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Short Communication

Determination of chlorpheniramine maleate in tablets and injections by ^{1}H-NMR spectroscopy*

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Introduction

Chlorpheniramine, a propylamine derivative with potent and long lasting antihistaminic action, is a common ingredient of products used to treat symptoms of allergic states and to lessen rhinorrhea [1]. As the maleate salt, it is commercially available in solid and liquid dosage forms, alone or as part of a multi-component formulation [2].

Existing methods for the assay of this compound as a drug substance and in dosage forms are many, both in number and in the type of analytical approach used [3–22], and they have included titrimetry [3, 4], gravimetry [5], colorimetry [6–8], spectrophotometry [9–12], fluorometry [13, 14], polarography [15], thin-layer chromatography [16], gas–liquid chromatography [17–19], and HPLC [20–22] among others. Although useful, these methods cannot be used for the positive identification of the analyte and, on occasions, they may be interfered by other ingredients in the formulation [11].

The present report describes a ^{1}H-NMR spectroscopic method for the analysis of chlorpheniramine maleate in tablets and injections which is not only simple, specific and accurate, but also well suited for identification purposes.

Experimental

Apparatus

All ^{1}H-NMR spectra were obtained with a 90 MHz, EM-390 spectrometer (Varian Associates, Sunnyvale, CA, USA), operating at an ambient probe temperature of 35 ± 1°C, a sweep time of 5 min, and a sweep width of 10 ppm. The instrument was adjusted to produce no interfering bands between 1.2 and 3.0 ppm.

Materials

Chlorpheniramine maleate was a USP reference standard or from a commercial source (Sigma, St Louis, MO, USA); deuterochloroform ($CDCl_3$, >99.5 atom % D), *tert*-butyl alcohol (TBA) and tetramethylsilane (TMS, >99.9%) were from Aldrich (Milwaukee, WI, USA); various lots of chlorpheniramine tablets (4 mg) and injections (10 mg ml^{-1}) were obtained from commercial sources.

Preparation of tablets

Method 1. Weigh and reduce to a fine powder not less than 20 tablets. Transfer an accurately weighed quantity of powder, equivalent to about 30 mg of chlorpheniramine maleate, to a separatory funnel containing 2 ml of water, and dissolve with gentle swirling. Make the solution basic with one drop of 3 N NaOH, and extract into 3 ml of CHl_3. Transfer the $CHCl_3$ layer to a test tube, and evaporate the solvent to dryness under a stream of dry nitrogen.

Method 2. Place an accurately weighed quantity of powdered tablet sample, equivalent to about 30 mg of chlorpheniramine maleate,

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in a glass-stoppered centrifuge tube, extract with 2 × 3 ml of $CHCl_3$ with the aid of a vortex mixer, and centrifuge. Decant the $CHCl_3$ extracts into a test tube, and evaporate to dryness under a stream of dry nitrogen.

Preparation of injections

Method 1. Transfer an accurately measured volume of injection, equivalent to about 30 mg of chlorpheniramine maleate, to a separatory funnel, make basic with 1 drop of 3 N NaOH, and proceed as described for tablet samples, Method 1.

Method 2. Transfer an accurately measured volume of injection, equivalent to about 30 mg of chlorpheniramine maleate, to the vacuum jar of a freeze drier, freeze the solution at about −40°C, and freeze dry to a dry residue at about 10^{-3} torr.

NMR assay

To the dry residue add about 9 mg of TBA, accurately weighed, and 1 ml of 1% TMS in $CDCl_3$. Effect solution with the aid of a vortex mixer. Using a Pasteur pipette, transfer 0.5 ml of the solution to a NMR tube, and obtain the ^{1}H-NMR spectrum. Assign all chemical shifts with reference to TMS taken as 0.0 ppm on the δ scale. Integrate the resonance at 2.18 ppm (singlet, 6 Hs) and between 1.95 and 2.70 ppm (multiplet, 4 Hs) for chlorpheniramine, and at 1.25 ppm (singlet, 9 Hs) for the internal standard, at least five times each, and calculate the average integral values. The quantity of chlorpheniramine maleate (as $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$) in the dosage form is calculated from one of the following equations:

$$\text{mg/tablet} = (A_u/A_s) \times (EW_u/EW_s) \times C \times (W/T),$$

$$\text{mg/ml injection} = (A_u/A_s) \times (EW_u/EW_s) \times (C/V),$$

where A_u and A_s are the average integral values for chlorpheniramine maleate and TBA, the internal standard, respectively; EW_u and EW_s are the formula masses of chlorpheniramine maleate and TBA divided by the corresponding number of absorbing protons (i.e. 390.90/10 = 39.09 and 74.12/9 = 8.24), respectively; C is the amount of internal standard used in the assay (mg); W is the average tablet mass (mg); T is the mass of powdered tablet used in the assay (mg); and V is the volume of injection used in the assay (ml).

Inter-method comparison

The assay results by the proposed method were compared against those obtained by a reversed-phase high-performance liquid chromatographic (RP-HPLC) method in the isocratic mode. For this purpose, an Econosphere C_{18}, 5 μm, 150 mm × 4.6 mm i.d. column (Alltech, Deerfield, IL, USA), a mixture of methanol–water–phosphoric acid (55.0:44.8:0.2, v/v/v) containing 0.2 g l^{-1} of sodium hexanesulphonate as mobile phase, and detection at 215 nm, 0.5 AUFS, were used. Tablet samples were extracted into methanol–water (1:1) with the aid of sonication. A portion of filtered extract, or a volume of injection, was then diluted quantitatively with methanol–water (1:1) to a concentration of about 160 μg (tablets) or 200 μg ml^{-1} (injections), and an aliquot was injected into the chromatograph through a sample injection valve fitted with a 20 μl loop.

Results and Discussion

The analytical results presented in this report were obtained using a sample preparation method that entails the extraction of the free base form of chlorpheniramine into $CHCl_3$ from an alkaline aqueous solution of tablets or injections. In this manner, solid and liquid dosage forms were prepared using the same procedural steps. However an alternative sample preparation method is also described, namely the extraction of the maleate salt into $CHCl_3$. Although this approach is simpler for tablet samples, it cannot be applied to injections directly owing to the greater solubility of the maleate salt in an aqueous medium than in an organic one. This difficulty can be overcome by first freeze drying the injection sample [23]. By comparing spectra obtained from dosage forms with those from standard preparations, it was verified that no interfering excipients from tablets or preservatives from injections were extracted into $CHCl_3$. $CDCl_3$ was found convenient as a solvent for NMR determinations since it readily dissolved both the analyte and TBA, the internal standard. The protons of TBA resonated as a strong singlet, at a convenient (*ca* 1.25 ppm) upfield location, well separated from the resonances of

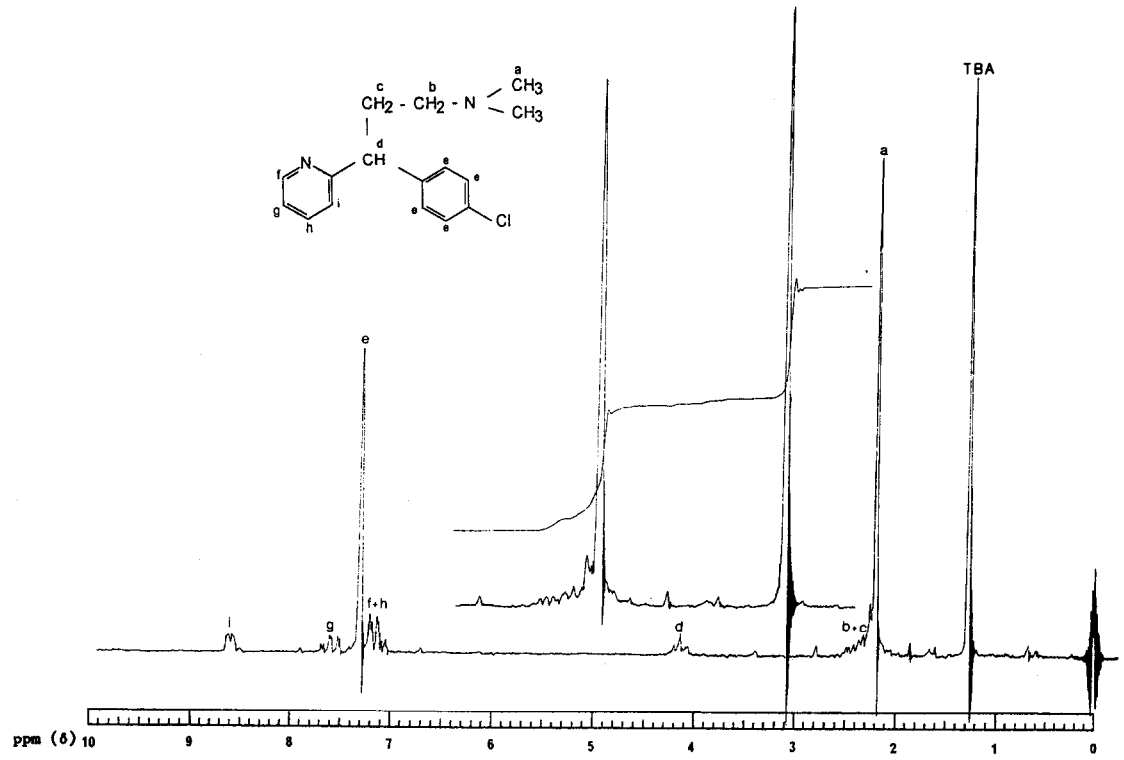

Figure 1
^{1}H-NMR spectrum of a mixture of chlorpheniramine and TBA, the internal standard, in $CDCl_3$. The inset is an expansion of the 1.0–3.0 ppm region to show details of the peak integrations.

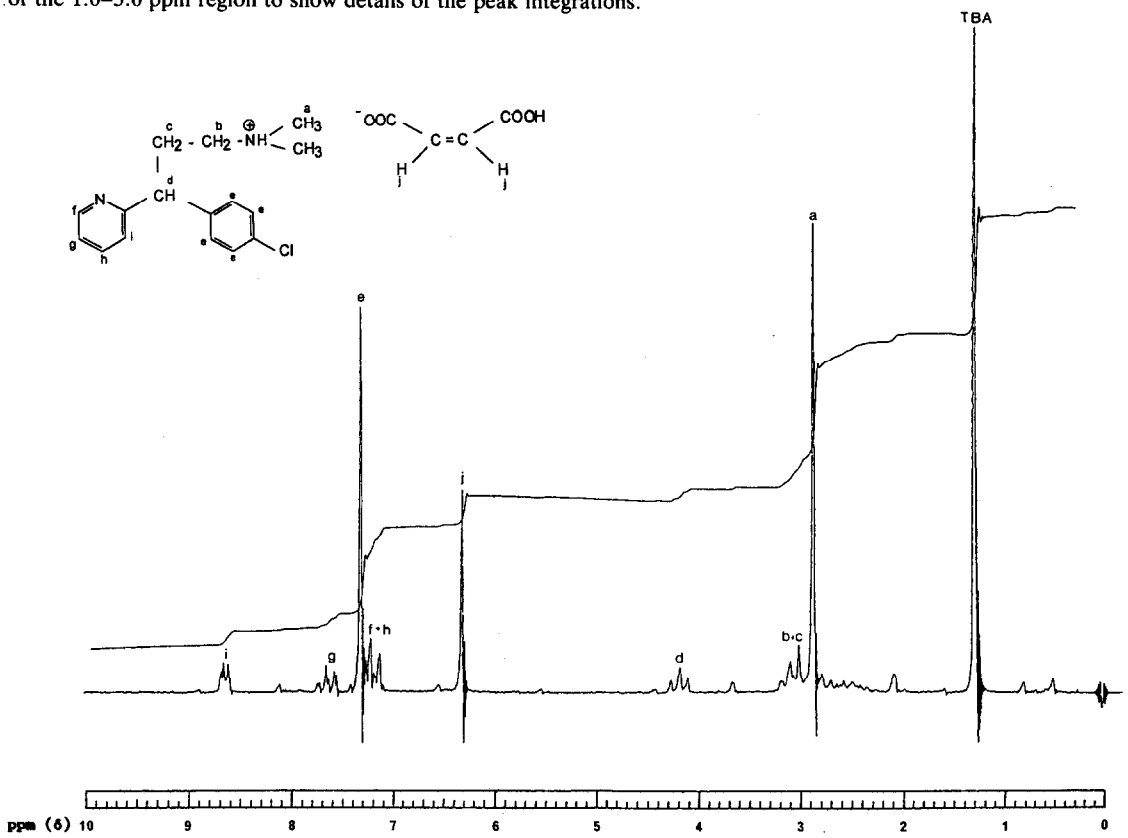

Figure 2
^{1}H-NMR spectrum of a mixture of chlorpheniramine maleate and TBA, the internal standard, in $CDCl_3$. The signal for the olefinic proton of the maleate moiety appeared at about 6.3 ppm.

Table 1
^{1}H-NMR spectral assignments for chlorpheniramine, chlorpheniramine maleate and TBA in $CDCl_3$

Assignment	No. of protons	Chemical shift (ppm)		Multiplicity
		Free base	Maleate	
$-N(C\underline{H}_3)_2$	6	2.18	2.85	Singlet
$-C\underline{H}_2-C\underline{H}_2-N<$	4	1.90–2.70	2.00–3.30	Multiplet
$>C\underline{H}-C-C-N<$	1	4.15	4.15	Multiplet
Phenyl	4	7.30	7.30	Singlet
Pyridinyl C_2 + C_4	2	7.20	7.20	Multiplet
Pyridinyl C_3	1	7.60	7.65	Multiplet
Pyridinyl C_5	1	8.60	8.63	Multiplet
$-C\underline{H}=C\underline{H}-$	2	—	6.30	Singlet
TBA	9	1.25	1.25	Singlet

chlorpheniramine. Representative ^{1}H-NMR spectra of mixtures of chlorpheniramine or of its maleate salt with TBA are shown in Figs 1 and 2. Resonance assignments are summarized in Table 1. The quantities of chlorpheniramine were calculated on the basis of the resonances for its $-N(CH_3)_3$ and $-CH_2-CH_2-N<$ protons and of those for the $-C(CH_3)_3$ protons of TBA.

Table 2
Recovery of chlorpheniramine maleate from standard mixtures*

Mixture no.	TBA added (mg)	Chlorpheniramine maleate		
		Added (mg)	Found (mg)	Recovery (%)
1	9.6	37.5	37.3	99.5
2	10.2	32.5	32.5	100.0
3	9.3	29.8	29.9	100.3
4	9.2	23.4	23.2	99.1
5	10.1	25.7	25.6	99.6
6	9.5	27.8	27.9	100.4
7	10.0	31.5	31.5	100.0
Mean				99.8
SD				0.47
RSD (%)				0.47
8	9.0	39.2	39.4	100.5
9	9.8	33.4	33.2	99.4
10	9.9	28.6	28.5	99.7
11	9.5	27.9	28.0	100.4
12	9.3	27.2	27.3	100.4
13	9.4	31.8	31.7	99.7
14	9.4	31.0	31.0	100.0
15	9.7	32.5	32.4	99.7
Mean				100.0
SD				0.41
RSD (%)				0.41

*Mixtures 1–7 were treated as described for tablets; mixtures 8–15 were first reconstituted in water to simulate injections.

To evaluate accuracy, a set of 15 synthetic mixtures of chlorpheniramine maleate and the internal standard in the proportions shown in Table 2 were analysed by the proposed method. The overall mean ± SD of recovered chlorpheniramine was 99.9 ± 0.44%. These results indicated that the drug was consistently recovered in a quantitative manner and that the accuracy of the method was independent of the relative proportions of drug to internal standard for the range of concentrations examined.

Determination of the drug content of several lots of commercial chlorpheniramine maleate tablets and injections by the proposed NMR spectroscopic method yielded the results presented in Tables 3 and 4. Assay values ranged from 99.8 to 100.3% for tablets, and from 99.7 to 100.2% for injections. In turn these results were compared with those obtained by a RP-HPLC method and they were found to correlate closely. Inter-method differences for tablets and injections amounted to *ca* 0.6 and 2.7% of labelled, respectively. All the samples were found to meet the official requirements for labelled potency.

In summary, the proposed NMR spectroscopic method is shown to be a simple and reliable means of quantifying chlorpheniramine maleate as a drug substance and in dosage forms. Furthermore, it permits the simultaneous identification of the analyte without the need for a sample of pure standard.

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Table 3
Results of the assay of commercial tablets by the proposed ^{1}H-NMR method and a RP-HPLC method*

Lot no.	Amount declared (mg/tablet)	Amount found (mg/tablet)	Amount found (% of declared)
1	4	3.99	99.8
2	4	4.00	100.0
3	4	4.00	100.0
4	4	3.99	99.8
5	4	4.01	100.3
Range			99.8–100.3
Mean			99.8
HPLC method:			
Mean (n = 2)			99.2

*USP XXII requirement: 93.0–107.0% of the labelled amount.

Table 4
Results of the assay of commercial injections by the proposed ^{1}H-NMR method and a RP-HPLC method*

Lot no.	Amount declared (mg ml^{-1})	Amount found (mg ml^{-1})	Amount found (% of declared)
1	10	9.97	99.7
2	10	10.00	100.0
3	10	10.02	100.2
4	10	10.00	100.0
5	10	9.98	99.8
Range			99.7–100.2
Mean			99.0
HPLC method:			
Mean (n = 3)			101.7

*USP XXII requirement: 90.0–110.0% of the labelled amount.

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