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QUANTITATIVE DETERMINATION OF TERFENADINE BY PROTON MAGNETIC RESONANCE TECHNIQUE

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ABSTRACT

A simple, rapid and efficient quantitative method has been achieved for the determination of terfenadine powder and its tablet form (Triludan)® . The method is based on comparison between the integration value of the singlet signal of the t-butyl protons, or the multiplet signal of the aromatic protons of terfenadine against the singlet singnal of the unsaturated residue of (an internal standard) maleic acid protons. The procedure as well as the results of the proposed method are accurate, precise and reproducible.

INTRODUCTION

Terfenadine, 1-(4-t-butylphenyl) -4 [4(α -hydroxybenzhydryl) piperidino] butanol ,is one of the recently used antihistaminics of great therapeutic value. Different methods has been reported for its assay, including non-aqueous[1], spectrometric and first derivative absorption methods [2]. In addition, other colourimetric methods are based on its interaction with π and σ acceptors such as 7, 7, 8, 8, tetracyanoquinodimethane or iodine, followed by measurement of the colour obtained at 845 nm and 290 nm due to n- π and n- σ complexes respectivetly[3]. Thin layer chromatography[2] and HPLC techniques[4-8] are also reported for determination of the drug in bulk and dosage forms . Moreover, radioimmuno-assay was also introduced[4,9]. The use of PMR techique has been reported[10] for the assay of carbamazepine tablets (Tegretol)®. Thus , it seemed interesting to develope a method for the determination of terfenadine in its powder

and tablet forms (Triludan)® by PMR method, using maleic acid as an internal standard .

EXPERIMENTAL

Apparatus:

All spectra were recorded on a Varian T-60 MHz spectrometer using DMSO-d6 as solvent and maleic acid as an internal standard.

Materials:

Terfenadine : Merrel, Don Pharmaceuticals Ltd. Rushampark, Egham, Surrey, U. K.

Triludan tablets : each tablet labelled to contatin 60 mg terfenadine, produced by Merrel.

Deutrated DMSO-d6 : from Aldrich.

Methods :

(A) Assay of Authentic Sample of Terfenadine:

Terfenadine (10-60 mg) was introduced into glass stoppered weighing bottles containing 20 mg of maleic acid. Deuterated dimethylsulphoxide (DMSO-d6) (0.8 ml) was added to each bottle, and shaken well till complete dissolution. The solution was filtered and the clear filterate , transferred to NMR tube and the spectrum was run. All peak field positions are referenced to tetramethylsilane (TMS) at 0.00 ppm.

The peaks at δ 1.3, 7.4-7.88 and 6.5 were integrated (three times for each) and the average was calculated. The Ratio (Id/Is) was plotted against the concentration of the drug in milligrams (where Id and Is are integral values of the drug and standard signals in mm respectively)

(B) Assay of Terfenadine Tablet form (Triludan)® :

Ten terfenadine tablets were accurately weighed grinded and finally powdered . The average weight of one tablet was calculated. An amount of the powder equivalent to about 200 mg of the drug was placed into 50 ml beaker containing 10 ml of chloroform. Solution was

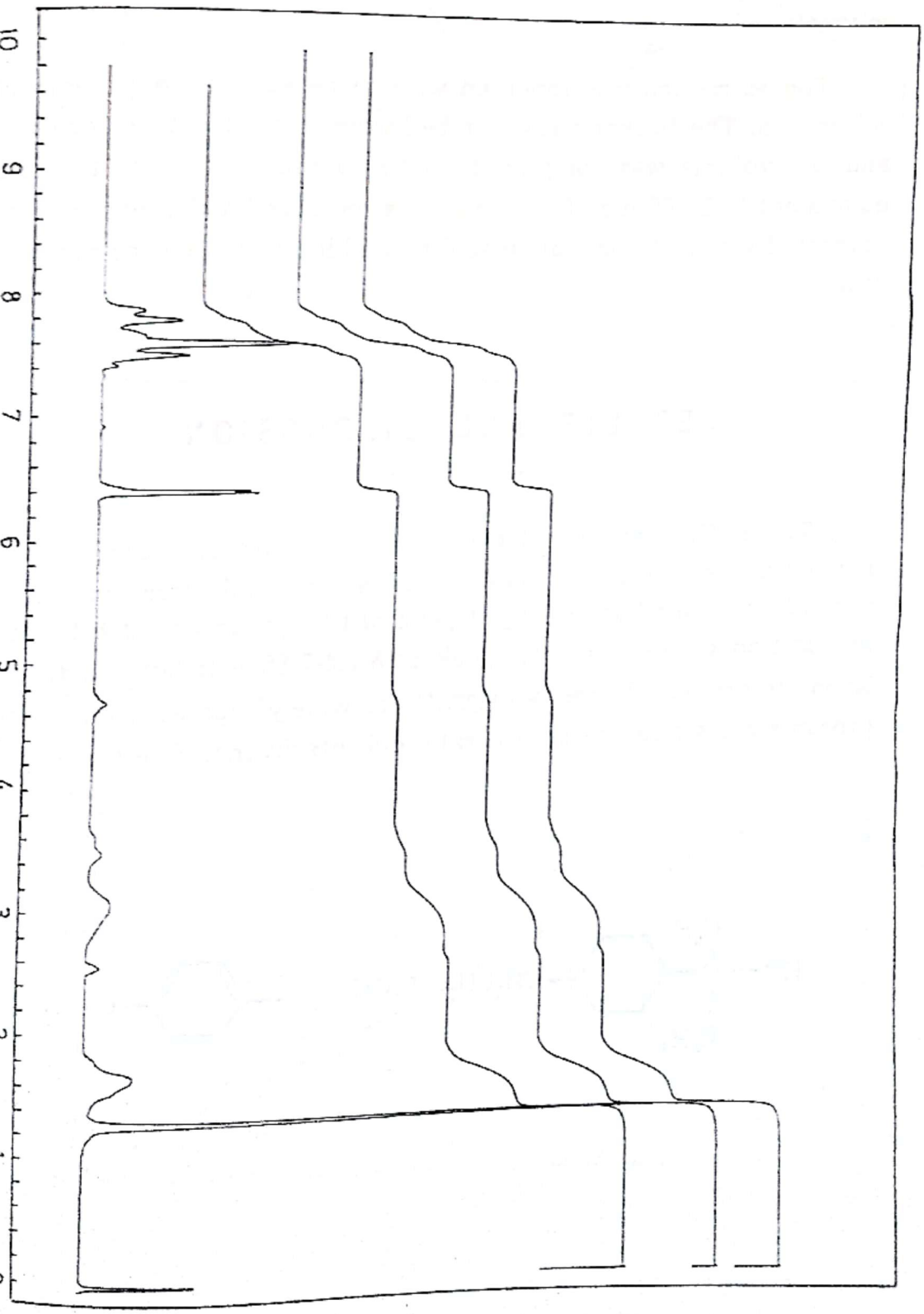


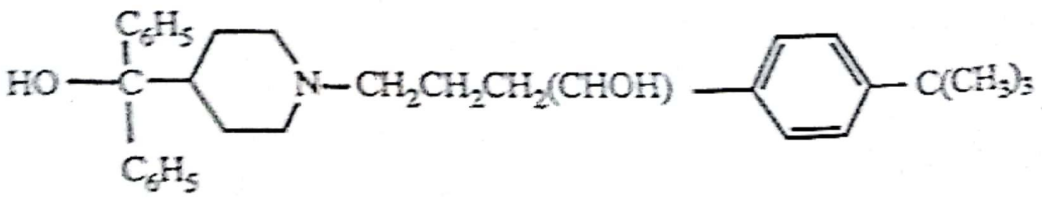
FIG. (1) PMR SPECTRUM OF TERFENADINE IN DMSO-D6 CONTAINING MALEIC ACID

stirred for about 10 min then filtered through cotton wad into 50 ml volumetric flask.

The extraction was repeated with three successive portions of chloroform. The beaker and filter bed were washed with chloroform and the volume was completed up to 50 ml. Different aliquots equivalent to 20-60 mg of the drug were measured and evaporated to dryness. Exactly 20 mg maleic acid was added and the spectrom was run.

RESULTS AND DISCUSSION

The PMR spectrum of terfenadine solution in deuterated-dimethylsulphoxide using maleic acid as internal standard (Fig 1) showed an isolated sharp singlet peak of t-butyl protons at δ 1.3 ppm in addition to the multiplet peak at δ 7.4-7.88 attributable to the aromatic protons. These two signals are widely separated from other proton signals allowing an accurate and interference free route.



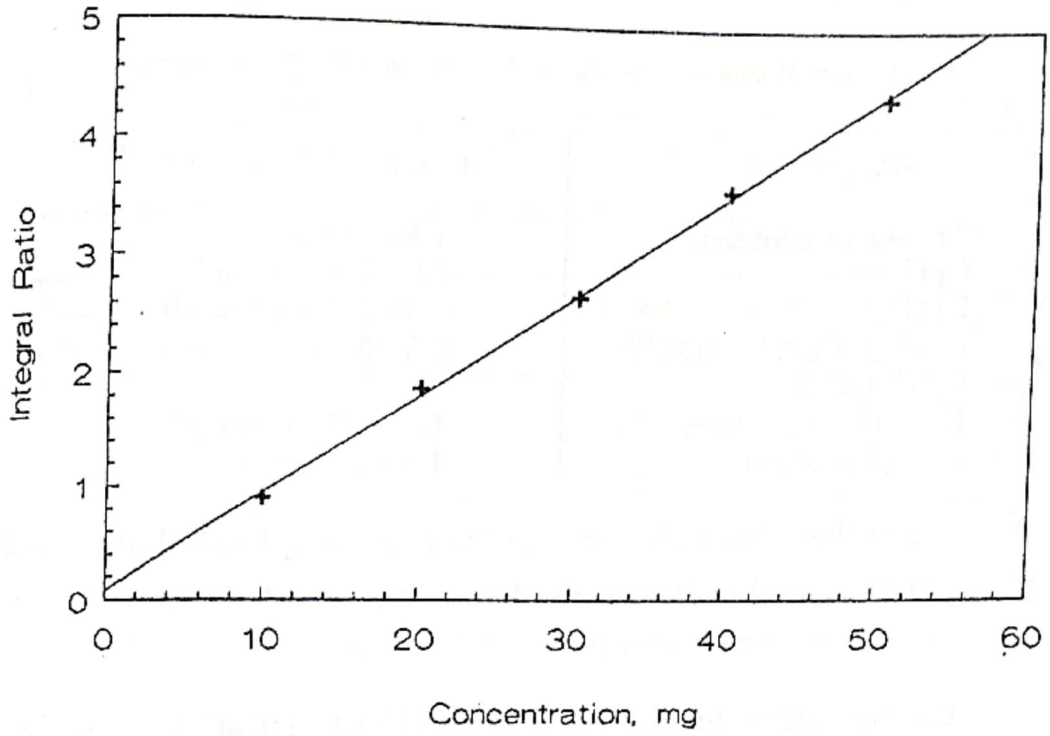


Fig. (2): Calibration Graph of Terfenadine (Using the Integral of Aromatic Protons)

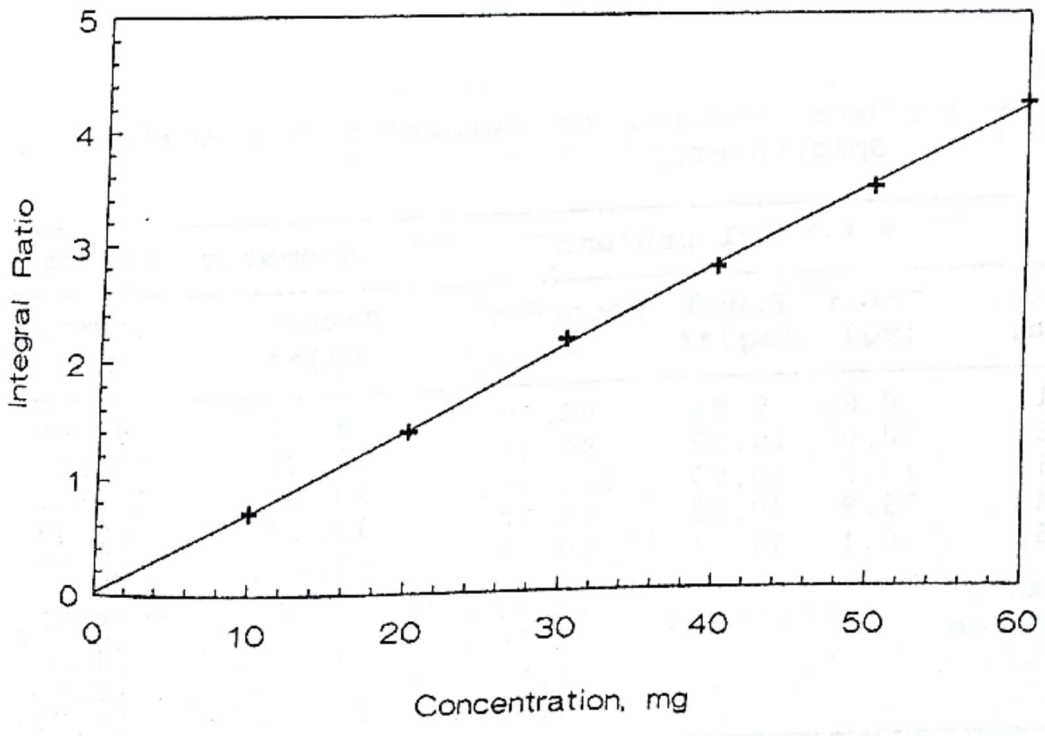


Fig. (3): Calibration Graph of Terfenadine (Using the Integral of t-Butylprotons)

Proton Magnetic Resonance Assignments for Terfenadine

Assignment	Chemical shift (ppm)
Aromatic protons	7.4 - 7.88
C_1 (H)	4.5 - 4.8 (t, broad)
C_4 (H_2)	3.4 - 3.7 (m, broad)
C_2-(H_2), C_6-(H_2), (O-H)	2.5 - 3.2 (m, broad)
C_2(H_2), C_3(H_2), Piperidine protons	1.5 - 1.9 (m, broad)
t-butyl protons	1.3 (s, sharp)

Since the other hydrogen signals of the drug located at δ 2.5-4.8 ppm are not suitable for quantitative analysis, yet they only help in confirming the identity and purity of the drug.

On the other hand, maleic acid [HOOC-HC=CH-COOH] was chosen as an internal standard due to the nice location of its two olefinic protons which are chemically and magnetically equivalent and absorb sharply at δ 6.5 ppm. This singal is relatively far from the signals of t-butyl and aromatic protons of the test drug.

Table 1 : Determination of Authentic Terfenadine by PMR Spectrometry.

	* t-butyl protons			Aromatic protons	
Exp. No.	Taken (mg)	Found (mg)**	Recovery %	Found (mg)**	Recovery %
1	10.0	9.81	98.10	9.84	98.46
2	20.0	19.89	99.45	20.10	100.50
3	30.1	30.69	101.96	30.40	101.01
4	39.9	40.05	100.38	39.70	99.49
5	50.1	49.41	98.62	49.43	98.66
Mean			99.70		99.62
Variance			2.33		1.24
S.D.			1.52		1.11
S.E.			0.681		0.500

* Mixed with 20 mg of maleic acid.
** Average of three experiments.

Table 2 : Determination of terfenadine in Triludan tablets by the proposed method* compared with the non-aqueous method (2) (using the integral of t-butyl protons).

Proposed method			Non aqueous method		
Taken mg	Found mg**	Recovery %	Taken mg	Found mg	Recovery %
20	19.8	99.00	20	19.72	98.60
30	30.2	100.66	40	39.70	99.25
40	39.5	98.75	60	60.07	100.11
50	50.6	101.20	80	79.50	99.37
60	59.5	99.16	100	101.00	101.00
Mean		99.75			99.67
Variance		1.20			0.839
S.E.		0.491			0.410
t		0.125 (2.3)			
F		1.43 (5.05)			

* Mixed with 20 mg of maleic acid.
** Average of three experiments.

Table 3 : Statistical Analysis of the Results Obtained by the PMR Spectrophotometric Procedure Compared with Non Aqueous Method upon Analysis of Terfenadine.

	PMR *	Non aqueous
Mean	99.62	100.19
N	5	5
Variance	1.24	1.37
S.D.	1.11	1.17
S.E.	0.500	0.525
t	0.787 (2.3)	
F	1.11 (5.50)	

* Using the integral value aromatic protons.

Table 1 represents the results of PMR technique applied for determination of authentic terfenadine. Results obtained showed good precision with mean percentage recovery at 99.7± 0.681 and 99.62 ± 0.500 for t-butyl and aromatic protons, respectively.

A linear relationship was obtained on plotting the integral ratio (Id/Is) against the concentration of the drug in milligrams where Id and Is are the integral values of the drug and standard, repectively (Figs 2 & 3).

Application of the proposed method for quantitative analysis of terfenadine in its tablet dosage form is shown in table 2. Accurate and precise results are obtained with a mean percentage recovery of 99.75 ± 0.491.

Results obtained by applying the PMR method for the determination of terfenadine tablet form (Triludan)® are compared with the non aqueous method as shown in Table 3.

Statistical analysis of the results obtained revealed good correlations between the PMR and the non aqueous method. Thus, the PMR procedure is specific, simple and rapid. In addition, the method is valid in presence of other binding agents and excepients e.g., starch or magnesium stearate.

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التحليل الكمى لمادة الترفينادين بأستخدام الرنين النووى المغناطيسى للهيدروجين

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فى هذا البحث تم استنباط طريقة سريعة وجديدة بإستخدام الرنين النووى المغناطيس للهيدروجين لتعيين مادة الترفينادين فى صورة مسحوق أو أقراص (المعروفة بإسم ترايلودان) . وتعتمد هذه الطريقة على المقارنة بين المتمم الوجدانى الإحادى لبروتونات ثلاثى البيوتيل أو البروتونات الحلقية لمادة الترفينادين وبين المتمم الوجدانى لبروتونات حامض الماليك .

وقد أوضحت النتائج المطبقة على المسحوق والمستحضر الصيدلى (أقراص الترايلودان) أن الطريقة بسيطة وعالية الدقة ومتكررة .