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Short communication

Quantitative analysis of methocarbamol in solid dosage forms with ^{1}H-NMR spectroscopy

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1. Introduction

Methocarbamol, 3-(2-methoxyphenoxy)-1,2-propandiol 1-carbamate is a drug used as a skeletal muscle relaxant. Methods used for the assay of methocarbamol in biological and pharmaceutical samples have included GC [1] and HPLC [2–5]. In the USP XXIII, the assay of methocarbamol in dosage forms also relies on HPLC determination [6]. This work describes a rapid, specific and very simple method for the determination of methocarbamol involving the application of ^{1}H-NMR spectroscopy. Maleic acid was used as the internal standard and dmso-d_6 served as the NMR solvent. The concentration of drug per unit dose was calculated from the integration values for the resonance signals of methocarbamol at 3.77 ppm and maleic acid at 6.28 ppm. Good results were also obtained for the determination of methocarbamol and paracetamol in pharmaceutical methocarbamol–paracetamol mixture dosage forms with one single experiment. One assay can be completed in less than 20 min and the method is selective enough to permit the assay in the presence of certain excipients of dosage forms

2. Materials and methods

2.1. Reagents

Standard USP methocarbamol RS was obtained from Sanofi Inc/Turkey. Paracetamol and dmso-d_6 were obtained from Aldrich. Certified grade monobasic potassium phosphate, phosphoric acid and potassium hydroxide were obtained from Merck Inc. Certified Caffeine was obtained from Leco Corporation. HPLC grade Methanol was obtained from Carlo Erba and 0.45 μm Nylon filters were obtained from Waters.

2.2. Instrumentation

NMR; Bruker DPX-400, 400 MHz High Perfor-

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mance Digital FT NMR. HPLC; Hewlett Packard Series 1100 Liquid Chromatograph including 7725 rheodyne injector (20 μl loop), HP UV-Vis detector, vacuum degasser, gradient pump module and column compartment oven. A 5 μm packing L1 column (4.6 mm × 10 cm) from Phenomenex was used for the separations.

2.3. Assay preparation for NMR

Twenty tablets were weighed and finely powdered. A portion of well-mixed powder equivalent to 21–27 mg methocarbamol was weighed accurately and transferred to a glass stoppered tube. About 18–22 mg of accurately weighed maleic acid and about 0.7–1 ml of dmso-d_6 were added. The solution was mixed by means of a vortex mixer and centrifuged. Using a capillary pipette, about 0.5 ml of the supernatant was transferred to an analytical NMR tube and two drops of D_2O were added. From the spectrum, the signals at about 3.77 and 6.28 ppm were integrated.

3. Calculations

The amount of methocarbamol ($C_{11}H_{15}NO_5$) per unit dose was obtained from the equation as follows [6];

$$W_{\text{met}} = W_{\text{mal.Ac.}} \times E_{\text{met.}}/E_{\text{mal.Ac}} \times A_{\text{met.}}/A_{\text{mal.Ac.}}$$

where, $A_{\text{met.}}$ is the integral value for the OCH_3

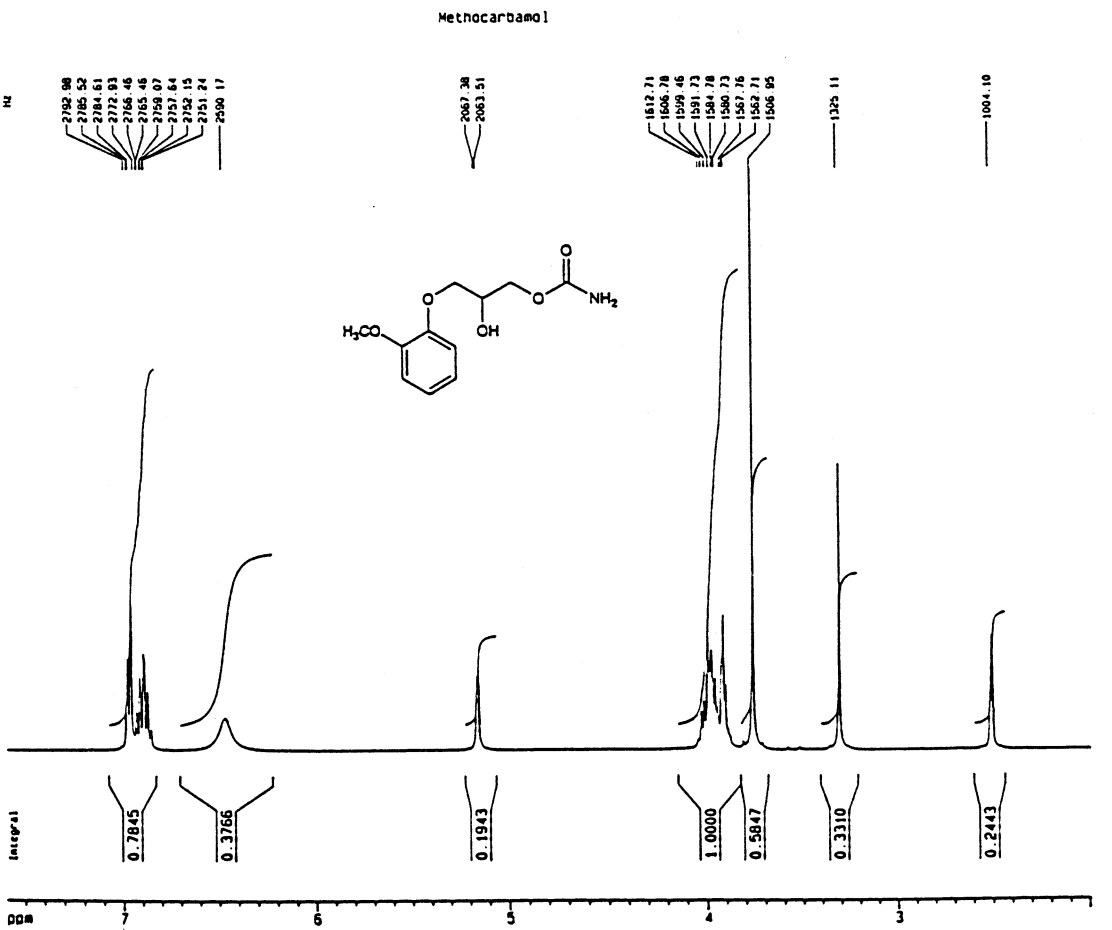

Fig. 1. ^{1}H-NMR spectrum of methocarbamol in dmso-d_6.

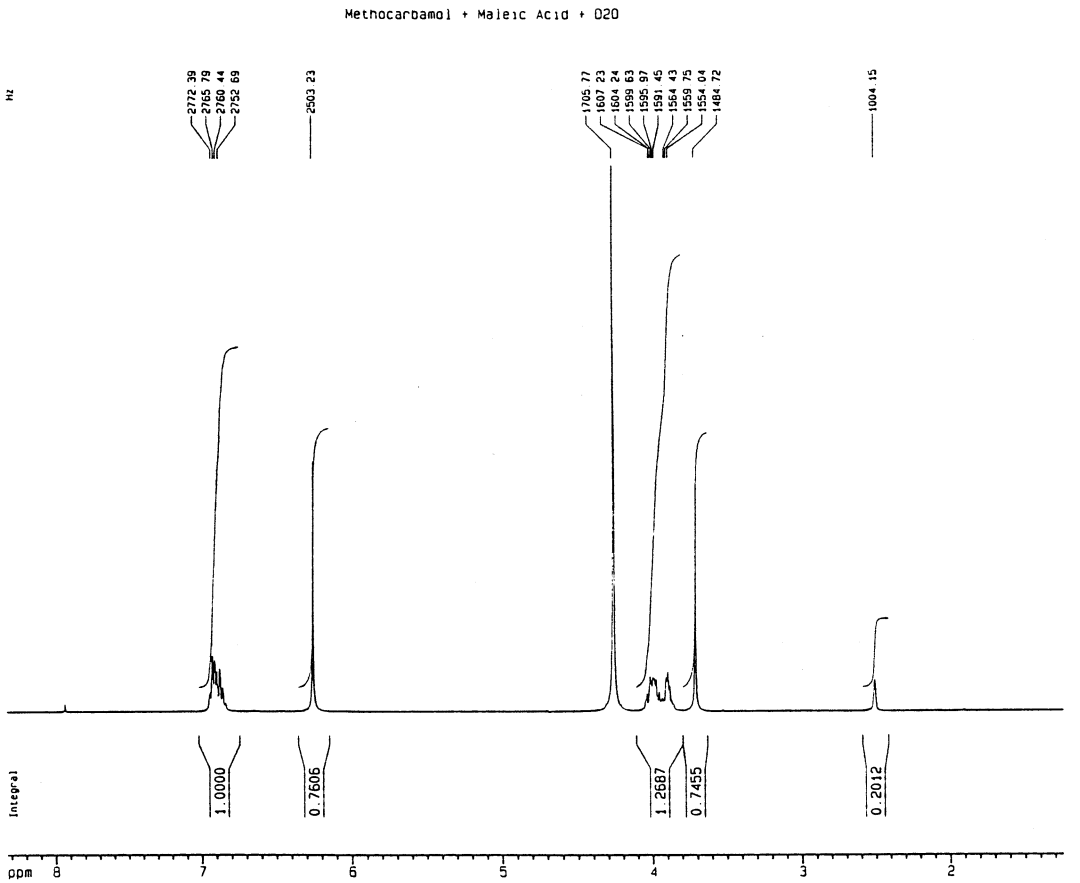

Fig. 2. ^{1}H-NMR spectrum of methocarbamol + maleic acid in dmso-d_6.

protons of methocarbamol absorbing at 3.77 ppm, $A_{mal.Ac.}$ is the integral value of olefinic protons absorbing at 6.28 ppm, $E_{met.}$ is the formula weight of methocarbamol divided by the number of absorbing protons (241.25/3 = 80.42), $E_{mal.Ac.}$ is the formula weight of maleic acid divided by the number of absorbing protons (116.07/2 = 58.04), $W_{mal.Ac.}$ is the weight of maleic acid, in mg, used in the assay, and W_{met} is the weight of methocarbamol.

4. Results and discussion

Fig. 1 shows the 400 MHz ^{1}H-NMR spectrum of methocarbamol in dmso-d_6. In the spectrum, the OCH_3 protons give a sharp singlet at 3.77 ppm, the methylene and methine protons give a multiplet at 3.91–4.03 ppm, the hydroxyl proton gives a doublet at 5.16 ppm, the amine protons give a broad singlet at 6.48 ppm and five aromatic protons give a multiplet at 6.88–6.98 ppm. The singlets occuring at 2.51 and 3.31 ppm are due to dmso-d_6 and water, respectively. In the NMR spectrum of maleic acid the olefinic protons give a sharp singlet at 6.28 ppm and the carboxyl protons give a very broad singlet at 11.40 ppm.

Fig. 2 shows the 400 MHz ^{1}H-NMR spectrum of methocarbamol + maleic acid in dmso-d_6 after deuterium exchange with D_2O. The singlets at 3.70 and 6.28 ppm were used in the quantitative analysis.

The methods were also applied to the medicaments involving methocarbamol–paracetamol.

Since the acetamido methyl protons of paracetamol give a sharp singlet at 1.98 ppm and don't interfere with the signals of methocarbamol and maleic acid used in the analysis, the quantification of both methocarbamol and paracetamol in one experiment was realised (Fig. 3).

The method given for methocarbamol tablets in USP XXIII was also suitable for paracetamol–methocarbamol mixtures. Fig. 4 shows that, the peaks of these products and the internal standard caffeine don't interfere with each other. The resolution, R, between the peaks is more than 9.5. Results obtained from ^{1}H-NMR method and USP XXIII method are given in Table 1. The results were also compared statistically in each series by paired t-test and no significant difference was found ($P > 0.05$). As it can be seen from the table, the relative standard deviation values are much more lower than USP XXIII method showing that the repeatability of the proposed method is high enough.

Mean recovery and relative standard deviation of the method were obtained as 99.86 and 0.39 for methocarbamol in the synthetic preparations by adding known amounts of methocarbamol (Table 2).

5. Conclusion

Methacarbamol content of a pharmaceutical dosage form can be determined with the use of maleic acid as the internal standard. The statistical results show that the method can be easily applied since it is simple, rapid and specific. It is sufficiently sensitive and rapid to be utilized in

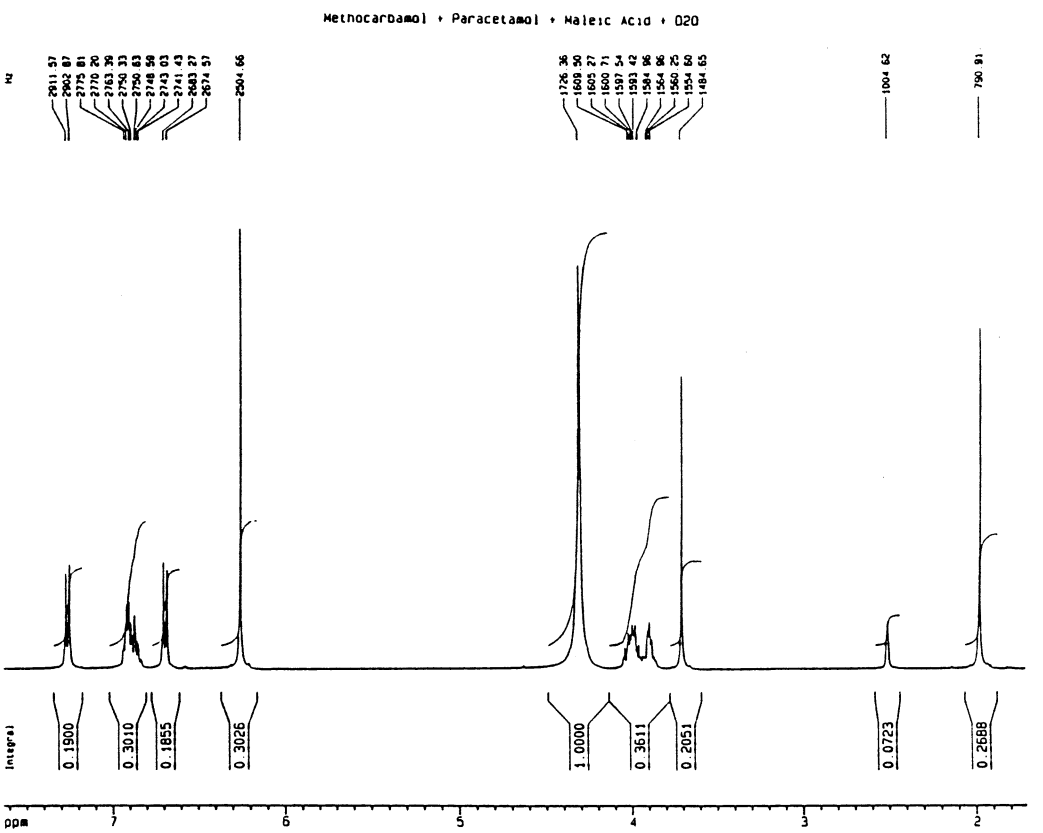

Fig. 3. ^{1}H-NMR spectrum of methocarbamol + paracetamol + maleic acid in dmso-d_6.

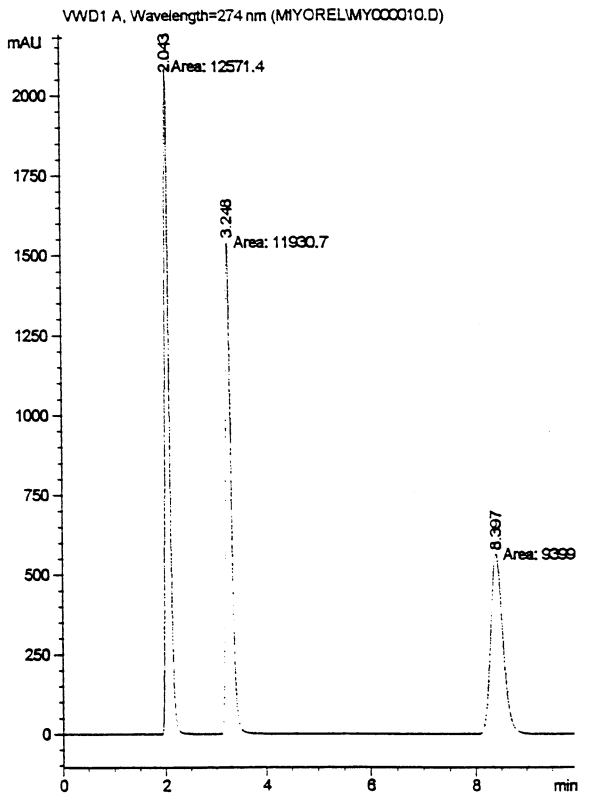

Fig. 4. HPLC analysis of paracetamol + caffeine + methocarbamol (the conditions given for methocarbamol in USP XXIII).

Table 2
Recovery data obtained for methocarbamol by using ^{1}H-NMR method

Sample no.	Methocarbamol		
	Added (mg)	Found (mg)	Recovery (%)
1	25	24.9	99.6
2	25	24.9	99.6
3	25	24.8	99.2
4	25	25.0	100.0
5	25	24.9	99.6
6	25	25.0	100.0
7	25	25.1	100.4
8	21	21.1	100.5
9	22	21.9	99.5
10	23	23.0	100.0
11	24	23.9	99.6
12	25	24.9	99.6
13	26	26.1	100.4
14	27	27.0	100.0
$\bar{X} = 99.86$			
RSD = 0.39			

assaying individual tablets and also can serve as an identification and a stability indicating assay for methocarbamol. It is observed that the proposed method is more simple and precise. It also permits to make the determination of methocarbamol and paracetamol in pharmaceutical mixture dosage forms with one single experiment. The proposed method can easily take place in pharmacopeias since the general ^{1}H-NMR quantitative analysis method is recommended in USP XXIII [6].

Table 1
Determination and the statistical results of the developed ^{1}H-NMR and USP XXIII methods

Tablet name	Content		Statistical parameters	NMR method		USP XXIII method	
	Methocarbamol (mg)	Paracetamol (mg)	$n = 5$	Methocarbamol	Paracetamol	Methocarbamol	Paracetamol
Miyokalm	500	–	Mean	494.40	–	492.54	–
			%	98.88	–	98.51	–
			SD	2.80	–	8.35	–
			CV% (RSD)	0.94	–	1.69	–
Miyorel	375	300	Mean	373.50	295.74	368.22	296.82
			%	99.60	98.58	98.19	98.94
			SD	0.56	2.32	4.93	2.76
			CV% (RSD)	0.15	0.78	1.34	0.93

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