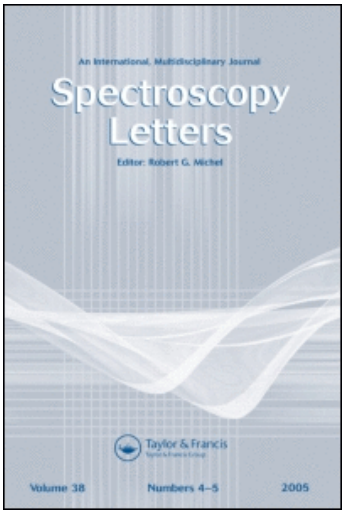


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# PMR Spectrometric Analysis of Clofibrate

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# PMR SPECTROMETRIC ANALYSIS OF CLOFIBRATE

Key Words : NMR analysis, Clofibrate; Clofibrate, NMR analysis.

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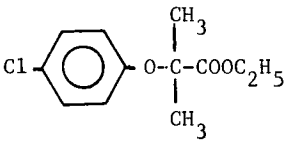
Abstract

A PMR analytical method is developed for the quantitation of Clofibrate (ethyl 2-(p-chlorophenoxy)-2-methylpropionate) as a drug entity and in capsule dosage form. Standard deviations of ± 1.07% and ± 1.34% were obtained for the pure drug and capsules, respectively. The results obtained comply with official standards required by different pharmacopeias. The PMR spectrum, in addition, provides a very specific mean for identification of Clofibrate. The procedure proved to be simple, rapid, accurate and precise.

## Introduction

Clofibrate I(ethyl 2-(p-chlorophenoxy)-2-methylpropionate) is a well tolerated drug, widely and commonly used as antichol-esterolemic agent (1,2).



I



Literature review of the methods pertaining to the determination of I is scarce. A gas-liquid chromatographic method (3) and a combined thin-layer chromatography and gas-liquid chromatography procedures (4) were reported. The method officially adopted by the United States Pharmacopeia (5) involves the application of ion-exchange resin followed by the concomitant determination of the absorbance of the standard and assay preparations in 1-cm cells of the wavelength of maximum absorbance at 226 nm. These assay procedures are lengthy and tedious. The present work extends the use of PMR spectroscopy for the quantitative determination of I as the pure drug and in its capsule dosage form. This is substantiated by virtue of the high unit dosage form of the drug (500 mg). Moreover, the PMR spectrum provides an identification of I.

Experimental

Apparatus and Chemicals - NMR spectrometer[1] was used. Standard clofibrate[2], commercial capsules[3] I, internal standard malonic acid II[4], deutrated acetone[5] (acetone-$D_6$), and acetone[4] were used. All chemical shifts reported are in reference to tetramethylsilane at 0 ppm.

Preparation of I capsule sample solution

Weigh and mix thoroughly the contents of not less than 20 capsules. Weigh accurately a portion of the oil, equivalent to about 500 mg of I, into a glass stoppered tube. Add the specified amount of II, accurately weighed and 3 ml of acetone. Stopper the tube and shake thoroughly for about 2 minutes. Transfer about 0.4 ml of the sample solution to an analytical NMR tube. Place in an NMR spectrometer and obtain the spectrum, adjusting the spin rate to eliminate the spinning side-bands as much as possible. Integrate the peaks of interest (the four aromatic protons quartet of I centred at 7.03 ppm. and the $CH_2$ - singlet of II appearing



1. Varian T-60A 60MHz.
2. USP Clofibrate Reference Standard.
3. Atromid-S, ICI, - Imperial Chemical Industrial Ltd., Pharmaceutical Division, Macclesfield, Cheshire, England.
4. B.D.H. Chemicals, Poole, England.
5. Koch - Light Laboratories Ltd., Colnbrook Bucks, England.

at 3.36 ppm) at least three times and determine the average integrals. The amount of I may then be calculated as follows:

$$\text{mg of I} = \frac{A_x}{A_a} \times \frac{E.W._x}{E.W._a} \times \text{mg II}$$

Where :

$A_x$ = integral value of the signal representing I.

$A_a$ = integral value of the signal representing II.

$E.W._x$ = formula weight of I/4 = 60.68

$E.W._a$ = formula weight of II/2 = 52.03



## Results and discussions

The PMR spectrum of I in deutrated acetone (Fig. 1) displays the following characteristic signals : $-CH_2\underline{CH_3}$ triplet at 1.23 ppm, $-(CH_3)_2$ singlet at 1.57 ppm, $-\underline{CH_2}\ CH_3$ quartet at 4.2 ppm, and the four aromatic protons quartet at 7.03 ppm. The four aromatic protons quartet centred at 7.03 ppm was chosen for quantitation of I, since it is widely separated from the signals of II as well as from that of the solvent. This peak is ideal for precise integration, thus allowing facile and accurate determination. Malonic acid II is employed as an internal standard, since it exhibits two protons methylene singlet at 3.36 ppm (Fig.2) which is widely separated from those of I. Moreover, the use of II as internal standard has been previously established (6).

Since I and II are freely soluble in acetone, it becomes the solvent of choice. Besides, its methyl protons singlet at 2.07 ppm

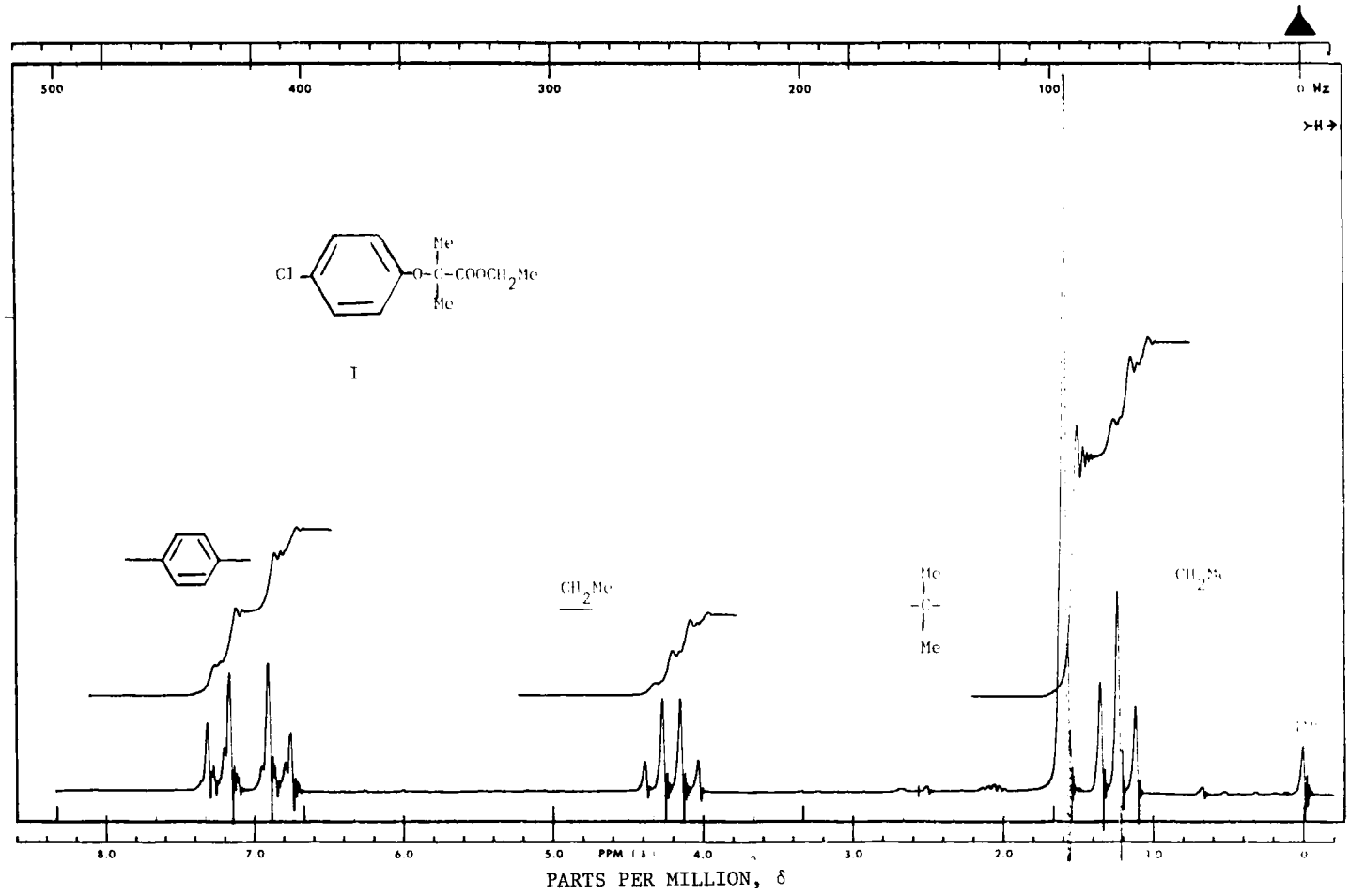



Figure I - PMR spectrum of clofibrate I and TMS, tetramethylsilane in deutrated acetone (acetone-$D_6$)

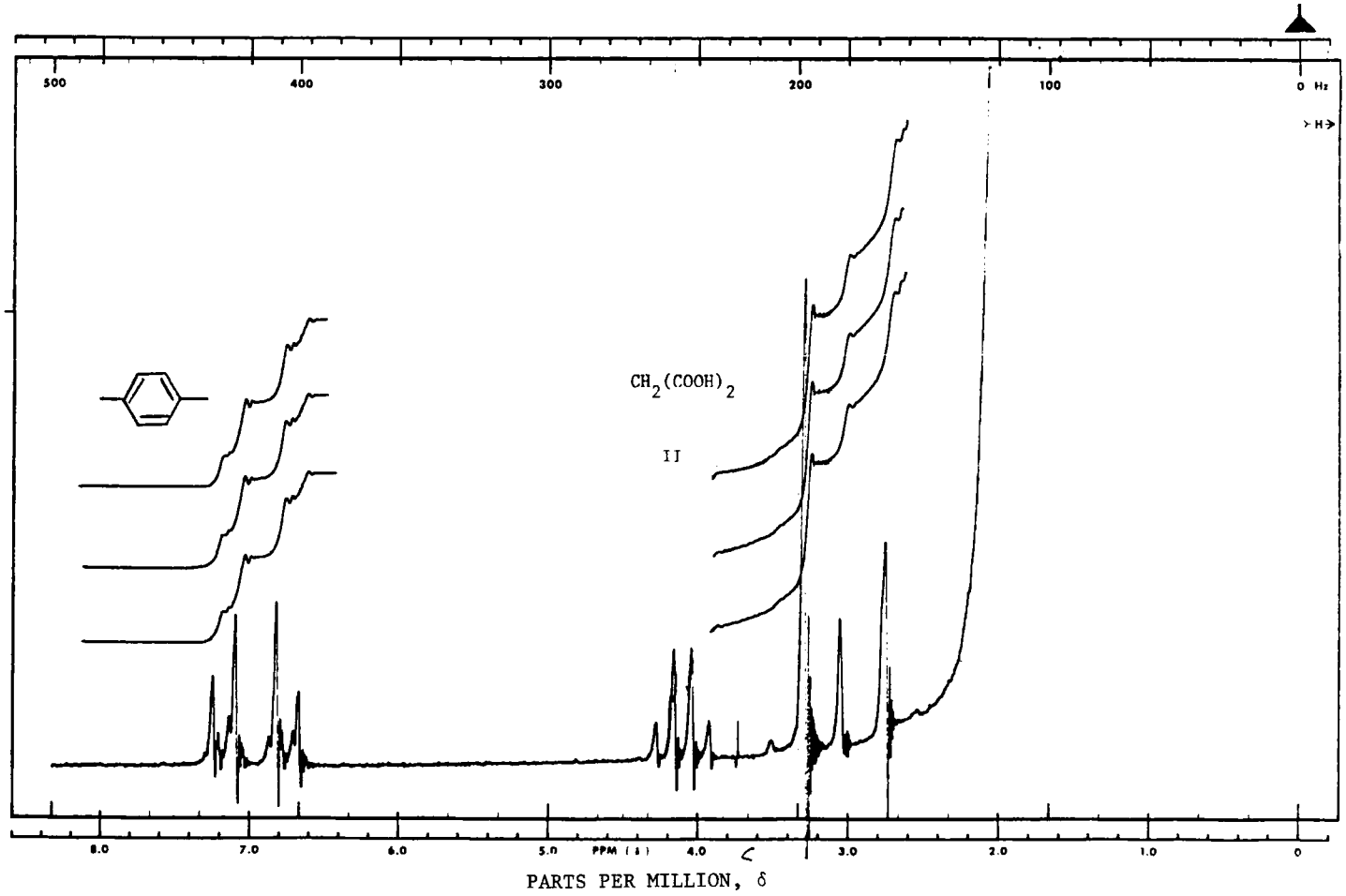



Figure 2 - PMR spectrum of clofibrate I, malonic acid II, and TMS, tetramethylsilane in acetone.

(Fig.2), does not interfere with the downfield protons of both I and II. Accordingly, the use of deutrated solvent is unnecessary.

A series of known standard I mixtures were prepared and assayed. It is evident from Table I that the method is both accurate and precise with an average of 99.70 $\pm$ 1.07 %.

Table 1 - Determination of clofibrate in standard by PMR.

| Standard Mixture | Internal Standard added, mg | Clofibrate | | |
|---|---|---|---|---|
| | | Added, mg | Found, mg | Recovery, % w/w |
| 1 | 50 | 100 | 99.91 | 99.91 |
| 2 | 50 | 100 | 98.26 | 98.26 |
| 3 | 61 | 151 | 150.87 | 99.91 |
| 4 | 75 | 175 | 171.67 | 98.10 |
| 5 | 135 | 262 | 266.74 | 101.81 |
| 6 | 135 | 280 | 277.17 | 98.99 |
| 7 | 171 | 294 | 293.32 | 99.77 |
| 8 | 132 | 304 | 305.49 | 100.49 |
| 9 | 250 | 454 | 453.45 | 99.76 |
| 10 | 227 | 490 | 490.23 | 100.04 |
| | | | Average | 99.70 |
| | | | SD | $\pm$ 1.07 |

By applying the procedure to commercial capsules of I, the results are in good agreement with the declared dosages (Table II), with an average of 99.43 ± 1.34%. Therefore, the method is superior to other reported methods, being simple, rapid, accurate and specific. Moreover, the simultaneous detection of impurities in the drug can be achieved.

Table II - Determination of clofibrate capsules by PMR.

| Sample | Internal Standard Added, mg | Clofibrate | | |
|---|---|---|---|---|
| | | Declared per capsule | Found, mg per capsule | Recovery, % w/w |
| 1 | 246 | 500 | 497.26 | 99.45 |
| 2 | 280 | 500 | 486.70 | 97.37 |
| 3 | 283 | 500 | 487.88 | 97.57 |
| 4 | 300 | 500 | 501.78 | 100.36 |
| 5 | 300 | 500 | 498.72 | 99.74 |
| 6 | 320 | 500 | 490.51 | 98.10 |
| 7 | 320 | 500 | 495.62 | 99.12 |
| 8 | 350 | 500 | 504.10 | 100.82 |
| 9 | 375 | 500 | 505.56 | 101.11 |
| 10 | 400 | 500 | 503.35 | 100.67 |
| | | | Average | 99.43 |
| | | | SD | ± 1.34 |

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