Original Article
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Determination of Metoclopramide Hydrochloride in Pharmaceutical Formulations using N-Oxidation by Caroate

Karoat ile n-oksidasyon kullanilan farmasötik formülasyonlarda metoklopramit hidroklorit tayini

Mykola Blazheyevskiy[1], Deghinmotei Alfred-Ugbenbo[2], Olena Oleksandrivna Mozgova[1], Valery Petrovich Moroz[3]
[1]Department Of Inorganic And Physical Chemistry, National University Of Pharmacy, Ukraine
[2]Department Of Pharmaceutical Chemistry, Bayelsa Medical University, Nigeria
[3]Department of Analytical Chemistry and Analytical Toxicology, National University of Pharmacy, Ukraine

Corresponding Author Information
Deghinmotei Alfred-Ugbenbo
audeghinmotei@gmail.com
+2348077868934
https://orcid.org/0000-0003-4835-1638
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ABSTRACT
Objectives: To develop two (titrimetric and spectrophotometric) simple, rapid, sensitive and cost-effective methods for the determination of metoclopramide(MCP) in pharmaceutical dosage forms.
Methods: The titrimetric method (A) was based on the N-oxidation reaction involving the use of potassium hydrogenperoxomonosulfate and subsequent iodometric back titration of a known residual reagent. The spectrophotometric method (B) was based on derivatization of MCP with potassium hydrogenperoxomonosulfate in the presence iodide to produce a chromogen (triiodide) with a wavelength of maximum absorption at 350 nm.
Results: Method "A" was applicable over the concentration range of 0.25-3.5 mg to end volume 10 mL. In method "B", Beer's law was obeyed over the concentration range of 0.3-3.5 µg/mL with a molar absorptivity of 24600 L/mol cm. The limits of quantification were calculated to be 0.25 mg/10 mL (A) and 0.2 µg/mL (B), respectively.
Conclusion: The proposed methods were suitable for determination of MCP as a pure substance, in tablets and injection.
Keywords: Analytical method, metoclopramide, titrimetry, spectrophotometry

ÖZ
Amaç: Farmasötik dozaj formlarında metoklopramid (MCP) tayini için iki (titrimetrik ve spektrofotometrik) basit, hızlı, hassas ve uygun maliyetli yöntem geliştirmek.
Gereç ve Yöntemler: Titrimetrik yöntem (A), potasyum hidrojenperoksomonosülfatın kullanımını içeren N-oksidasyon reaksiyonuna ve ardından bilinen bir artık reaktifin iyodometrik geri titrasyonuna dayanıyordu. Spektrofotometrik yöntem (B), 350 nm'de

maksimum absorpsiyon dalga boyuna sahip bir kromojen (triiyodür) üretmek için MCP'nin potasyum hidrojenperoksomonosülfat ile iyodür varlığında türevlendirilmesine dayanıyordu.
Bulgular: Yöntem "A", 0,25-3,5 mg konsantrasyon aralığında 10 mL'lik son hacme uygulandı. "B" yönteminde, 24600 L/mol cm molar absorptivite ile 0,3-3,5 µg/mL konsantrasyon aralığında Beer yasasına uyuldu. Kantifikasyon limitleri sırasıyla 0,25 mg/10 mL (A) ve 0,2 µg/mL (B) olarak hesaplandı.
Sonuç: Önerilen yöntemler, tabletlerde ve enjeksiyonda saf madde olarak MCP tayini için uygundur.
Anahtar kelimeler: Analitik yöntem, metoklopramid, titrimetri, spektrofotometri

INTRODUCTION

Metoclopramide (MCP, *syn*. Reglan, Clopra, Gimoti etc) known as (4-amino-5-chloro-[N]-[2-(diethylamino) ethyl]-2-methoxybenzamide) (Figure. 1) is primarily utilized as antiemetic or a gastrointestinal prokinetic drug in adults and children medicine as well

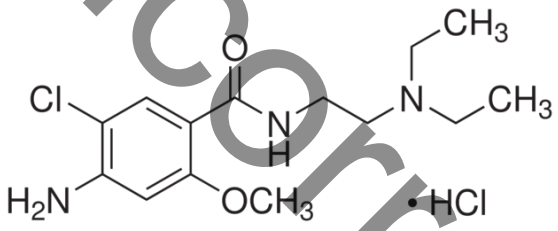

Figure 1. Structural formula of MCP

as for gastroparesis in patients with diabetes nausea, vomiting, a feeling of fullness satiety, and loss of zest.[1-4]

Because it has a wide application and a great therapeutic in empirical and clinical medicine, many researches are concentrated on its determination in dosage forms. For the quantification of MCP in pharmaceutical products and biological fluids, several analytical methods have been proposed such as high-performance liquid chromatography,[5-6] spectrofluorimetric,[7] electrochemical,[8-10] chemiluminescence,[11] tandem mass spectrophotometry.[12] Liquid chromatography is the official method for assay of MCP in the British Pharmacopoeia(BP) and United States Pharmacopoeia (USP).[13,14] Several of these mentioned procedures are not simple for routine analysis, utilize costly or complicated instruments, may require heating, or relatively have poor selectivity.

Titrimetry and visible spectrophotometry are perhaps the most widely used technique reported for the determination of MCP in pharmaceuticals.[15-24] Further, literature survey revealed the use of spectrophometric method for estimation of MCP in injection dosage form by direct UV-spectroscopy at a wave length of 270 nm with maximum absorbance using 0.1 M HCl as solvent.[25] Injections have little or no interference compared to other dosage forms such as tablets or suspensions since they contain almost no excipients. A stability indicating method has been developed for quantification of MCP in bulk by UV spectrophotometry in presence of its degradation products. The LOD and LOQ values were found to be 3.26 µg/mL and 9.89 µg/mL respectively.[26]

Redox titrimetric method of analysis is a possible alternative the various available analytical methods they are not only sensitive, precise, cost effective but relatively accurate.

The present investigation aims to develop simple, sensitive, and cost-effective methods for the determination of MCP in pure preparation, injection and tablets using redox techniques.

The titrimetric method was based on the *N*-oxidation reaction involving the use of potassium hydrogenperoxomonosulfate as the titrant. A known excess of reagent is added and, after a specified time, the residual reagent is determined iodometrically. The spectrophotometric method depends upon the oxidation of MCP with Oxone® in alkali medium (pH 9.9)

followed by coupling with iodide in acidic medium (pH 4.0) to give a yellow-brown colored chromogen (triiodide) with a wavelength of maximum absorption at 350 nm.

MATERIALS AND METHODS

Reagents:

Metoclopramide hydrochloride, 98.8% ACROS Organics™; CAS 7232-21-5, $C_{14}H_{23}Cl_2N_3O_2$; Melting Point 171-173°C.

MCP was oxidized to a metoclopramide hydrochloride *N*-oxide with the aid of potassium peroxymonosulfate (KHSO5), a component in the commercial product called Oxone®; Formula of Oxone®: 2KHSO5 ·KHSO4 ·K2SO4; CAS Number. 70693-62-8, extra pure, min. 4.5% active oxygen, ACROS Organics™; Its formula weight is 614.78 g/mol. Moreover, it is considered as "green" oxidizing agent because of its non-toxic effects.

Standard Drug Solution:

A stock standard solution of pure preparation containing 1×10^{-2} mol/ L (3.363 mg/mL) MCP was prepared in double-distilled water and used in titrimetric method.

Injection: 2 mL «Polpharma» (Poland) N 5 injection containing active substance of metoclopramide hydrochloride 10 mg; excipients: sodium pyrosulfite 2 mg, sodium chloride 14 mg, water for injection up to 2 mL; and tablet containing MCP. Tablet: Cerucal® 10 mg N50, AWD Pharma, manufactured «PLIVA Hrvatska» (Croatia). Each tablet contains active substance metoclopramide hydrochloride monohydrate 10.54 mg (which corresponds to anhydrous metoclopramide hydrochloride 10.00 mg); excipients: potato starch 36.75 mg, lactose monohydrate 76.65 mg, gelatin 2.16 mg, silicon dioxide 2.60 mg, magnesium stearate 1.30 mg. According to the quality certificate, the quantitative content Metoclopramide hydrochloride ($C_{14}H_{23}Cl_2N_3O_2$) was 9.9 mg. They were all purchased from local commercial sources.

Apparatus: Unicam SP 800 instrument, Beckman DB spectrophotometer. 10 mL microburette. Air thermostat TS-80m.

Solutions: $KHSO_5$, 1.73×10^{-2} mol/L from analytical-grade Oxone. Potassium Iodide, 5 % from analytical-grade potassium iodide. Iodide, 1 mol/L from analytical-grade potassium iodide. Sulfuric acid, $c(H_2SO_4)$ = 0.5 mol/L, volumetric solution. Sodium thiosulfate standard solution [$c(Na_2S_2O_3{\cdot}5H_2O)$ = 0.1 mol/L]. *Buffer solutions*: 20 g/L of potassium hydrogen phthalate (pH 4.0); 0.2 M solution potassium pyrophosphate with values of 8.6 and 9.3. For pH = 9.9: dissolve 28.62 g of sodium carbonate ($Na_2CO_3 \cdot 10H_2O$) and 8.40 g of sodium bicarbonate ($NaHCO_3$) in 1liter volume distilled water.

Synthesis of MCP N-oxide:

A mixture of Metoclopramide hydrochloride (0.71 g, 2 mmol), (0.76 g, 2.5 mmol) Oxone® ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) and 20% aqueous solution of sodium carbonate (25 mL) and solution was stirred at room temperature until disappearance of the starting material. The solution was treated in an ultrasonic bath for 15 minutes. Water was removed from the mixture by evaporation under vacuum and the resulting solution was lyophilized at room temperature. The residue was taken up with ethyl acetate to give MCP *N*-oxide (figure 3) in quantitative yield as a colorless solid. Further information about maximization of yield is already published.[27]

Titrimetric assay

The procedure for quantitative determination of MCP in pure preparation:

0.35404 g of MCP was dissolved in 100 mL of double distilled water. Using a pipette, volumes (10 mL) of a prepared solution were accurately transferred to 100 mL measuring flask, 10 mL of 0.02 mol/L previously prepared solution of the $KHSO_5$, pH 9.9 buffer solution (75 mL) and water were added to make the final volume of a 100 mL solution. They

were mixed to homogeneity (start stop clock). Within a chosen period of time (10-15 min), 20.00 mL was pipetted to the reaction mixture in a 150 mL conical flask. 4.0 mL of 0.5 mol/L Sulfuric acid and 5 mL of 5 % solution of potassium iodide were added while shaking. The formed iodine was titrated with 0.01 mol/L sodium thiosulfate using a micro burette until the mixture turns colourless. The blank titration was repeated omitting MCP (control titration). MCP content in the pure preparation, %(X), was calculated by the following equation:

$$X = \frac{(V_0 - V_1) \times K \times T \times 100 \times 100 \times 100}{m \times V_a \times 10 \times (100 - w)} \times 100\%, \quad (1)$$

where V_0 is 0.01 mol/L sodium thiosulfate volume used for titration in blank determination, mL;
V_1 is 0.01 mol/L sodium thiosulfate volume used for titration in procedure, mL;
K is correction factor of 0.0100 mol/l sodium thiosulfate solution concentration;
T is a mass of a substance, which reacts with 1 ml of 0.01 mol/L sodium thiosulfate, g/mL;
100 is volumetric flasks capacity, mL;
V_a is volume of reaction mixture taken for analysis, mL;
m is mass of a substance to be determined, g;
w is substance moisture content, %;
10 is volume of the pipette, which is used for measuring the solution aliquot, mL.
1.00 mL of standard 0.0100 mol/l sodium thiosulfate solution is equivalent to 0.0016813 g/mL of MCP, which should be 99-101 % in the preparation in terms of the anhydrous base.

Quantitative determination of MCP in tablets Cerucal® 10 mg:
Twenty tablets containing MCP were weighed and ground into fine powder for methods A and B, and weighed quantity of the crushed tablet equivalent to 200 mg of MCP (2.5880 g) was transferred to a 100 mL flask and shaken with 60 mL of water for about 20 min, then made up to the mark with water, mixed and filtered using a Whatman N42 filter paper. Transfer using a pipette accurately measured volumes (15 mL) of the prepared solution to 100 mL measuring flask. Same procedure as mentioned in the procedure for determination of MCP in pure preparation was repeated.
MCP content in one tablet, mg (X), has been calculated by the following equation:

$$X = \frac{(V_0 - V_1) \times K \times T \times 10 \times 100}{15 \times 20 \times 20}, \quad (2)$$

where V_0 is 0.01 mol/L sodium thiosulfate volume used for titration in blank determination, mL;
V_1 is 0.01 mol/L sodium thiosulfate volume used for titration, mL;
K is correction factor of 0.0100 mol/l sodium thiosulfate solution concentration;
T is a mass of a substance, which reacts with 1 ml of 0.01 mol/L sodium thiosulfate, g/mL (1.6813 mg/mL MCP);
15 is volume of a dosage form solution taken for analysis, mL; 20 is volume of the pipette, which is used for measuring the solution aliquot, mL; 100 is volume of flask used, mL; 20 is number of tablets taken for analysis.
1.00 mL of standard 0.0100 mol/l sodium thiosulfate solution corresponds to 0.0016813 g/mL of MCP, which should be 95-105 % in the preparation in terms of the anhydrous base.[28]

Quantitative determination of MCP in 0.5 % injection dosage form:
Accurately measured volumes (10.0 mL) of solution for injection (content five-six ampoules) were transferred using a pipette to a 100 mL measuring flask and same procedure as in determination of MCP in pure preparation was repeated. The titration was repeated without the addition of a buffer solution (pH 9.9), the same volume of double distilled water was used

in its place. For 0.1 mol/L hydrochloric acid solution, 2 mL instead of 10 mL was added (control titration).
MCP content in the solution for injection, g to 100 mL(X), was calculated by the following equation:

$$X = \frac{(V_0 - V_1) \times K \times T \times 10 \times 100}{10.00} \quad (3)$$

where V_0 is 0.01 mol/L sodium thiosulfate volume used for titration in blank determination, mL;
V_1 is 0.01 mol/L sodium thiosulfate volume used for titration in procedure, mL;
K is correction factor of 0.0100 mol/L sodium thiosulfate solution concentration;
T is a mass of a substance, which reacts with 1 ml of 0.01 mol/L sodium thiosulfate, g/mL;
10.00 is volume of a dosage form solution taken for analysis, mL;
100 is recalculation to 100 mL;
10 is dilution factor.
1.00 mL of standard 0.0100 mol/l sodium thiosulfate solution corresponds to 0.0016813 g/mL of MCP, which should be 90-110 % in the preparation in terms of the anhydrous base.
Spectrophotometric assay
Procedure for obtaining results for calibration graph:
Into 50 mL flask an aqueous solution(standard) of MCP (0.5-5.0 mL) was added, and then 1.73×10^{-4} mol/L $KHSO_5$ solution (3.00 mL). The flask was washed with adequate water to make the volume up to 8.0 mL, to which buffer solution (20 mL) was added and kept for 10-15 min. Then 0.5 mol/L sulfuric acid solution (1 mL) was added and the volume adjusted to 45 mL with the solution containing 20 g/L of potassium hydrogen phthalate; 5 mL of 5 % solution of potassium iodide was also added (5 mL). Prepared solutions were kept for 60 secs and the absorbance at 350 nm measured against distilled water. A control measurement was carried out similar to the working experiment, with the difference that double-distilled water was used instead of the investigated drug solution. The difference in optical densities obtained in the control and working experiments, respectively(ΔA), was plotted versus the concentration of MCP.
Spectrophotometric determination of MCP in tablets Cerucal® 10 mg:
Twenty tablets were weighed and pulverized. The equivalent to 200 mg of MCP was dissolved in double distilled water and filtered; the residue was rinsed, volume adjusted to 100 mL, and further diluted with same diluent to obtain the working concentration (1×10^{-4} mol/L). The prepared aqueous solution of MCP (2.00 mL) and 1.7×10^{-4} mol/L $KHSO_5$ solution (3.00 mL) were pipetted into a 50 mL graduated flask, and subsequent addition of reactants, diluents and buffers as in the above-written spectrophotometric procedure for obtaining results for calibration graph. The prepared solution was made up to 50 mL (after being kept for 60 seconds) and measured absorbance measured; the amount of MCP present in the sample was computed from the calibration curve.

Spectrophotometric determination of MCP in 0.5 % injection dosage form:
Accurately measured volumes 5.0 mL of solution for injection were transferred using a pipette to a 100 mL measuring flask and brought to a final volume of 100 mL with water. Then an aqueous solution of MCP (3.00 mL) was transferred to a 50 mL graduated flask and same procedure as further written in Spectrophotometric determination of MCP in tablets Cerucal® 10 mg was carried out. For control measurement: In place of a sulfuric acid solution and a buffer solution with a pH of 9.9, double-distilled water was used.
Recovery studies:

The recovery was calculated as the percentage of values obtained by standard pharmacopoeial method as provided by the certificate of analysis from quality control laboratory.

RESULTS AND DISCUSSION

The stoichiometry of the reaction for synthesis of MCP N-Oxide was assessed and found to be 1:1 (MCP: $KHSO_5$). The product of the *N*-oxidation reaction of MCP, was identified. The study of kinetics showed that the optimal time of quantitative interaction is 10-15 min at pH = 9.9 (Figure. 2). These conditions were the basis for the development of a new oxidimetric method for the quantitative determination of MCP using potassium hydrogen peroxomonosulfate as an analytical reagent. In titrimetric method, when the reaction between the tertiary amine group present in MCP with $KHSO_5$ was completed, the excess $KHSO_5$ was detected iodometrically.

The results of MCP determination in pure substance by oxidimetry using potassium hydrogenperoxomonosulfate (Oxone) are shown in Table 1.
The results for both titrimetric and spectrophotometric determination of MCP in tablets and solution for injection dosage forms are presented in the Table 1.

ii: According to the quality certificate, the quantitative content MCP was 9.9 mg (98.7 %).
iii: According to the quality certificate, the quantitative content MCP 1.0 mL of solution for injection contains 4.9 mg of MCP (0.49 g per 100 mL).

During study of the influence of iodide concentration on the absorbance of the final solution, steady absorbance was obtained when the iodide concentration was 0.1 mol/L. The molar absorptivity at 350 nm was found to be 2.46×10^4(table 2, figure 4). Calculations based on the association constant for tri-iodide ($\log K = 2.9$) show that >97 % of the iodine was found as tri-iodide in solutions containing >0.05 mol/L iodide, thus a percentage of the reduction in molar absorptivity observed in lower iodide concentrations may be explained as a consequence of incomplete formation of tri-iodide. Notwithstanding, an explanation for the occurrence of such significant reduction in the presence of higher KHSO5 concentrations may currently be difficult; as Nisli G. et al[29] suggest, it may be due to incomplete KHSO5-iodide reaction under these conditions. Results of recovery studies (table 1) show in all cases that δ^* was within recommended limits.

CONCLUSION

Two simple methods for the determination of MCP in tablets and in injection were developed. The methods are based on *N*-oxidation reactions. The present spectrophotometric method is the simplest method ever reported and the iodometric titration method is the first ever reported for the determination of MCP. The titrimetric method is applicable over wide linear dynamic ranges and was successfully applied to the tablets and injection. The statistical characteristics and recovery study information reveal the reproducibility and accuracy of the methods. Besides the simplicity and sensitivity of the procedures, the relative cheap cost of apparatus and reagents is also an advantage. The methods are also useful due to high tolerance limit for common excipients found in pharmaceutical formulations. These merits coupled with the use of simple and relatively inexpensive instrument and high selectivity of the methods suggests their possible application in routine quality control laboratories.
Conflicts of interest: No conflict of interest was declared by the authors. The authors alone are responsible for the content and writing of the paper.

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Table 1. Results of Titrimetric and Spectrophotometric determination of pure substance (i), tablets (ii) and injection (iii) dosage forms containing metoclopramide using Oxone

Statistical Parameters	**A. Titrimetric method**						**B. Spectrophotometric method**			
	i. Pure substance (g)		**ii. Tablets Cerucal® (mg/tablet)**		**iii. Injection «Metoclopramide hydrochloride 0.5% » (g /per 100 mL)**		**ii. Tablets Cerucal® 10 mg/tablet**		**iii. Injection «Metoclopramide hydrochloride 0.5% » (g /per 100 mL)**	
Found	%	99.10	mg	9.89	g	0.489	mg	10.11	g	0.482
		99.81		9.95		0.488		10.05		0.486
		98.72		10.11		0.494		9.95		0.491

		99.10		10.03		0.496		9.83		0.496
		98.20		9.92		0.498		9.72		0.503
Metrological characteristics (n= 5, P = 0.95)	$\bar{x}$	98.99% (Re = 100.19 %)	9.98 mg (Re =100.81%)		0.493 g/per 100 mL (Re =100.61%)		$\bar{x}$ = 9.93 mg (Re=100.30 %)		0.492 g/per 100 mL(Re =100.41%)	
	S	0.59	$8.98 \cdot 10^{-2}$		0.44×10^{-2}		0.16		$8.3 \cdot 10^{-3}$	
	$\Delta\bar{x}$	0.74	$1.08 \cdot 10^{-2}$		0.54×10^{-2}		0.20		0.010	
	RSD(%)	0.60	0.90		0.88		1.60		1.68	
	δ^* (%)	+ 0.19	+0.81		+0.61		+0.30		+0.41	
Max. Error, *$\delta = (\bar{x} - \mu)$ 100 % / μ; μ – content found by standard pharmacopoeial procedure.										

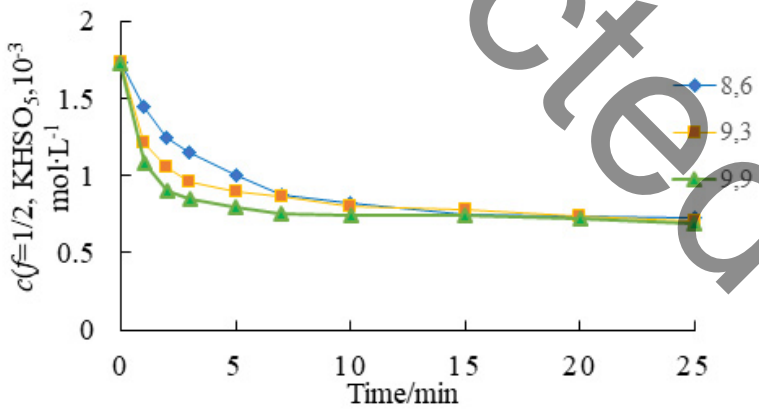

Figure 2. Concentration versus time plot of potassium hydrogen peroxymonosulfate during the oxidation of MCP. pH: 8.6; 9.3 and 9.9;. c(f=12,KHSO5) = 1.73 ×10-3 molL; &1089;(MCP) = 1 ×10-3 molL.

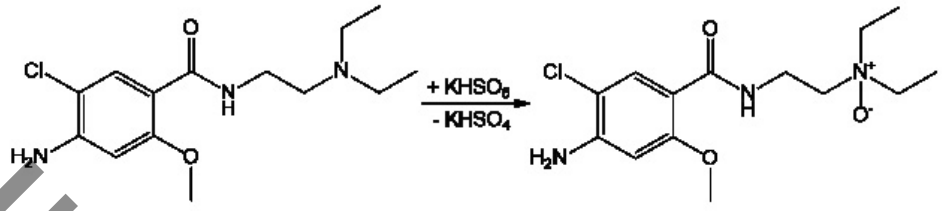

Figure 3. Scheme of interaction between MCP and potassium hydrogenperoxomonosulfate

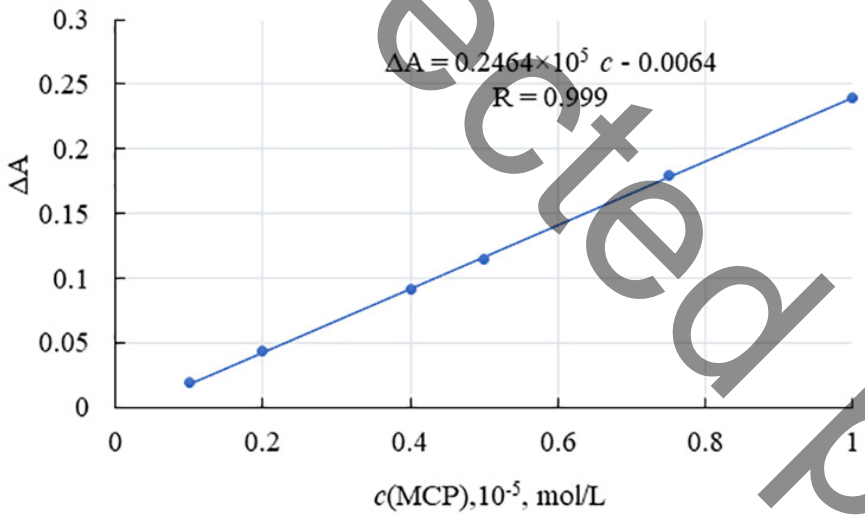

Figure 4. Calibration graph for the spectrophotometric determination of MCP