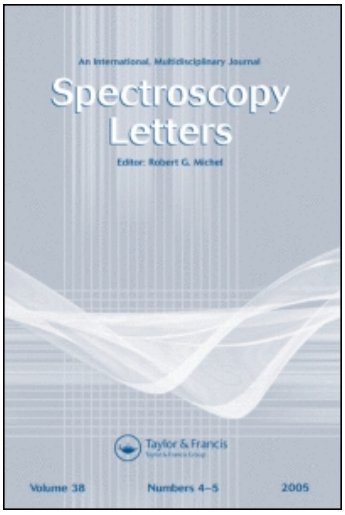

Spectroscopy Letters
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597299

PMR Spectrometric Analysis of Tolmetin Sodium in Capsules Forms

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To cite this Article Al-obaid, Abdulrahman M. , Mohamed, Mohamed E. and Gad-kariem, El-Rasheed A.(1989) 'PMR Spectrometric Analysis of Tolmetin Sodium in Capsules Forms', Spectroscopy Letters, 22: 3, 269 — 277
To link to this Article: DOI: 10.1080/00387018908053876
URL: http://dx.doi.org/10.1080/00387018908053876

SPECTROSCOPY LETTERS, 22(3), 269-277 (1989)

PMR Spectrometric Analysis of Tolmetin Sodium in Capsules Forms

Key Words PMR spectrometry, Pharmaceutical analysis, Assay of tolmetin sodium.

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Abstract

An analytical method is described for the assay of tolmetin, 1-methyl-5-(4-methylbenzoyl)-1H-pyrrole-2-acetic acid, as sodium salt, (Tolectin® - 200 mg) using PMR. The protocol reported in this study is simple, precise and yields accurate results of 99.78±0.84 and 100.67±2.08 for the authentic material and capsules respectively. In addition, the PMR spectrum obtained provides a means for qualitative identification of the drug and checking its purity. The principle of the method involves comparison of the integral of the well-defined singlet (positioned at 2.41 δ) to that of the sharp singlet due $-CH_3$ (positioned at 1.91 δ) of sodium acetate as an

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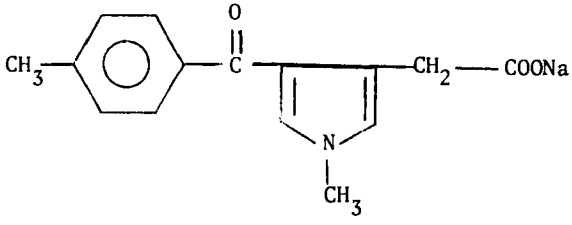
internal standard in presence of maleic acid using DMSO-d_6 solvent. The rationale for the use of maleic acid in the assay procedure has been discussed.

Introduction

Tolmetin, 1-methyl-5-(4-methylbenzoyl)-1H-pyrrole-2-acetic acid sodium salt is commonly used as a non-steroidal antirheumatic drug with analgesic properties in man. Extensive clinical trials have established the efficacy of the drug in the treatment of adult and juvenile rheumatic arthritis and in osteoarthritis (1,2) of both large and small joints.



Tolmetin sodium

Several procedures involving thin layer chromatography and gas-liquid chromatography (3-5), high performance liquid chromatography (6,7), colorimetry (8), direct-current polarography (9) and differential pulse polarography (10) were reported for the detection and quantitation of tolmetin and of tolmetin in capsule dosage form and of tolmetin and its metabolites in biological fluids.

It was deemed useful to develop a simple and accurate method using PMR as a tool for both qualitative and quantitative assay of the active ingredient in the capsule dosage form (Tolectin® - 200 mg).

Experimental

A Varian FT-80A spectrometer was used throughout the study.

Materials and methods

Materials

DMSO-d_6 NMR grade purchased from Winlab Limited, Maidenhead, Berkshire, United Kingdom, was used as solvent. Sodium acetate and maleic acid employed were products of Riedel-Dehaen AG, Seezle - Hannover, West Germany. Authentic tolmetin sodium (lot No. 87P2427) and tolmetin capsules were kindly donated by Cilag AG, 8201 Schaffhausen, Switzerland and Cilag Scientific Office in Riyadh respectively.

Procedure

For authentic tolmetin sodium

Dissolve 125 mg of tolmetin sodium, 125 mg maleic acid and 50 mg sodium acetate in 2 ml DMSO-d_6. Transfer about 0.4 ml of the clear solution into an NMR tube. Run a PMR spectrum, adjusting the spin rate to eliminate spinning side bands as much as possible. Integrate the peaks of interest (singlet at 1.91 δ for $-CH_3$ sodium acetate internal standard and singlet at 2.41 δ for aromatic $-CH_3$ in tolmetin). Record the mean of three integrations in each case. The amount of tolmetin sodium is computed as follows:

$$\text{mg of tolmetin sodium} = \frac{S_1}{S_2} \times \frac{EW_1}{EW_2} \times W2$$

S_1 = integral value for singlet of aromatic $-CH_3$ in tolmetin.

S_2 = integral value of $-CH_3$ singlet of sodium acetate internal standard.

EW_1 = mol. wt. of tolmetin sodium/3.

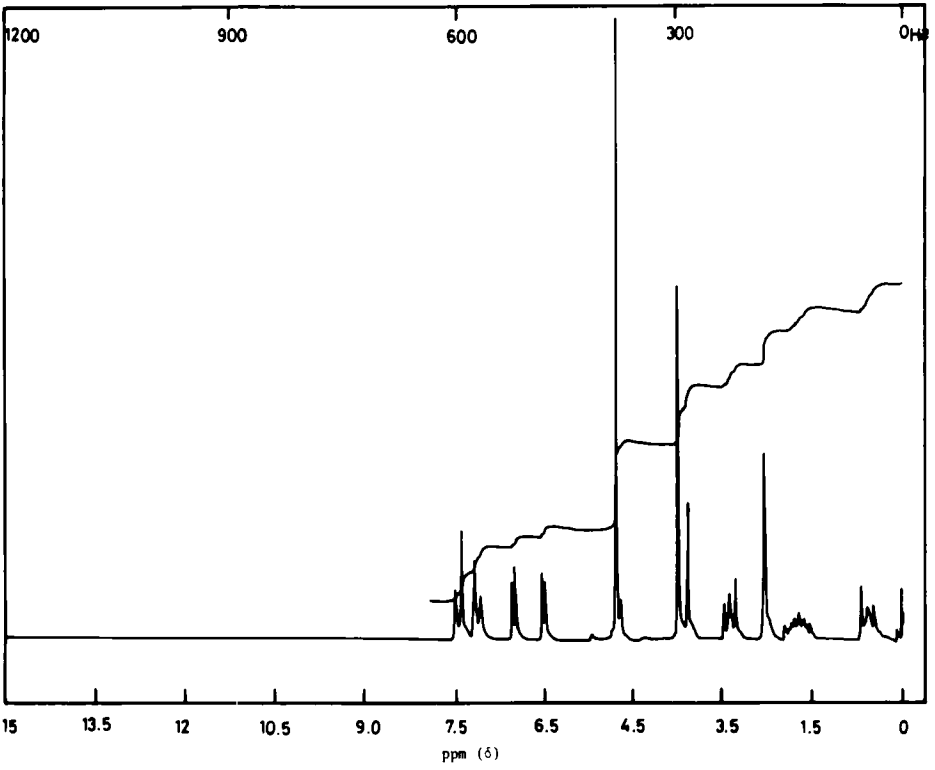


Fig. 1. PMR spectrum of tolmetin sodium in D_2O.

EW_2 = mol. wt. of sodium acetate/3.

W_2 = Wt. (mg) of sodium acetate internal standard.

For tolmetin capsules

From the mixed contents of 20 capsules weigh accurately a quantity of powder containing 125 to 175 mg of tolmetin sodium. Mix with 2 ml DMSO-d_6; add 125 mg maleic acid and 50 mg sodium acetate internal standard. Shake vigorously for 40 min and centrifuge for 5 min at 3000 rpm. Transfer about 0.4 ml of the

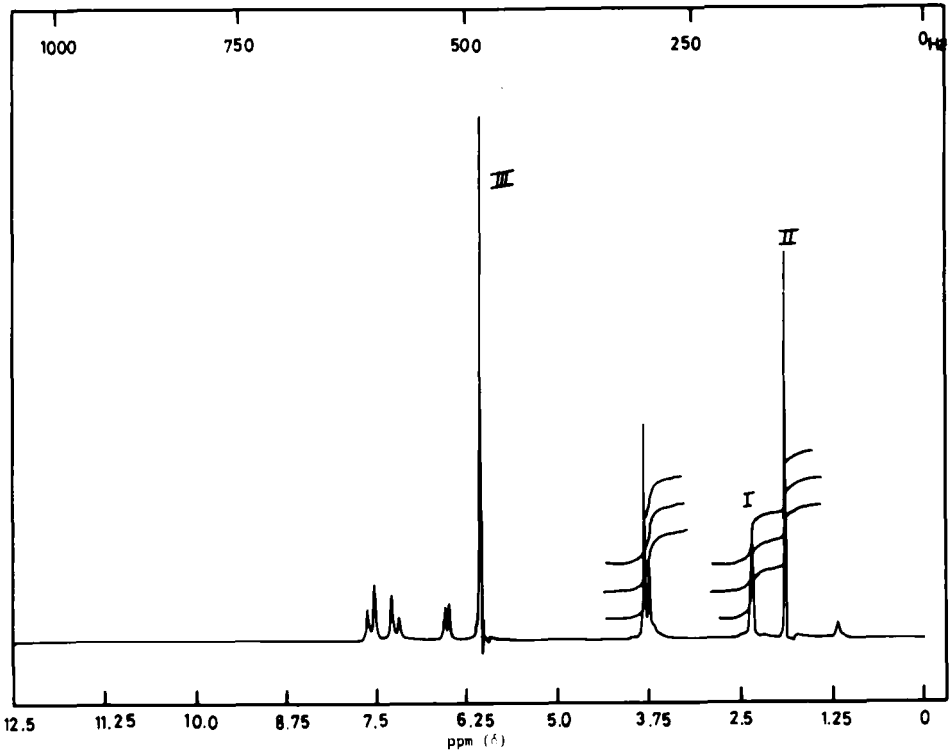


Fig. 2. PMR spectrum of tometin sodium (I), sodium acetate (II), and maleic acide (III).

clear supernatent into an NMR tube. Complete as prescribed under authentic tolmetin sodium commencing at the words, "Run a PMR spectrum, adjusting the spin rate ..."

Results and Discussion

The selection of a suitable solvent and an internal standard was considered carefully. Tolmetin sodium is insoluble in CCl_4 and $CHCl_3$ but soluble in D_2O; however on addition of maleic acid as an internal standard tolmetin precipitated as a free acid. Although

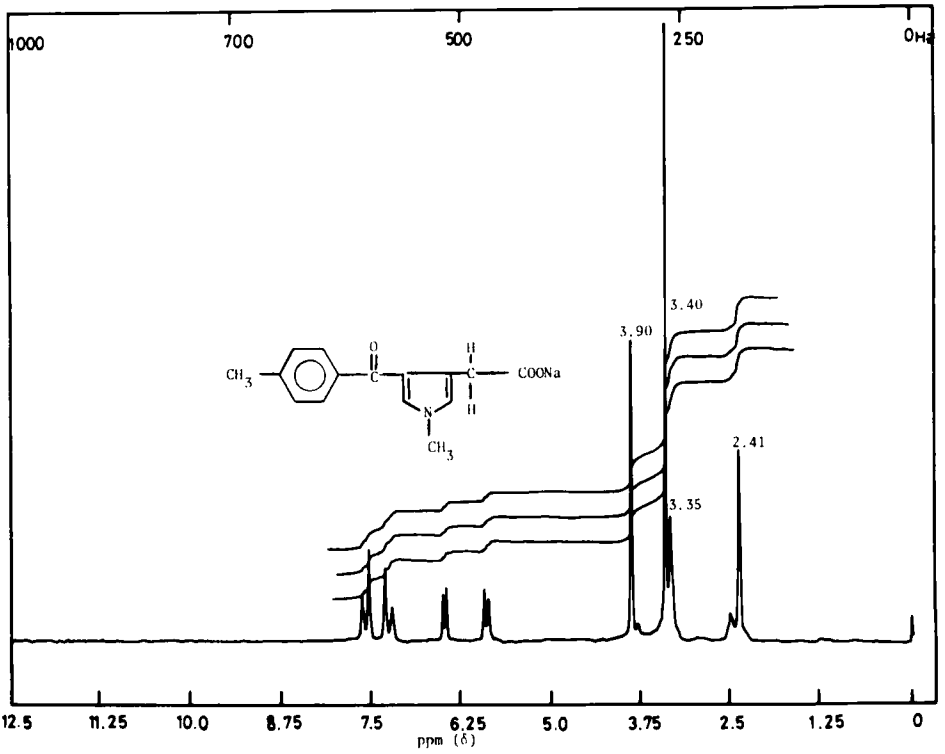


Fig. 3. PMR spectrum of tolmetin sodium in DMSO-d_6.

both sodium acetate and tolmetin sodium are adequately soluble in D_2O, yet the PMR spectra (Fig. 1) recorded show many close peaks such that the selection of a specific integral to compare with the standard is rendered difficult. It is also worthwhile to state that maleic acid could not be used as an internal standard since its only singlet peak at 6.11 δ overlaps with those of the aromatic protons of the pyrrole nucleus of tolmetin.

The problem was circumvented by using DMSO-d_6 which proved a satisfactory solvent for tolmetin sodium and sodium acetate in

TABLE I

PMR Analysis of Tolmetin Sodium Capsules (Tolectin® - 200 mg)

Sample No.	Internal standard added (mg)	Tolmetin sodium claimed (mg)	Amount of tolmetin sodium found (mg)	% Found	Mean%±S.D.*
1	51.6	125.8	125.8	100.0	
2	51.0	125.8	127.7	101.5	
3	53.2	126.4	122.8	97.3	
4	53.0	126.2	132.0	104.6	
5	53.2	150.8	150.0	99.5	
6	51.8	150.0	150.0	100.	
7	53.2	150.0	152.1	101.4	
8	52.0	149.5	154.0	102.8	
9	52.8	176.1	176.0	100.0	
10	50.4	175.2	181.3	103.5	
11	50.3	178.3	174.7	98.0	
12	50.0	175.0	174.0	99.4	100.67±2.08

*Standard deviation

presence of maleic acid. The PMR spectrum of maleic acid possesses a sharp singlet at 6.11 δ due to -CH = CH- (Fig. 2) showing no overlap with the spectra of the internal standard and the drug at the selected peaks.

The use of sodium acetate as an internal standard is due to its sharp singlet at 1.91 δ (Fig. 2) well away from the integral peaks of tolmetin sodium and maleic acid.

TABLE II

PMR Analysis of Authentic Tolmetin Sodium

Sample No.	Internal standard added (mg)	Tolmetin sodium added (mg)	Amount of tolmetin sodium found (mg)	% Recovery	Mean%±S.D.*
1	50.5	133.5	134.5	100.7	
2	52.3	132.8	133.6	100.6	
3	51.3	159.5	158.4	99.3	
4	53.0	161.3	160.2	99.3	
5	49.6	129.0	127.2	98.6	
6	52.6	129.3	129.5	100.2	99.78±0.84

*Standard deviation

The PMR spectrum of tolmetin sodium (Fig. 3) exhibits sharp singlets at 2.41 δ, 3.35 δ and 3.40 δ due to aromatic $-CH_3$, aliphatic $-CH_2-$ and $-N-CH_3$ respectively. The singlet at 3.9 δ is probably due to water since the drug exists as a dihydrate. The integrals of the singlets at 1.91 δ for aliphatic $-CH_3$ of the internal standard and 2.41 δ for tolmetin sodium (Fig. 2) were used as indicators of the concentration.

Accordingly a series of solutions for authentic tolmetin sodium and capsules (Tolectin® - 200 mg) were prepared and assayed as shown in Tables I and II. The mean percent results of the recoveries were 99.78±0.84 and 100.67±2.08 for authentic drug and its capsules respectively.

In conclusion the PMR method provides a precise, simple and accurate procedure for the quantitative determination of tolmetin sodium. Furthermore, the method proves useful for the identification of tolmetin sodium in its pharmaceutical form.

Acknowledgement

The authors cordially thank Messrs Cilag AG, 8201 Schalffhausen, Switzerland and Cilag Scientific Office, Riyadh, Saudi Arabia for providing authentic tolmetin sodium and capsules used in this work. Furthermore, the authors express their thanks to Khalid N.K. Lodhi for his assistance in recording the PMR spectra.

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Date Received: 10/20/88
Date Accepted: 11/23/88