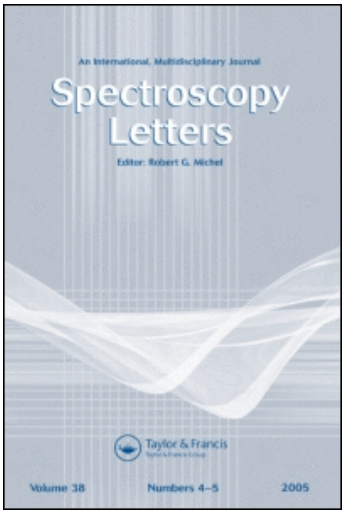

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Proton NMR Spectrometric Analysis of Glibenclamide and Tolazamide and Some of Their Pharmaceutical Preparations

Abdullah A. Al-badr[a]
[a] Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

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PROTON NMR SPECTROMETRIC ANALYSIS OF GLIBENCLAMIDE AND TOLAZAMIDE AND SOME OF THEIR PHARMACEUTICAL PREPARATIONS

Kay Words: PMR Spectrometry, Glibenclamide PMR Analysis, Glyburide PMR Analysis, Tolazamide PMR Analysis.

Abdullah A. Al-Badr
Department of Pharmaceutical Chemistry
College of Pharmacy,King Saud University
Riyadh, Saudi Arabia.

ABSTRACT

An analytical method is described for the assay of two important oral hypoglycemic agents, namely, glibenclamide (glyburide); and tolazamide; using PMR technique. The method is rapid, accurate, specific and precise.

The principle of the method involves comparing the integral of a chosen signal in the PMR spectrum of the drug under investigation with that of the methylene group signal of the internal standard, benzyl benzoate.

INTRODUCTION

Glibenclamide 1, also known as glyburide; 5-chloro-N[2-[[[(cyclohexylamino) carbonyl] amino] sulfonyl] phenyl] ethyl]-2-methoxybenzamide and Tolazamide 2; N-[[(Hexahydro-1H-azepin-1-yl) amino] carbonyl] -4-methylbenzenesulphonamide, are oral hypoglycemic agents.

Various techniques have been adopted for the assay of glibenclamide, among these are, polarographic[1-3], chromatographic[4-11], and nonaqueous titrimetric[12-13] techniques. Determination of glibenclamide in body fluids and pharmaceutical dosage forms have been reported. Hajdu et al[4] has reported a UV spectrophotometric assay

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of the drug in serum. A colorimetric method for the assay of glibenclamide in serum is reported[14]. A spectrofluorimetric method have been reported by Becker for the analysis of the drug[15]. Several chromatographic procedures for the assay of glibenclamide including TLC[16], GLC[17], and HPLC[18-20] have been reported. A number of radioimmunoassays have been developed which have the desired sensitivity for metabolic studies. Some of these[21-23] show cross reactions with the two major metabolites of glibenclamide, others[24,25] do not.

Although most of the above methods were found to be applicable to the analysis of tolazamide, the drug was also analysed by spectrofluorimetric[26], gas chromatography[27], gas chromatography/mass spectrometry[28] and pyrrolysis-gas chromatography[29] techniques.

Glibenclamide is official in British Pharmacopoeia 1980[30], tolazamide is official in the USP XX[31], the official method of assy of both drugs and their tablets are titrimetric and spectrophotometric.

This work describes a rapid, accurate, specific and simple method for the assay of glibenclamide and tolazamide, involving the application of PMR spectrometry.

EXPERIMENTAL

A Varian T 60-A PMR spectrometer was used throughout this study, authentic glibenclamide and its tablet (Doanil)^{R} were supplied by Hoechst AG. W. Germany, authentic tolazamide and its tablet (Tolinase)^{R} were supplied by Upjohn Co., Kalamazoo, MI 49001, U.S.A.

The 60 MHz spectra of glibenclamide, glibenclamide plus benzyl benzoate and the spectra of tolazamide and tolazamide plus benzyl benzoate are shown in Figs. 1,2,3,4 respectively. The following table describes the different conditions considered on the analysis of the drugs.

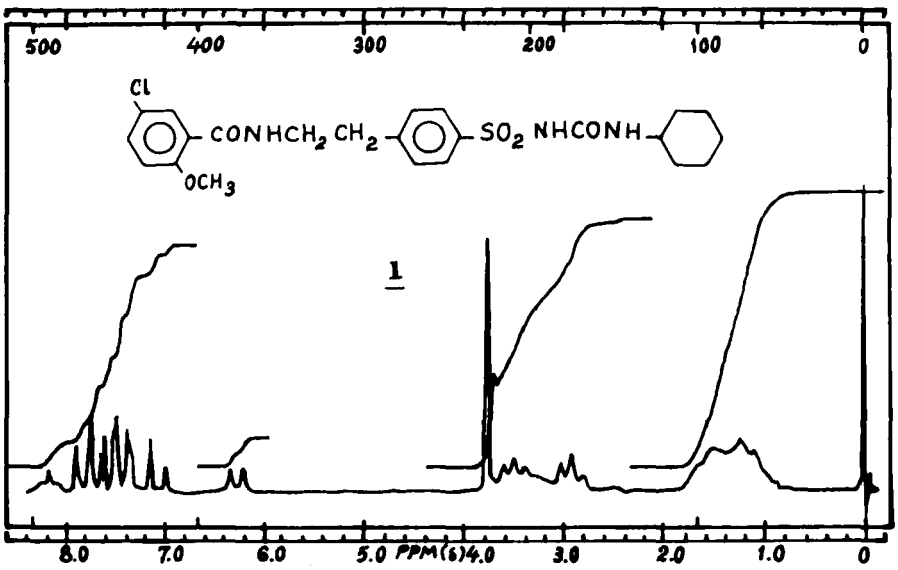

Fig. 1: NMR Spectrum of glibenclamide in deuterated dimethylsulphoxide and tetramethylsilane (TMS).

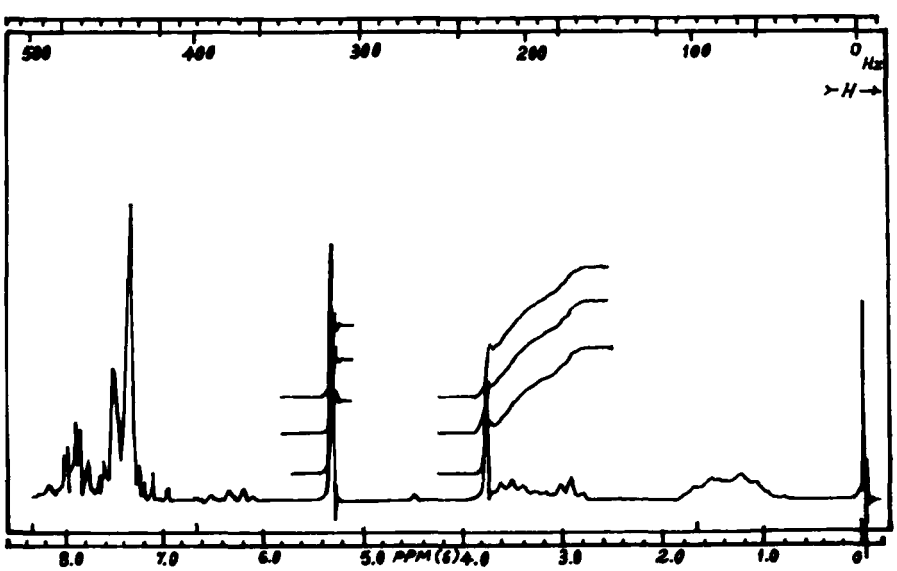

Fig. 2: NMR Spectrum of glibenclamide and benzyl benzoate in deuterated dimethylsulphoxide and tetramethylsilane (TMS).

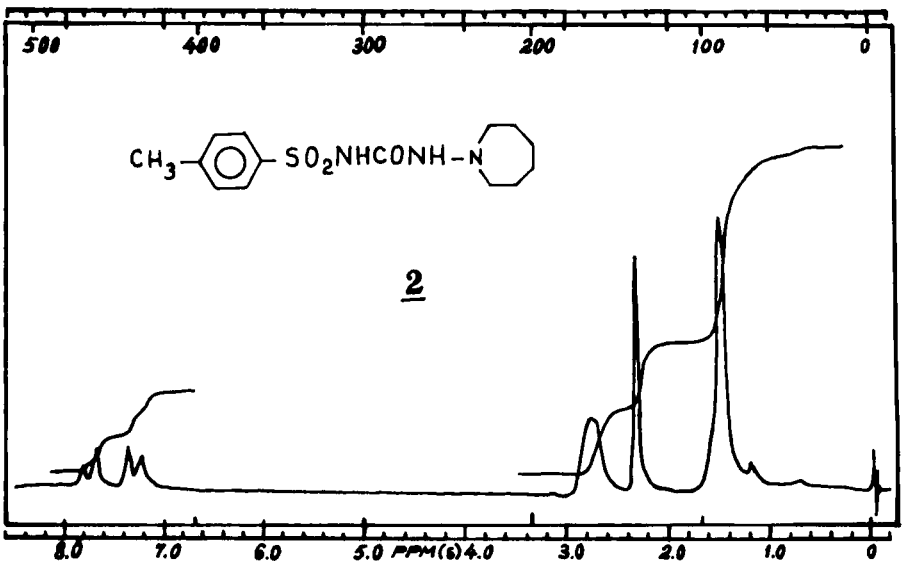

Fig. 3: NMR Spectrum of tolazamide in deuterated chloroform and tetramethylsilane (TMS).

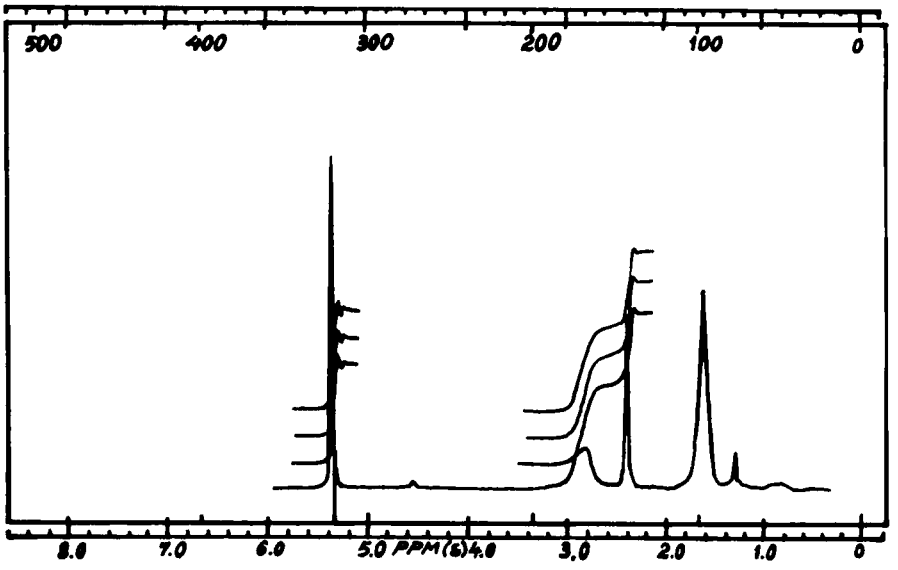

Fig. 4: NMR Spectrum of tolazamide and benzyl benzoate in deuterated chloroform and tetramethylsilane (TMS).

	Glibenclamide	Tolazamide
Internal standard and its signal (ppm)	benzyl benzoate (5.39)	benzyl benzoate (5.39)
Chosen signal of the drug (ppm)	methoxy group (3.8)	methyl group (2.42)
Solvent used	DMSO-D6	$CDCl_3$

PROCEDURE

1. Glibenclamide

a) For authentic drug: Weigh accurately a quantity of the authentic glibenclamide powder and dissolve in 0.5 ml of dimethylsulfoxide containing 50 mg of benzyl benzoate. Run the NMR spectrum, reducing the spining side-bands as much as possible. Integrate the peaks of interest at least three times and calculate the amount of the drug. Eight separate samples were analysed and results are shown in Table 1.

The amount of glibenclamide may be calculated as follows:

$$\text{mg of Glibenclamide} = \frac{A_1}{A_2} \times \frac{EW_1}{EW_2} \times W_2$$

A_1 = mean of three integrations of the methoxy group singlet of glibenclamide.

A_2 = mean of three integrations of the methylene group singlet of benzyl benzoate.

EW_1 - Mol. Wt. of glibenclamide/3

EW_2 = Mol. Wt. of benzyl benzoate/2

W_2 = Wt.(mg) of benzyl benzoate.

b) For glibenclamide tablet: Weigh an amount of the powdered tablets equivalent to certain weight of the drug, dissolve the powdered tablet in 1 ml of dimethylsulfoxide containing

Table 1: Authentic Glibenclamide

Sample No.	Claimed	Found	% Recovery
1	50	50.55	101.10
2	100	98.41	98.41
3	95	94.62	99.60
4	125	124.90	99.62
5	95	93.46	98.38
6	100	120.28	102.28
7	80	79.44	99.30
8	85	84.14	98.99

Average % recovery = 99.75

SD ± 1.34

Table 2: Assay of Glibenclamide Tablets

Sample No.	Claimed	Found	% Recovery
1	110	110.84	100.76
2	120	120.47	100.39
3	90	88.94	98.82
4	80	81.28	101.60
5	75	75.79	101.05
6	100	98.93	98.93
7	60	60.96	101.60
8	80	79.44	99.30

Average % recovery = 100.31

SD ± 1.14

50 mg of benzyl benzoate. Proceed as described under the authentic drug. Eight separate samples were analysed and results are shown in Table 2.

2. Tolazamide

a) For authentic drug: Weigh accurately a quantity of the authentic tolazamide powder. Dissolve in 0.5 ml of $CDCl_3$ containing 100 mg of benzyl benzoate and proceed as described under authentic glibenclamide. Eight separate samples were analysed and results are shown in Table 3.

The weight of the tolazamide may be calculated as follows:

$$\text{mg of tolazamide} = \frac{A_1}{A_2} \times \frac{EW_1}{EW_2} \times W_2$$

A_1 = mean of three integrations of the methyl group singlet of tolazamide.

A_2 = mean of three integrations of the methylene group singlet of benzyl benzoate.

EW_1 = Mol. Wt. of tolazamide/3

EW_2 = Mol. Wt. of benzyl benzoate/2

W_2 = Wt. (mg) of benzyl benzoate.

b) For tolazamide tablet: Weigh and finely powder 20 tablets. To a quantity of the powdered tablets equivalent to about 100 mg of tolazamide add 1 ml of $CDCl_3$ containing 100 mg of benzyl benzoate. Shake vigoroursly for 5 minutes and filter. Transfer 0.5 ml of the clear filtrate to an NMR tube and proceed as described under the authentic glibenclamide. Eight separate samples were analysed and results are shown in Table 4.

RESULTS AND DISCUSSION

The signals at 3.8 ppm (methoxy group of glibenclamide) and at

Table 3: Analysis of Tolazamide Powder

Sample No.	Claimed	Found	% Recovery
1	55	55.43	100.78
2	80	77.58	96.98
3	70	69.87	99.82
4	90	87.34	97.04
5	100	100.46	100.98
6	50	50.49	100.98
7	55	57.06	103.75
8	60	58.69	97.82

Average % recovery = 99.70

SD ± 2.32

Table 4: Analysis of Tolazamide Tablets

Sample No.	Claimed	Found	% Recovery
1	100	99.51	99.51
2	90	89.09	98.98
3	95	94.50	99.48
4	90	87.72	97.47
5	70	71.73	102.48
6	75	76.86	102.48
7	75	74.61	99.48
8	100	102.79	102.79

Average % recovery = 100.33

SD ± 1.97

2.42 ppm (methyl group of tolazamide) were chosen for the quantitation of the drugs. Benzyl benzoate was used as internal standard throughout this study as it is cheap, available in pure form and its signal does not interfere with the signals of the drugs.

Tables 1 and 2 show the percentage recoveries obtained when the proposed method was used for the assay of glibenclamide and its tablet form, the result demonstrate good precision and the average percent recoveries were 99.75 ± 1.34 and 100.31 ± 1.14 for the authentic glibenclamide and its tablets, respectively.

When the method was adopted for the quantitation of tolazamide the average percent recoveries were 99.70 ± 2.32 and 100.33 ± 1.97 for authentic tolazamide and its tablets, respectively (Tables 3 and 4).

Furthermore, the method was found to be specific for these drugs, no interference by the tablet excepients and helpful in checking the identity and purity of the drugs.

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