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^{1}H-NMR SPECTROSCOPIC ASSAY METHOD FOR METOCLOPRAMIDE HYDROCHLORIDE IN TABLETS AND INJECTIONS

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ABSTRACT

A simple, accurate and specific proton nuclear magnetic resonance (^{1}H-NMR) spectroscopic method has been developed for the assay of metoclopramide hydrochloride in tablets and injections. In deuterium oxide, the analyte and acetamide, the internal standard, produced corresponding resonance signals at 1.35 ppm and 2.03 ppm of utility for quantitative purposes. The average ± SD recovery of drug from 10 synthetic formulations was 99.7 ± 0.7% of the added amount. The assay of commercial products by the proposed method resulted in average assay values of 100.43 (range = 98.8-100.8, n = 6)% of declared for tablets, and of 99.45 (range = 99.6-100.4, n = 4)% of declared for injections. These results were

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validated by a high performance liquid chromatographic (HPLC) method.

INTRODUCTION

Metoclopramide hydrochloride is a substituted benzamide commonly used for the prevention of the nausea and vomiting that develops during emetogenic cancer therapy[1], and for stimulating the motility of the upper gastrointestinal tract[2].

During the course of regulatory analytical work on commercial dosage forms of this drug, the need arose for a method that would permit verification of both product potency compliance and identity of the active ingredient. However, with the possible exception of those methods relying on the use of mass spectrometry[3,4], the analysis of metoclopramide in biological[1,5-15] and pharmaceutical[16-23] samples have entailed techniques that can quantify the drug but without providing conclusive evidence on its identity. Both requirements can be accomplished simultaneously and in a simple and straightforward manner by the ^{1}H-NMR spectroscopic method described in this report.

EXPERIMENTAL

Apparatus - All ^{1}H-NMR spectra were recorded on a 90 MHz, EM-390 spectrometer (Varian Instrument Group, Sunnyvale, CA), 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 1.2-2.2 ppm.

Materials - Metoclopramide monohydrochloride (Sigma Chemical Co., St. Louis, MO); acetamide, 99+ mol % (Eastman Kodak Co., Rochester, NY); deuterium oxide, 99.7 atom % D (D_2O, Merck & Co., Inc., Rahway, NJ); sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4, 99+ atom % D (TSP, Merck & Co., Inc., Rahway, NJ); metoclopramide hydrochloride 5 mg tablets and 5 mg/mL injections were obtained from commercial sources.

Preparation of Tablets - Weigh and reduce to a fine powder not less than 20 tablets. Transfer a quantity of powder, equivalent to about 120 mg of metoclopramide hydrochloride, to a centrifuge tube, add 10 mL of methanol, and mix with the aid of a vortex mixer. Centrifuge, transfer 5 mL of the clear supernant to a test tube, and evaporate to dryness with the aid of a stream of dry nitrogen.

Preparation of Injections - Combine the contents of various ampules, and transfer an accurately measured volume of the solution, equivalent to about 60 mg of metoclopramide hydrochloride, 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.

Assay - To the residue add about 40 mg of acetamide, accurately weighed, and 2 mL of D_2O, and effect solution with the aid of a vortex mixer. Using a Pasteur pipet, transfer 0.5 mL of the solution to an NMR tube that contains a few crystals of TSP, and record the ^{1}H-NMR spectrum. Assign all chemical shifts with reference to TSP taken as 0.0 ppm on the δ scale. Integrate the triplet centered at 1.36 ppm (6 H's, metoclopramide) and the

singlet at 2.03 ppm (3 H's, acetamide) at least 5 times each, and calculate the average integral values. The quantity of metoclopramide hydrochloride (as $C_{14}H_{22}ClN_3O_2.HCl.H_2O$) in the dosage form is calculated using one of the following equations: mg/tablet = $(A_{sp}/A_{st}) \times (EW_{sp}/EW_{st}) \times (C_{st}/C_{sp}) \times T$ or mg/injection = $(A_{sp}/A_{st}) \times (EW_{sp}/EW_{st}) \times (C_{st}/V)$, where A_{sp} = av. integral value of the signal for metoclopramide hydrochloride; A_{st} = av. integral value of the signal for acetamide; EW_{sp} = formula weight of metoclopramide hydrochloride/number of absorbing protons, i.e., 354.28/6 = 59.05; EW_{st} = formula weight of acetamide/number of absorbing protons, i.e., 59.07/3 = 19.70; C_{st} = weight of acetamide used in the assay, mg; C_{sp} = weight of sample taken, mg; and V = volume of injectable taken, mL.

RESULTS AND DISCUSSION

Both metoclopramide hydrochloride and acetamide, the internal standard, were readily soluble in D_2O, the NMR solvent. The protons of acetamide resonated at a convenient upfield position, well resolved from the resonances of the analyte. Neither compound gave evidence of degrading in D_2O during a 3 day observation period.

A 90 MHz ^{1}H-NMR spectrum of a mixture of metoclopramide hydrochloride and acetamide in D_2O is shown in Figure 1. The following assignments were inferred for metoclopramide: triplet at 1.36 ppm, $(-C-CH_3)_2$; quartet at 3.35, $-N(CH_2-C)_2$; triplet at 3.38 ppm, $-C-CH_2-N$; triplet 3.79 ppm, $-CO-N-CH_2-C$; singlet at 3.92 ppm, $-OCH_3$; singlet at 6.52 ppm, aromatic C_3 proton; and singlet at 7.75

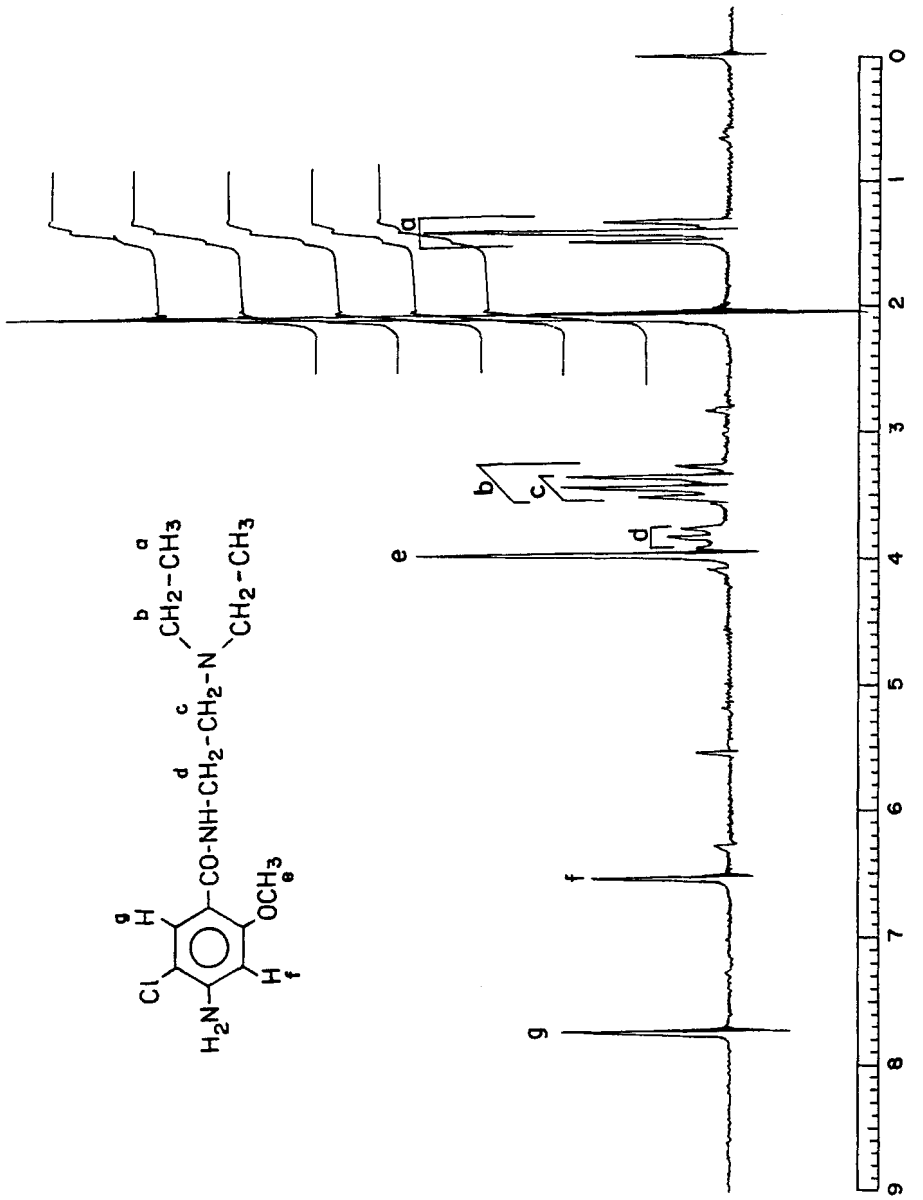

FIGURE 1

90 MHz ^{1}H-NMR spectrum of a mixture of metoclopramide hydrochloride and acetamide, the internal standard, in D_2O.

TABLE 1

Determination of metoclopramide hydrochloride in standard mixtures by ^{1}H-NMR

Standard mixture No.	Acetamide added, mg	Metoclopramide.HCl		
		Added, mg	Found, mg	Rec., %
Sample prepared by method A[a]:				
1	9.5	30.1	29.95	99.5
2	10.1	29.7	29.85	100.5
3	9.8	25.3	23.88	98.4
4	10.3	15.1	15.10	100.0
5	9.8	27.8	27.69	99.6
Sample prepared by method B[b]:				
6	10.2	40.1	40.02	99.8
7	9.1	35.5	35.78	100.8
8	9.7	29.8	29.68	99.6
9	10.5	28.6	28.37	99.2
10	9.6	29.9	29.78	99.6
Pooled av.				99.7
Pooled SD				0.7
Pooled CV, %				0.7

[a]Method A: Sample was dissolved in water (6 mL) and then freeze-dried.

[b]Method b: Sample was dissolved in methanol (10 mL), filtered, and the solution was evaporated to dryness, first under nitrogen and next in vacuo at 50°C.

TABLE 2

Determination of metoclopramide hydrochloride in commercial tablets and injections by ^{1}H-NMR spectroscopy and HPLC[a].

Dosage form, amount decl.	Lot No.	Amount found, mg	Amount found, % of decl.
Tablet, 5mg			
^{1}H-NMR assay:			
	1	5.02	100.4
	2	4.94	98.8
	3	5.04	100.8
	4	5.12	102.4
	5	4.99	99.8
	6	5.02	100.4
Av.		5.02	100.43
Range		4.94 - 5.12	98.8 - 102.4
HPLC assay:			
Av.		5.08	101.04
SD, n = 3		0.45	0.32
Injection, 5 mg/mL			
^{1}H-NMR assay:			
	1	4.98	99.6
	2	4.91	98.2
	3	4.98	99.6
	4	5.02	100.4
Av.		4.97	99.45
Range		4.91 - 5.02	98.2 - 100.4
HPLC assay:			
Av.		4.98	99.56
SD, n = 3		0.11	2.14

[a]Chromatographic conditions: column, 3 μm Pecosphere 3x3C cartridge, C_{18} (Perkin-Elmer, Norwalk, CT); mobile phase, MeOH-H_2O-AcOH-TEA (60+40+1.5+0.5, by volume) at 1 mL/min; detection, 286 nm.

ppm, aromatic C_6 proton. The internal standard exhibited a strong singlet at 2.03 ppm, CH_3-CO-N.

As a test for accuracy a set of 10 synthetic mixtures of various proportions of metoclopramide hydrochloride and acetamide were analyzed by the proposed method, with the results shown in Table 1. The average ± SD recovery of drug was 99.7 ± 0.7% of the added amount. The accuracy of the determinations was not affected by the relative proportions of drug to internal standard over the range of concentrations shown in the same Table.

The utility of the proposed method was demonstrated by analyzing various lots of commercial tablets and injections and finding the drug contents shown in Table 2. No interferences were noted from either excipients, preservatives or other additives that may be present in the dosage forms. In order to establish the validity of these results, the same samples were also analyzed by a HPLC method. In this case the tablet samples were directly extracted into water with the aid of sonication or the injections were diluted with water, and the solutions then injected into the liquid chromatograph. The results presented in the same Table indicate the existence of a close intermethod correlation.

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