablets relies on HPLC determination [9].

This work describes a rapid, specific and simple method for the assay of ranitidine hydrochloride, involving the application of PMR spectroscopy. One assay can be completed in less the 20 minutes and is selective enough

to permit the assay of ranitidine hydrochloride in the presence of certain excipients of tablets.

EXPERIMENTAL

Materials : Standard ranitidine was obtained from DEVA Inc/Turkey. 2-Chloroacetophenone, DMSO-d_6 (spectroscopic grade), methanol (HPLC grade) and ammonium acetate (analytical grade) were obtained from Merck.

Apparatus :

NMR : Bruker DPX-400, 400 Mhz High-Performance Digital FT-NMR.

UV : Beckman DU® 650 Spectrophotometer.

HPLC : Hewlett Packard Series 1050 Liquid Chromatograph, 7892 rheodyne injector (loop injector 20 µL), HP 1050 UV detector, 3396A Series integrator.

Assay of Tablets : Twenty tablets were weighed, powdered and mixed homogenously. A portion of powder equivalent to 90-110 mg ranitidine hydrochloride weighed accurately and transfered to a glass-stoppered tube. About 35-50 mg of accurately weighed 2-chloroacetophenone and about 1.5 ml of DMSO-d_6 were added. The soution was mixed by means of a vortex mixer and centrifuged. Using a capillary pipet, about 0.5 ml of the supernatant was transferred to an analytical PMR tube.

The tube was placed in the NMR spectrometer and the spectrum was recorded. The singlets at about 4.32 δ ppm and 5.19 δ ppm were integrated. The amount of ranitidine hydrochloride per unit dose was calculated using the equation given below.

Calculations: The amount of ranitidine hydrochloride (as $C_{13}H_{22}N_4O_3S.HCl$) per unit dose was obtained from the equation:

$$W_{Ran.HCl} = W_{int.st.} \times M_{Ran.HCl} / M_{int.st} \times H_{Ran.HCl} / H_{int.st.}$$

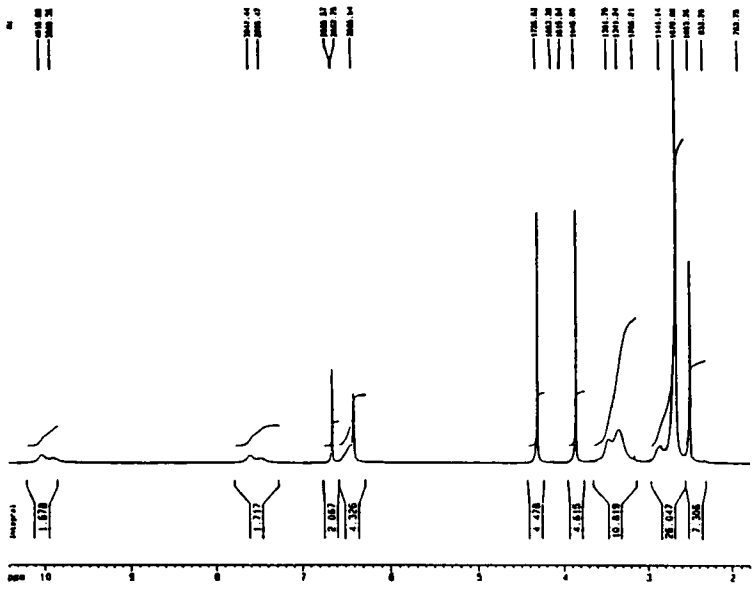


FIG. 1. PMR spectrum of ranitidine hydrochloride in DMSO-d_6.

Where, $H_{Ran.HCl}$ the average height of the integral step for the CH_2N protons of ranitidine hydrochloride absorbing at 4.32 δ ppm. $H_{int.st.}$ is the average height of the integral step for the methylenic protons of 2-chloroacetophenone absorbing at 5.19 δ ppm, $M_{Ran.HCl}$ is the formula weight of ranitidine hydrochloride divided by the absorbing protons (350.87 / 2 = 175.44), $M_{int.st.}$ is the formula weight of 2-chloroacetophenone divided by the number of absorbing protons (154.60 / 2=77.30). $W_{int.st.}$ is the weight of 2-chloroacetophenone used in the assay, mg, $W_{Ran.HCl}$ is the weight of ranitidine hydrochloride, mg.

RESULTS AND DISCUSSION

Since DMSO-d_6 promptly dissolved ranitidine hydrochloride and 2-chloroacetophenone, this solvent was chosen for the assay.

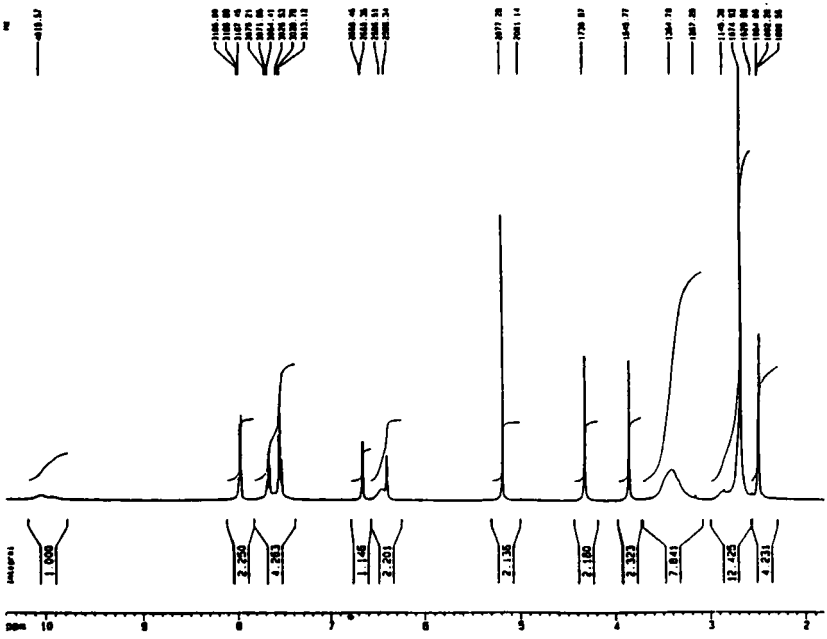


FIG. 2. PMR spectrum of ranitidine hydrochloride + 2-chloroacetophenone in DMSO-d_6.

Figure 1 shows the 400 MHz PMR spectrum of ranitidine hydrochloride in DMSO-d_6. The singlet which corresponds to the protons of the CH_2N group in 5-position of furan ring (2H) is used for the quantitative determination[10]. In the PMR spectrum of 2-chloroacetophenone, the methylene protons give a sharp singlet at 5.19 δ ppm and five aromatic protons give a multiplet at 7.30-8.20 δ ppm[11]. The singlet at 5.19 δ ppm is used in the quantitative analysis. Figure 2 shows 400 Mhz PMR spectrum of ranitidine hydrochloride+2-chloroacetophenone in DMSO-d_6.

The statistical results obtained by the developed PMR, HPLC and UV[8]) ahalysis methods of the commercial solid dosage froms are shown in Table 1.

Table 1. Determination and the statistical results of the developed PMR, USP XXIII and UV methods.

Tablet Name	Statistical Parameters	PMR Method n=5	USP XXIII Method n=5	UV Method n=5
ULCURAN tablet (150 mg)	x	149.64	149.02	149.64
	SD	0.089	2.755	0.446
	CV%	0.060	1.849	0.298
ULCURAN tablet (300 mg)	x	299.50	298.00	299.14
	SD	0.510	8.435	1.345
	CV%	0.170	2.830	0.450
RANIGEN tablet (150 mg)	x	149.72	149.30	149.58
	SD	0.516	3.744	0.499
	CV%	0.344	2.508	0.334
RANITINE tablet (150 mg)	x	149.86	149.87	148.97
	SD	0.270	1.916	0.748
	CV%	0.180	1.278	0.502
ZANTAC tablet (150 mg)	x	149.66	149.64	149.65
	SD	0.230	3.325	0.714
	CV%	0.154	2.222	0.477

The statistical results show that the PMR method can be easily used since it is simple rapid and spesific. It is sufficiently sensitive and rapid to be utility in assaying individual tablets, and also can serve as an identification test for ranitidine hydrochloride.

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