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ANALYSIS OF METOCLOPRAMIDE AND RELATED COMPOUNDS IN TABLETS BY LIQUID CHROMATOGRAPHY

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ABSTRACT

A rapid, sensitive, stability indicating, reversed phase HPLC method for the quantitation of Metoclopramide and its related compounds is described. The sample is extracted in methanol and injected on a reverse phase C_{18} column with a mobile phase of 0.15M ammonium acetate and acetonitrile (80:20) with UV detection at 268 nm. The method is highly specific, sensitive and has the ability to separate Metoclopramide from its related compounds; namely, 4-acetylamino-5-chloro-N[2(diethylamino)ethyl]-2-methoxybenzamide hydrochloride and 4-amino-5-chloro-2-methoxybenzoic acid in quantities of up to 10 ucg/mL. The method is highly reproducible with average assay recovery of 104.7 $\pm$ 1.1%.

INTRODUCTION

Metoclopramide (4-amino-5-chloro-N-[2-(diethylamino)ethyl-2-methoxybenzamide hydrochloride], I) is available in intravenous and oral dosage forms. It is used as an antiemetic and for gastrointestinal motility. There are several chromatographic methods in literature for the analysis of metoclopramide I, in biological fluids (1-3). Recently, a reversed phase liquid chromatographic method has appeared for the determination of

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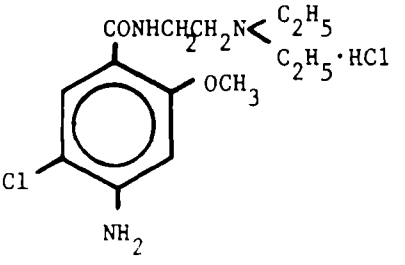
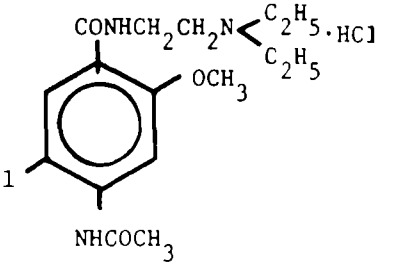
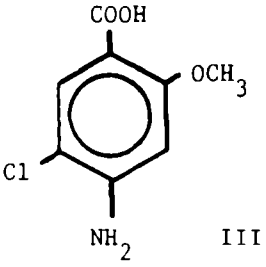
metoclopramide and one of its impurity/degradation product 4-amino-5-chloro-2-methoxybenzoic acid, III (4). This method did not address the question of separation of another major synthetic precursor of metoclopramide, 4-acetylamino[2-(diethylamino)ethyl]-2-methoxybenzamide hydrochloride, II. Although the separation between I and III by this method is adequate, it could only be performed on a specific brand column (Pecosphere C_8, Perkin-Elmer) (4). The method also fails to mention the minimum quantifiable limits of III.



I



II



III

The compendial method under consideration (5) for the determination of metoclopramide employs tedious extraction of the sample from tablets and spectrophotometric (UV) quantitation. Of course, this method will not be suitable for stability evaluations of the drug because it can not be used to determine the related compounds. This paper proposes an HPLC method that can be used for the quantitation of metoclopramide and its related compounds in tablet dosage forms.

MATERIALS AND METHODS

Chemicals and Reagents - Unless otherwise stated, all solvents and reagents were HPLC grade. Acetonitrile and methanol were from

EM Science (Cherry Hill, NJ); ammonium acetate was supplied by J.T. Baker Chemical Co. (Phillipsburg, PA). Compounds I, II and III were supplied by Secifarma (Italy). Metoclopramide tablets were obtained commercially (Reglan®, A.H. Robins, Lot 841135).

Apparatus - The liquid chromatograph consisted of a model 510 pump, model 481 variable wavelength detector, a 710B WISP autosampler (Waters, Milford, MA) and a chart recorder (Recordall, Fisher Scientific Co., Fairlawn, NJ). An octadecylsilane column (10u, u-bondapak C_{18}, 30 cm x3.9mm i.d., Waters, Milford, MA) was used. Columns with equivalent packing material were also used.

Mobile Phase - The mobile phase was prepared by mixing 0.15M ammonium acetate and acetonitrile in a 80:20 ratio. The pH of the mixed solution was adjusted to 6.5±0.05 by ammonium hydroxide or acetic acid as necessary. The ratio of the mobile phase constituents may be adjusted to achieve proper resolution of peaks of interest. The mobile phase was vacuum filtered and deaerated before use.

Standard Solution - The standard solution was prepared by accurately weighing 110 mg metoclopramide hydrochloride reference standard into a 100-mL volumetric flask, dissolving it with 50 mL of methanol and then diluting to volume with methanol.

Standard Solution with Related Compounds: Solution A - Accurately weighed, about 10 mg of II, was transferred to a 100-mL volumetric flask, dissolved and diluted to volume with methanol.

Solution B - Accurately weighed, 10 mg of III was transferred to a 100-mL volumetric flask, dissolved and diluted to volume with methanol.

Solutions A and B plus Metoclopramide - To a separate 100-mL volumetric flask that contained accurately weighed 110 mg metoclopramide hydrochloride, 10 mL of Solution A and 10 mL of Solution B were pipetted. The contents were first dissolved with 50 mL of methanol and then diluted to volume with methanol.

Sample Solution - Twenty metoclopramide tablets (10 mg per tablet label claim) were accurately weighed, finely powdered and average tablet weight determined. An accurately weighed portion of this powder, equal to one (average) tablet weight, was transferred to a 100-mL volumetric flask, dissolved with 50 mL methanol and then diluted to volume with methanol.

Method Validation - The specificity of the method was demonstrated by showing the separation of compounds I, II and III from each other and from tablet excipients. The linearity was shown by analyzing five concentrations of standard solution ranging from 0.1785 mg/mL to 1.7851 mg/mL, plotting the peak responses versus concentration and performing regression analysis. The accuracy of the method was assessed by determining the recoveries of compounds I, II and III. The precision was measured for six replicates of metoclopramide standard solution. Commercial metoclopramide tablets were also analyzed by Pharmacopeial Forum, in-process revision method and results compared with the proposed HPLC method.

Chromatographic Conditions - System Suitability - With all system components in place, the column was equilibrated with mobile phase at a flow rat of 1.0 mL/min for at least 30 minutes, or until a steady baseline was achieved. The detector was set at 268nm with a sensitivity of 0.05AUFS. The column temperature was ambient and the chart recorder set at a speed of 0.5 cm/min. Six replicate 5uL aliquots of standard solution were chromatographed. The resolution factor (R), relative standard deviation (RSD) and tailing factor were determined from peak responses.

Procedure - All solutions were filtered through a 0.45-um membrane filter prior to chromatography. Equal volumes of ~5uL of standard solution, standard solution with related compounds and sample solution were chromatographed. The detector response was recorded (as peak area or height) and used to determine the quantity (mg) and percent of label claim as shown by the following equation:

Calculations

mg/tablet = Concentration of Standard (mg/mL)

$$\times \frac{\text{Peak area (sample)}}{\text{Peak area (standard)}} \times \text{dilution of sample} \times \frac{\text{Average Tab Weight}}{\text{Sample Weight}}$$

$$\times \frac{299.80}{336.26}$$

299.80 = Formula Weight of Metoclopramide
336.26 = Formula Weight of Metoclopramide Hydrochloride

$$\% \text{ of label} = \frac{\text{mg/tablet}}{\text{mg/label claim}} \times 100$$

RESULTS AND DISCUSSION

The proposed HPLC method is quite specific as evident from the separation of metoclopramide, I, the synthetic precursor, II, impurity and/or degradation product, III (Figure 1). The retention times are listed in Table 1. No interference is observed from excipients.

Standard solution concentrations of metoclopramide from 0.1785 to 1.785 mg/mL are assayed using the HPLC procedure. The results show a linear response of concentrations versus peak area with a correlation coefficient (R) of 0.999.

TABLE 1. - Retention Times of Metoclopramide and Related Compounds

	Name of Compound		Retention Time (minutes)
1.	Metoclopramide HCl	Drug Substance	5.874 ± 0.110
2.	4-acetylamino-5-chloro-N-[2(diethylamino)ethyl] -2-methoxybenzamide HCl	Precursor	4.698 ± 0.070
3.	4-amino-5-chloro-2-methoxybenzoic acid	Possible Impurity	1.970 ± 0.029

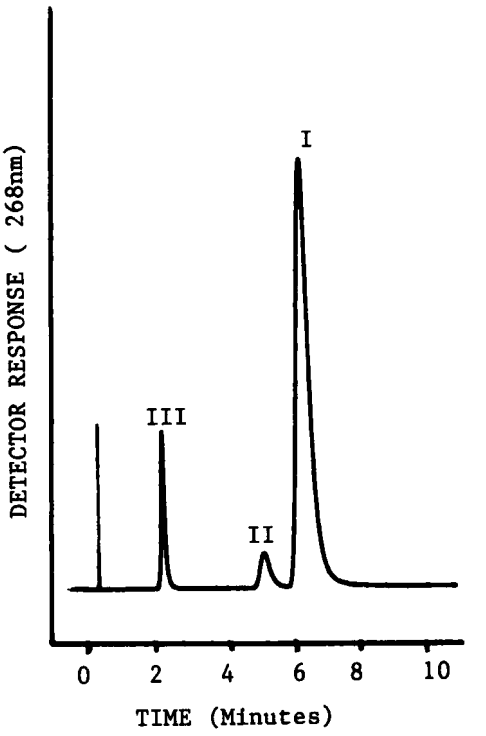


FIGURE 1. A TYPICAL CHROMATOGRAM OF METOCLOPRAMIDE AND RELATED COMPOUNDS. Peaks: I = Metoclopramide hydrochloride; II = 4-acetylamino,5-chloro-N-[2-(diethylamino)ethyl] 2-methoxybenzamide hydrochloride; III = 4-amino,5-chloro, 2-methoxybenzoic acid.

The accuracy of the method is established by determining the recovery of the standard and also, the recovery of synthetic precursor and possible impurity. The results are summarized in Table 2. The detection limit for the precursor or possible impurity is found to be 10 ucg/mL by this method.

Six replicate injections of metoclopramide standard solution are analyzed consecutively at 100% theory to determine the

TABLE 2. - Recovery of Metoclopramide and Related Compounds

Name of Compound	Concentration (mg/mL)	Recovered (mg/mL)	% Recovered
Metoclopramide	1.000	1.014	101.4
4-acetylamino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxybenzamide HCl	0.01004	0.00998	96.0
4-amino-5-chloro-2-methoxybenzoic acid	0.0106	0.0102	96.2

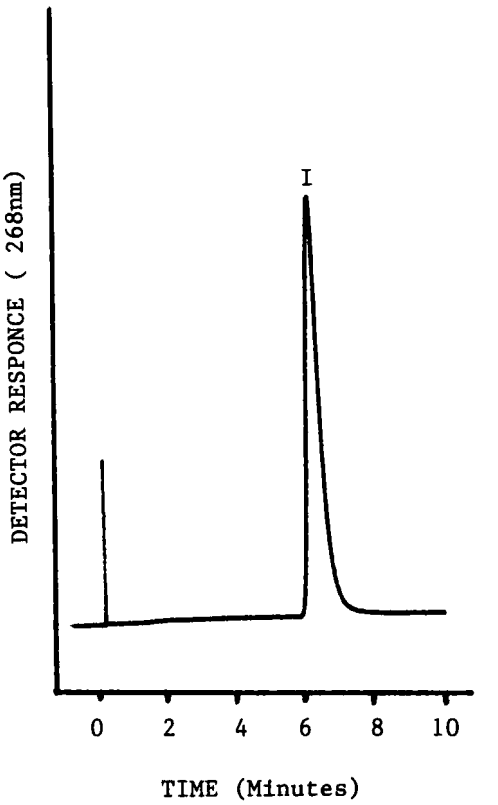


FIGURE 2. A TYPICAL CHROMATOGRAM OF METOCLOPRAMIDE STANDARD SOLUTION. Peak: I = Metoclopramide hydrochloride.

precision of the system. The results show a reproducibility of 100.6 ± 0.9%.

The performance of the system is measured per USP XXI-NF XVI, (6). The resolution is found to be greater than 2. The six replicate injections are reproducible with a Relative Standard Deviation (RSD) of less than 2.0%. The tailing factor has an upper limit of 1.5. Figure 2 is a typical chromatogram of metoclopramide standard.

Six replicate assays of commercially available metoclopramide tablets (10 mg) are carried out by this method and also by the Pharmacopeial Forum in-process revision method. The results are summarized in Table 3. The assay values are fairly consistent with both methods with average recovery of 104.7 ± 1.1% by proposed HPLC method and 103.6 ± 1.6% by Pharmacopeial Forum method. However, related compound and degradation products can only be determined by the proposed HPLC method.

TABLE 3. - Assay of Commercial Tablets by HPLC and Pharmacopeial Forum

Proposed HPLC Method			Pharmacopeial Forum Method		
mg/Sample	mg Found	% Found	mg/Sample	mg Found	% Found
10.06	10.62	105.6	10.06	10.64	105.8
10.11	10.49	103.8	10.06	10.26	102.0
10.13	10.55	104.1	10.02	10.37	103.5
10.10	10.42	103.2	9.93	10.48	105.5
10.03	10.57	105.4	10.02	10.28	102.6
10.03	10.63	106.0	9.97	10.21	102.4
Mean:	10.55	104.7		10.37	103.6
±SD:	0.08	1.1		0.16	1.6
RSD:	0.76	1.1		1.54	1.5

In conclusion, the data presented here show that the proposed HPLC method is a precise, specific, reproducible and stability indicating procedure on the basis of its ability to separate precursors and possible degradation products for the assay of metoclopramide tablets. This procedure is recommended for regular Quality Control release and shelf-life stability evaluations of these tablets.

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