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ATOMIC ABSORPTION SPECTROMETRIC DETERMINATION OF METOCLOPRAMIDE HYDROCHLORIDE USING AMMONIUM REINECKATE

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ABSTRACT

An accurate, rapid and simple atomic absorption spectrometric method was developed for the determination of metoclopramide hydrochloride (MCP-HCl). The proposed method has been depended on the reaction of ammonium reineckate with MCP-HCl to form a stable precipitate of ion-pair complex, which was dissolved in acetone. The pink colored complex was determined by atomic absorption spectrometer at wavelength 357.9 nm. The studied drug could be evaluated in the range of 20 ─ 120 µg/mL. The optimization of various experimental conditions was described. The results obtained showed good accuracy of 99.36 with repeatability of 0.854 and intermediate precision of 1.351. Application of the proposed method to representative pharmaceutical formulation was successfully presented.

KEYWORDS: Ammonium reineckate, atomic absorption spectrometric method, ion-pair complex, metoclopramide.

1. INTRODUCTION

Metoclopramide hydrochloride (MCP-HCl), **figure (1),** is 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2- methoxybenzamide hydrochloride.[1] It is a substituted benzamide used for its prokinetic and antiemetic properties. It stimulates the motility of the upper

gastrointestinal tract without affecting gastric, biliary, or pancreatic secretion and increases gastric peristalsis, leading to accelerated gastric emptying. It is used in disorders of decreased gastrointestinal motility such as gastroparesis or ileus; in gastro-oesophageal reflux disease and dyspepsia; and in nausea and vomiting associated with various gastrointestinal disorders, with migraine, after surgery, and with cancer therapy.[2] It is official in British Pharmacopoeia which recommended acid-base titration with potentiometric end point detection.[1] The wide use of MCP-HCl has prompted the development of several analytical methods for its determination in pharmaceuticals include colorimetry,[3-6] UV spectrophotometry,[7-9] turbidimetry,[10] spectrofluorimetry,[11-14] chemiluminescence,[15-17] voltammetry,[18-21] potentiometry,[22-25] conductimetry,[26] gas chromatography[27-29] and liquid chromatography in biological fluids[30-34] and in pharmaceuticals.[35-39] The main purpose of this work is to establish a sensitive, accurate and precise atomic absorption spectrometric method for the determination of MCP-HCl in bulk powder and in pharmaceutical preparation depending on its ability to form a stable ion pair complex with ammonium reineckate. The proposed method was optimized and validated as per the International Conference on Harmonization (ICH) guidelines, and was found to comply with the acceptance criteria.[40]

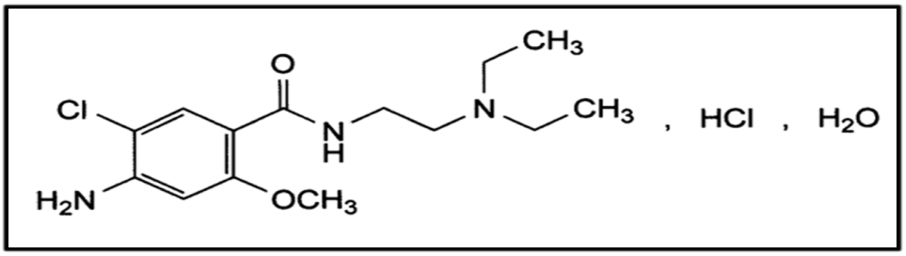

Figure (1): Structural formula of MCP-HCl.

2. EXPERIMENTAL

2.1. Materials

MCP-HCl was kindly supplied by Sanofi-Aventis company, Egypt and certified to contain 99.99%. Primperan® tablet with batch number 6EG022 manufactured by Sanofi-Aventis company. Each tablet was labeled to contain 10 mg of MCP-HCl.

2.2. Chemicals and reagents

All reagents used were of analytical grade, water used throughout the procedure was freshly distilled and deionized.

- Ammonium reineckate $NH_4[Cr(NH_3)_2(SCN)_4]$, (Sigma-Aldrich, Germany), prepared as 10^{-2} M aqueous solutions.

- Acetone, (Sigma-Aldrich, Germany).

2.3. Apparatus

GBC Elemental atomic absorption flame spectrometer, model: GBC 932 AA (Australia), equipped with air-acetylene burner, spray chamber, adjustable nebulizer and computed with GBC AAS software. Chromium was measured at wavelength 357.9 nm, slit width 0.2 nm, relative noise 1 nm, lamp current 10 mA, integration time 4 seconds.

2.4. Standard solution of MCP-HCl

A standard solution of MCP-HCl (2 mg/ mL) was prepared by dissolving 200 mg of the drug powder in 50 mL of distilled water using a 100-mL volumetric flask and completing to volume with distilled water.

2.5. Procedures

2.5.1. General procedure

Aliquots of standard MCP-HCl solution (2 mg/mL) containing (2–12 mg) were transferred into a series of 10 mL volumetric flasks and 3 mL of 10^{-2} M ammonium reineckate solution was added. The mixtures were left to react for 15 minutes under stirring at room temperature. The resulting precipitate was then filtered off on Whatman filter paper. The precipitate was separated and dissolved in least amount of acetone, and completed to the mark in 100 mL volumetric flasks with distilled water. The solutions were then aspirated directly in the atomic absorption spectrometer and measured the chromium ion concentration at wavelength 357.9 nm.

2.5.2. Optimization of experimental conditions

(i). Effect of volume and concentration of ammonium reineckate solution: The general procedure for the method was repeated using a fixed amount of MCP-HCl (8 mg) and different volumes (1 – 5 mL) of different concentration (10^{-3} – 10^{-2} M) of ammonium reineckate solutions.

(ii). Effect of Time required for complete precipitation: The general procedure for the method was repeated using a fixed amount of MCP-HCl (8 mg) and the solution allowed to stand different time intervals ranging from 0 – 30 minutes.

2.5.3. Determination of stoichiometry of the reaction by molar ratio method[41]

The general procedure for the method was repeated using a fixed amount of MCP-HCl (8 mg) equivalent to (2.26 x 10^{-3} M) and different volumes (0.5 – 6 mL) of ammonium reineckate (2.26 x 10^{-3} M).

2.5.4. Validation of the method[40]

The method was tested for linearity, range, limits of detection and quantitaion, acuracy and precision according to ICH guidelines.

2.5.5. Procedure for pharmaceutical preparation

Accurate weight of **Primperan®** powdered tablets equivalent to 0.2 g of MCP-HCl was obtained and transferred to 100- mL volumetric flask and the volume was made up to 75 mL with distilled water. The solution was shaken vigorously for 10 min then sonicated for 30 min and filtered. The volume was completed to 100 mL with the same solvent to produce a stock solution labeled to contain 2 mg/mL of MCP-HCl. Necessary dilutions of the stock solution were made and analyzed using the general procedure of the described method.

2.5.6. Reported method[7]

Direct UV spectrophotometric determination of MCP-HCl by measuring the absorbance of zero order spectra at 272 nm.

3. RESULTS AND DISCUSSIONS

In the present study, a simple and sensitive atomic absorption spectrometric method was suggested for selective quantitative determination of MCP-HCl depending on its reaction with negatively charged ligand ammonium reineckate to form a stable ion pair complex. The formed precipitate is insoluble in aqueous media but is readily soluble in acetone. The amount of chromium in the formed complex of MCP-reineckate ion pair can be measured directly by atomic absorption spectrometer at 357.9 nm. These amounts corresponding directly to the concentrations of the reacted MCP-HCl.

3.1. Optimization of experimental conditions

The optimization of the method was carefully studied to achieve complete reaction formation, highest sensitivity and maximum absorbance.

3.1.1. Effect of volume and concentration of ammonium reineckate solution

Different volumes of different concentration of ammonium reineckate solutions were used, the results as shown in **Figure (2)** prove that; 3 mL of 10^{-2} M of ammonium reineckate solution was the optimum for complete precipitation.

3.1.2. Effect of Time required for complete precipitation

Different time intervals were tried to choose the optimum reaction time, the results as shown in **Figure (3)** prove that; the time required for complete precipitation was found to be 15 minutes. The mixture was left for 15 minutes at room temperature to assure complete coagulation and aggregation of the resulting precipitate to facilitate its filtration and prevent any loss in the precipitate during filtration process.

II.F.3.1.3. Stoichiometry of the reaction

Molar ratio method was applied for the determination of the stoichiometry of the reaction which was found to be a 1:1 ratio of MCP-HCl and ammonium reineckate salt as shown in **Figure (4)**. The results of molar ratio method was confirmed by the results of elemental analysis of the formed ion pair complex (C, 36.89; H, 4.95; N, 19.52; S, 28.32). Hence, each 20 µg/mL of MCP-HCl is equivalent to 2.935 µg/mL of chromium.

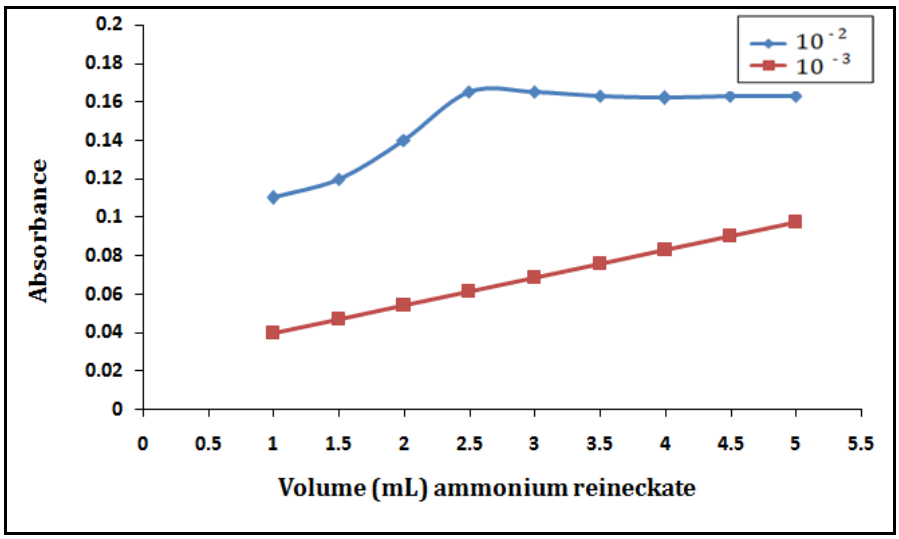

Figure (2): Effect of volume and concentration of ammonium reineckate on the absorbance of MCP-HCl (80 µg/mL).

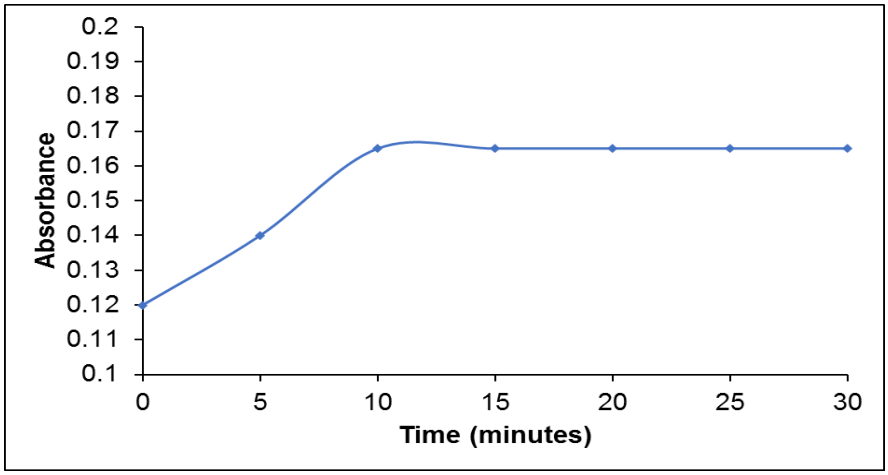

Figure (3): Effect of time required for complete precipitation of MCP - reineckate complex.

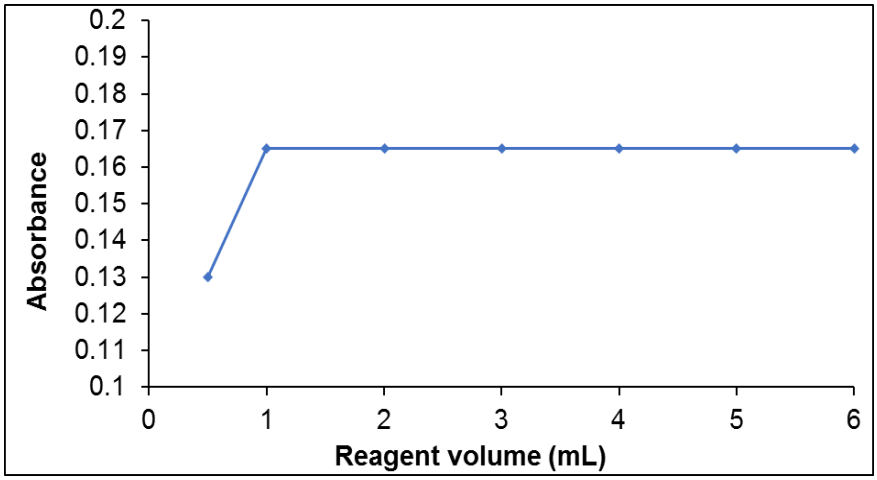

Figure (4): Stoichiometry of the reaction of MCP-HCl (2.26 x 10^{-3} M) with ammonium reineckate (2.26 x 10^{-3} M) by molar ratio method.

3.2. Method validation

- **Linearity and range**

Under the described experimental conditions, the calibration graph for the method was constructed by plotting the measured absorbance at 357.9 nm versus the final drug concentrations in µg/mL. The regression plot was found to be linear over the range of 20-120 µg/mL. The regression data were presented in **table (1)**. The high values of coefficient of determination and the small values of slope and intercept indicated the linearity of the calibration graph.

- **Limits of detection and quantitation**

LOD and LOQ values were calculated and the obtained results indicated the sensitivity of the proposed method for the analysis of the studied drug as shown in **table (1).**

- **Accuracy and precision**

Accuracy of the described method, calculated as the mean percent recovery (%R), was assessed by applying the described procedure for triplicate determination of three concentration levels covering the linearity range of the drug (20, 60, 100 µg/mL). The results in **table (1)** indicated the accuracy of the proposed method.

Moreover, the standard addition technique was applied to check the accuracy of the described method. It was done by adding known quantities of MCP-HCl in its pure form to already analyzed pharmaceutical preparation and the percent recovery of the pure added concentrations was calculated. The data listed in **table (2)** proved that the proposed method could selectively analyze the drug without any interference from any excipients.

Precision of the method, calculated as the percent of relative standard deviation (%RSD), was assessed by triplicate determination of three concentration levels covering the linearity range of the drug (20,60, 100 µg/mL) within one day for repeatability and on three successive days for intermediate precision. The small values of %RSD indicated high precision of the method as shown in **table (1)**.

3.3. Pharmaceutical application

The proposed procedure was applied for the determination of MCP-HCl in **Primperan®** tablets**.** Satisfactory results were obtained in good agreement with the label claimed, indicating no interference from excipients and additives. The obtained results were statistically compared to those obtained by the reported method.[7] No significant differences were found by applying student's *t*-test and *F* value at 95% confidence level,[42] indicating good accuracy and precision of the proposed method for the analysis of the studied drug in its pharmaceutical dosage form, as shown in **table (3)**.

Table (1): Regression and validation data for determination of MCP-HCl by the proposed atomic absorption spectrometric method.

Parameters		Proposed method
Wavelength (nm)		357.9
Linearity range (µg/mL)		20 ─ 120
- Regression equation - Slope (b) - Intercept (a)		$y^{*} = b\,x^{**} + a$ 0.0022 -0.0057
Coefficient of determination (r^2)		0.9996
LOD (µg/mL)		2.501
LOQ (µg/mL)		7.580
Accuracy (%R)***		99.36
Precision (%RSD)***	Repeatability	0.854
	Intermediate precision	1.351

y^{*} is the absorbence of chromium.

x^{**} is the concentration of MCP-HCl in µg/mL

*** Values for 3 determinations of 3 different concentrations.

Table (2): Recovery study of MCP-HCl by applying standard addition technique.

Pharmaceutical taken(µg/mL)	Pharmaceutical found(µg/mL)	Pure added (µg/mL)	Pure found (µg/mL)	%Recovery
40	39.86 *	20	20.23	101.15
		40	39.55	98.87
		60	59.55	99.25
Mean± %RSD				99.76 ± 1.226

*Average of five determinations

Table (3): Determination of MCP-HCl in Primperan® tablets by the proposed atomic absorption spectrometric and the reported methods.

Parameters	Proposed method	Reported method[7]
n*	5	5
Average (% Recovery)	100.91	99.81
%RSD	1.709	0.979
Student's *t*-test (2.306)**	1.238	——
F value (6.388)**	3.112	——

*Number of samples

**The values in parenthesis are tabulated values of "*t* "and "*F*" at (P = 0.05).

4. CONCLUSION

In this work a smart and simple recently developed atomic absorption spectrometric method was applied for the analysis of MCP-HCl. The proposed method was simple, sensitive, precise, do not need a special program and could be easily applied in quality control laboratories. They are also suitable and valid for application in laboratories lacking liquid chromatographic instruments.

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