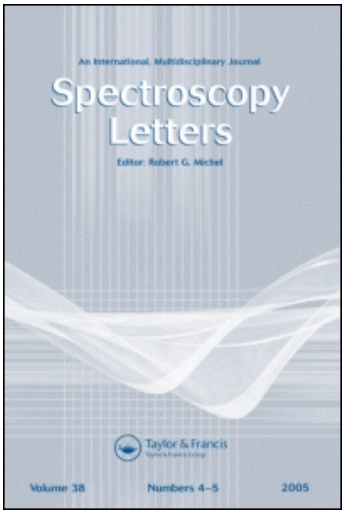

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Application of PMR Spectrometry in Pharmaceutical Analysis I. Assay of Clofibrate

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APPLICATION OF PMR SPECTROMETRY IN PHARMACEUTICAL ANALYSIS I. ASSAY OF CLOFIBRATE*

Key Words: PMR Spectrometry, Pharmaceutical Analysis, Assay of Chofibrate.

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ABSTRACT

A new method, involving the application of PMR spectrometry for the assay of clofibrate and its capsules, is proposed. Among other peaks the PMR spectrum of clofibrate has a well-defined singlet system which is chosen for quantitative measurement. The principle of the method involves comparing the integral of this signal to that of the sharp singlet (positioned at 0.00 ppm) of hexamethylcyclotrisilazane which is used as internal standard.

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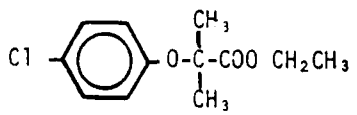
The proposed method, which is simple and rapid, gives accurate and reproducible results when applied for the assay of authentic clofibrate and its capsules. In addition, the PMR spectrum obtained helps in confirming the identity and purity of the drug.

INTRODUCTION

Clofibrate (I), ethyl 2-(4-chlorophenoxy)-2-methyl propionate, is an antihyperlipidemic agent. It is official in both B.P. 1973 and USP XIX (1975). The USP XIX describes a UV spectrometric method for the assay of the authentic drug and its capsules; where the absorbance of the methanolic solution is measured at 226 nm.[1] However, the method is tedious as it involves passing the methanolic solution through a column of an ion-exchange resin.[1] On the other hand, B.P. 1973 does not give an assay method for clofibrate or its capsules. Instead it lists a number of limit tests for: free acidity, free phenolic bodies and volatile related substances.[2]

Most of the methods available in the literature are directed to the quantitation of clofibrate and/or its metabolite clofibric acid (II) in tissues and biological fluids.[3-8]



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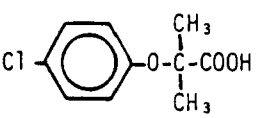

II

For example, Karmen and Haut described a GC method for the assay of clofibrate in human serum.[3] Sedaghat et al. combined TLC and GLC techniques for the estimation of clofibrate in plasma, urine, bile and faeces where the drug is separated by

TLC as the free acid which is then converted into methyl ester.[4] The latter is determined by GLC using eicosanoic acid as internal standard.

Few reports, on the analysis of clofibrate in pharmaceutical dosage forms, are available in the literature.[9-12] Diding et al. used GC/MS in studying the purity of clofibrate.[9] Pawelczyk and Wachowiak, in their study on the stability of clofibrate, determined both clofibrate and clofibric acid by measuring absorbance at 227 nm; while the acid content was obtained by direct titration with standard soltuion of sodium hydroxide.[10] It was of interest to develop a simple and rapid method for the assay of clofibrate and its capsules. This communication describes a new method involving the application of PMR spectrometry.

EXPERIMENTAL

A Varian T60-A NMR spectrometer was used throughout the study. The internal standard, hexamethylcyclotrisilazane, was purchased from ICN K & K Labs, Plainview, N.Y. Carbon tetrachloride, spectral grade, was used. Clofibrate capsules (Atromid S®, manufactured by I.C.I., Holburn, London, England) was used.

PROCEDURE

For authentic clofibrate: Place a weighed aliquot of clofibrate (W_c), in the range of 100-150 mg, in a test tube. Add 5.0 ml of solution of the standard in carbon tetrachloride. The concentrations of internal standard solution is about 10 mg/ml.

Shake the mixture well and transfer it to an NMR tube. Run the PMR spectrum of the mixture. Adjust the spinning rate so that no spinning side bands occur between 0.00 and 2.00 ppm. Integrate the singlet signals at 0.00 and 1.47 ppm three times. Calculate the average integral of each signal (I_s and I_c). Calculate the weight of clofibrate (W_c) using the following equation:

$$W_c = \frac{H_s M_c}{H_c M_s} \times \frac{I_c W_s}{I_s} = \frac{18 \times 242.7}{6 \times 222.3} \times \frac{I_c W_s}{I_s}$$

$$W_c = 3.275 \times \frac{I_c W_s}{I_s}$$

where I = integral of signal (mm)

H = number of protons within the signal

M = molecular weight

W = weight (mg).

The "s" subscript and "c" subscript stand for the internal standard and clofibrate respectively.

For clofibrate capsules (Atromid S®): Each capsule is claimed to contain 500 mg of clofibrate. Place a capsule in a dry small beaker and with a sharp blade carefully open the capsule. Extract clofibrate by four portions of carbon tetrachloride (5.0 ml each). Make sure to rinse thoroughly the capsule shells in order to affect complete extraction of clofibrate. Transfer quantitatively the four portions to 25.0 ml volumetric flask. Complete to volume with carbon tetrachloride.

In an NMR tube pipette accurately 5.0 ml of the clofibrate extract. Add to the tube 1.0 ml, accurately measured, of the

solution of the internal standard in carbon tetrachloride (concentration of internal standard solution 40-50 mg/ml). Shake the tube gently to effect mixing. Run the PMR spectrum of the solution and proceed as previously mentioned under authentic clofibrate.

RESULTS AND DISCUSSION

The PMR spectrum of the carbon tetrachloride solution of clofibrate, using hexamethylcyclotrisilazane as internal standard, is shown in Figure 1. All clofibrate signals, measured in δ-scale, are referenced to hexamethylcyclotrisilazane whose singlet is positioned at 0.00 ppm. Those signals are: triplet-quartet at 1.13 and 4.07 ppm respectively for the ethyl group. The para-substituted aromatic ring shows its characteristic pattern in the range 6.46 and 7.16 ppm. In addition, the two methyl groups give a singlet peak at 1.47 ppm. The last signal has been chosen for quantitative determination of clofibrate by comparing its integral to the integral of the peak of a known amount of the internal standard.

Table 1 shows the percent recoveries obtained when the proposed method is used for the assay of authentic clofibrate. The results demonstrated good precision (average recovery 99.60 ± 3.20%).

When the proposed method is used for the assay of two batches of clofibrate capsules (Atromid S®) give reasonable results as indicated in Table 2.

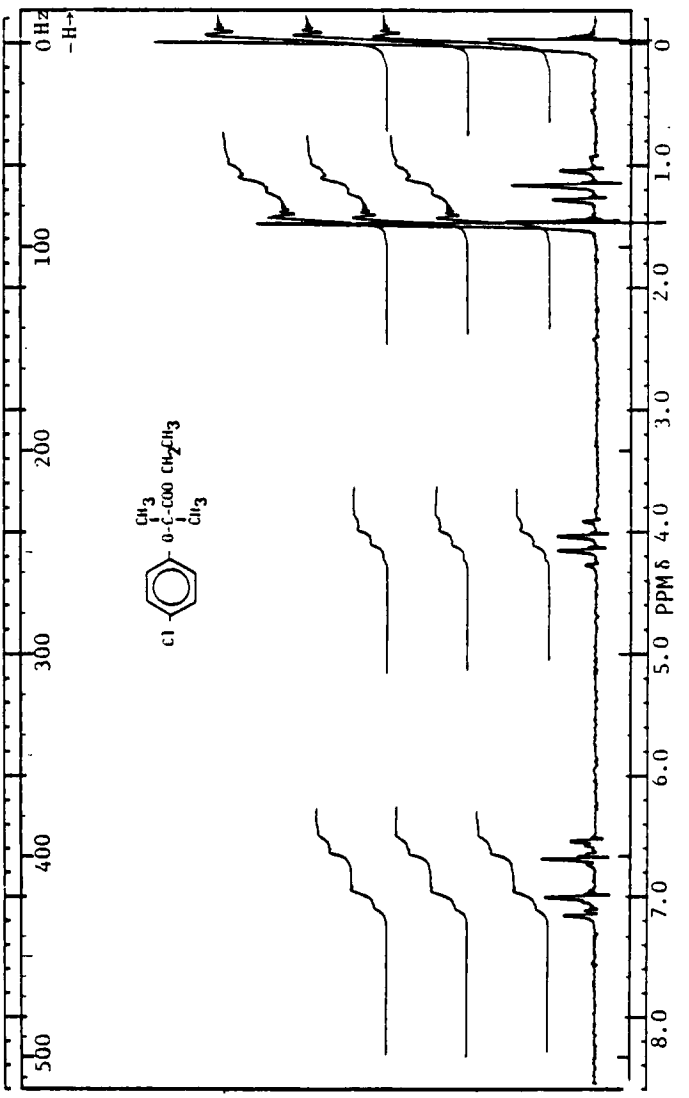

Figure 1

TABLE 1

The Percentage Recoveries of Authentic Clofibrate

Sample No.	W_s (mg)	I_s^a (mm)	I_c^a (mm)	W_c Taken (mg)	Found (mg)	% Recovery
1	50.30	37.0	25.5	107.00	113.35	105.90
2	50.30	37.0	23.5	105.00	104.46	99.50
3	50.30	37.0	22.5	99.00	100.02	101.00
4	50.30	36.5	22.16	98.00	99.85	101.90
5	49.65	28.5	27.25	160.00	155.48	97.20
6	49.65	28.50	26.75	147.00	152.63	103.85
7	49.65	28.50	26.25	154.00	149.78	97.30
8	49.65	28.16	24.66	149.00	142.04	95.30
9	49.65	27.75	24.25	145.00	142.11	98.00
10	49.65	28.50	27.33	160.00	155.94	97.50
11	49.65	28.33	24.50	143.00	140.64	98.40

Average Recovery = 99.60 ± 3.20[b]%

[a]Average of three measurements

[b]Standard deviation

TABLE 2

The Percentage Recoveries of Clofibrate from its Capsules

Sample No.	W_s (mg)	I_s^a (mm)	I_c^a (mm)	W_c (mg) Claimed	(mg) Found	% Recovery
1	50.00	65.00	36.50	100.00	91.95	91.95
2	50.00	40.50	23.00	100.00	93.00	93.00
3	50.00	29.00	50.50	100.00	91.30	91.30
4	40.00	40.50	28.50	100.00	92.20	92.20
5	40.00	53.0	38.00	100.00	93.90	93.90
6	40.00	43.5	30.00	100.00	90.35	90.35
7	40.00	41.0	29.0	100.00	92.65	92.65
8	40.00	40.0	28.0	100.00	91.70	91.70
9	40.00	39.0	28.0	100.00	94.00	94.00
10	40.00	38.00	27.0	100.00	93.00	93.00
11	40.00	39.50	28.0	100.00	92.90	92.90

Average Percentage Recovery = 92.45 ± 1.09[b]%

[a]Average of three measurements

[b]Standard deviation

B.P. 1973 states that "the average weight of the contents of ten capsules is not less than 92.5% and not more than 107.5% of the prescribed or stated weight."[2] While USP XIX requires that clofibrate capsules contain not less than 90.0% and not more than 110% of the labelled amount of $C_{12}H_{15}ClO_3$.[1]

The proposed method gives recoveries which comply with both B.P. 1973 and USP XIX. In addition the procedure is simple, rapid and accurate. Also, the method provides a spectrum of the drug which helps in its identification and checking its purity.

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