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Surfactant Cloud Point Extraction as a Procedure of Preconcentrating for Metoclopramide Determination Using Spectro Analytical Technique

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Abstract:

In current article an easy and selective method is proposed for spectrophotometric estimation of metoclopramide (MCP) in pharmaceutical preparations using cloud point extraction (CPE) procedure. The method involved reaction between MCP with 1-Naphthol in alkali conditions using Triton X-114 to form a stable dark purple dye. The Beer's law limit in the range 0.34-9 $\mu\text{g mL}^{-1}$ of MCP with $r = 0.9959$ ($n=3$) after optimization. The relative standard deviation (RSD) and percentage recoveries were 0.89 %, and (96.99–104.11%) respectively. As well, using surfactant cloud point extraction as a method to extract MCP was reinforced the extinction coefficient(ϵ) to $1.7333 \times 10^5 \text{L/mol.cm}$ in surfactant-rich phase. The small volume of organic solvent (500 μL /sample) provides an environmentally friendly and low-cost preconcentration method. The suggested method was utilized for analyzing of MCP in commercial pharmaceutical injections.

Key words: Cloud point extraction, Metoclopramide hydrochloride detection, 1-Naphthol, Pharmaceutical products, Spectrophotometry.

Introduction:

Metoclopramide, chemically known as (4-amino-5-chloro-[N]-[2-(diethylamino) ethyl]-2-methoxybenzamide) (Fig. 1). Because it has a wide application and a great therapeutic in empirical and clinical medicine, spacious researches concentrated on its determination in dose forms and biological fluids.

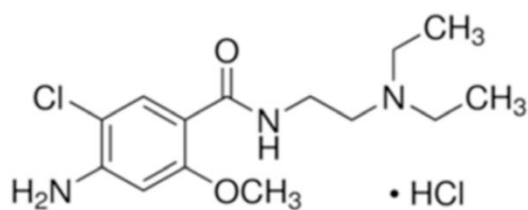


Figure 1. Metoclopramide (MCP) structure.

It is primarily utilized as antiemetic or a gastrointestinal prokinetic drug in adults and children medicine (1) as well as it is used for treatment of the symptoms of a certain type of stomach problems such as gastroparesis in patients with diabetes nausea, vomiting, a feeling of fullness satiety, and loss of zest (2).

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Metoclopramide works by rising the constriction or movements of the intestines and stomach.

For patients with gastroesophageal reflux disease (GERD), MCP is also utilized to treat stomach burn gastroesophageal reflux disease (GERD) is esophageal commotion from the in reverse flow of gastric acid into the esophagus. It is also used for prevention vomiting that happened after the cancer chemotherapy at higher doses (2).

For the quantification of metoclopramide in pharmaceutical products and biological fluids, several methods have been reported among the analytical methods are high-performance liquid chromatography (3,4), spectrofluorimetric (5), electrochemical (6,7), chemiluminescence (8) potentiometry (9) tandem mass spectrophotometry (1).

Several of these mentioned procedures are not simple for routine analysis and required costly or complicated instruments, heating step, as well as poor selectivity, and less sensitive. Visible spectrophotometry is perhaps the most widely used technique reported for the determination of MCP in pharmaceuticals (10-20). In recent times a notable interest has been increased in cloud point extraction-spectrophotometric technique to determine several of organic compounds of medicinal importance to solve this problem (21,22).

CPE method particularly based on formation of azo-day between the drug and chelating agent which extracted and analyzed spectrophotometrically.

This article presents screening methodology for extraction and determination of the drug MCP in pharmaceutical preparations by using CPE combined with spectrophotometric technique. The current work was relied on the diazotization-coupling reaction of MCP with 1-Naphthol as a reagent in the presence of alkaline medium to product the azo-dye which can readily extract to a non-ionic surfactant phase. The simplicity of the experimental procedure, short analysis time, selectivity, low usage of organic solvents, and a good analytical figure of merit demonstrate the advantages of cloud point extraction in routine spectrophotometric analysis of the MCP in pharmaceutical formulations.

Material and Methods:

Chemicals and Reagents

All experiments used analytical grades chemicals and utilized without further purification. Unless otherwise noted, Deionized water was used throughout. A pure grade (95.5%) metoclopramide (MCP) was acquired from Sigma Aldrich (USA). Stock solutions of MCP were prepared by dissolving pure standards 0.0955 g in distilled water and complete the volume to 100 mL volumetric flask with deionized water to give a final concentration is $1000 \mu\text{g mL}^{-1}$ then was relocated to a dark glass vial and saved in the dark at 4°C . Working solutions were prepared daily by serial dilution with deionized water. 2 ml of concentrated HCL (12.1 M) from (BDH, UK) was transferred 250 ml volumetric flask and diluted with distilled water in order to prepare 0.1M HCL. A 0.1 M of Sodium nitrite (Sigma-Aldrich, USA) was prepared by dissolving 1.7248 g in water and diluted to mark in a 250 mL volumetric flask mark. 0.9999 g of sodium hydroxide from (BDH) transferred and dissolved in water then diluted to 100 mL volumetric flask with distilled water. 10 ml of Triton X-114 from AMRESCO LLC (Solon, USA) with purity >99.9 was diluted with water in a 100 volumetric flask. A 1% (w/v) of sulfamic acid was prepared by dissolving 1 g with water in a 100 volumetric flask. 0.1000 g of 1-Naphthol which obtained from Sigma Aldrich (USA) was dissolved in an appropriate amount of water then diluted in 100 ml volumetric flask to obtain a final concentration $1000 \mu\text{g mL}^{-1}$ as stock solution. Three pharmaceutical injections containing MCP were acquired from different local markets.

Recommended CPE Procedure for MCP drug

Under ideal conditions, aliquots of MCP standard or sample solutions ($1-9 \mu\text{g mL}^{-1}$), 0.04ml of 0.1M HCL, 0.03ml of 0.1M NaNO_2 were transferred into a 10 mL volumetric flasks, then put it in ice for 5 minutes. Afterwards, 0.3 ml of sulfamic acid (1%), 0.4 mL of $1000 \mu\text{g mL}^{-1}$ 1-Naphthol and, 1 mL of 0.1 M NaOH were added. Subsequently, 0.6 mL of Triton X-114 (10%) was added to each flask, the solution mingled completely and diluted with water to the mark and left to stand in the thermostatic bath at 65°C for 25 minutes. Separation of an aqueous and surfactant-rich phase was accomplished by using centrifuge at 3500 rpm for 10 minutes. The aqueous phase was readily removed by using pipette then the surfactant-rich phase that has the azo-dye product was dissolved in 0.5 mL ethanol and the absorbance of the solution was measured at λ_{max} of 550 nm against a blank solution.

Pharmaceutical preparations (Injections)

Three pharmaceutical injections [each one contents (10mg /2mL) metoclopramide as an effective ingredient mixed well then, transferred to a 100 mL volumetric flask and made up with deionized water to the mark. An aliquot of the solution was then analyzed as described in proposed procedure.

Instrumentation

A double-beam spectrophotometer Shimadzu (UV-1800 (Kyoto, Japan)) equipped with 5-mm optical path cell was used for measuring all the absorption spectra. Thermostatic water bath model WNB7-45 Experts (England) is utilized for the whole of the CPE experiments.

Results and Discussion:

Preliminary studies and Absorption spectra

The first attempt of this study focused on the possibility the reaction of diazotized MCP drug with (1-Naphthol) reagent in basic medium by taking an aliquot of 10 mL containing a fixed concentrated of diazotized MCP ($3 \mu\text{g mL}^{-1}$), 0.03 ml of 0.1M HCL, 0.02 ml of 0.1M NaNO_2 , then the solution put in ice for 5 min thereafter 0.2 ml of 1% sulphamic acid, 0.4 ml of $1000 \mu\text{g mL}^{-1}$ 1-Naphthol and 0.005 ml of 0.1M NaOH, 1.0 mL of 10% Triton X-114 were added. The solution was subjected to heat in a controlled-temperature water bath at a temperature of 55°C for 15 min and the cloud point layer which contains the dark purple colored product was separated by centrifuge, dissolved in 0.5 mL ethanol then scanned

spectrophotometrically from 200 -800 nm against the reagent blank. The results revealed that the azo dye product gave maximum absorption signals at 550 nm as shown in the Fig. (2) with molar absorptivity of $1.7333 \times 10^5 \text{ L.mol}^{-1}.\text{cm}^{-1}$.

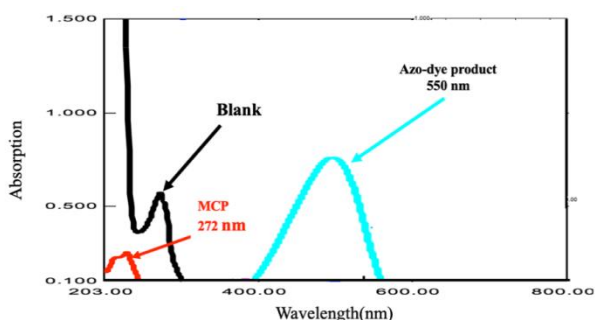


Figure 2. Absorption spectra of colored product obtained after CPE method

Optimization of cloud point extraction conditions

Number of significant experimental parameters which mainly effect on stability and sensitivity of the azo-dye were accurately studied and optimized. In the current work effect of their experimental parameters were accomplished by changing one parameter and observing the effect on the absorbance of the azo dye at the same time keeping the others constant. These parameters such as; the effect of HCL, NaNO_2 , reagent concentration, alkaline medium, amount of surfactant, equilibration temperature and incubation time have been systematically optimized.

Influence of HCL amount

The impact of HCL concentration was studied by using various volumes (0.01-0.08) ml of 0.1 M HCL. The maximum absorption was monitored at wavelength (550 nm). The highest absorption was obtained with 0.04 ml of HCL all further studies were then conducted using 0.04 ml of HCL solution, it was previously reported that HCL was more satisfactory acid compared with other acids such HNO_3 , H_2SO_4 , H_3PO_4 , and CH_3COOH for diazotization reaction of MCP (19) (Fig. 3).

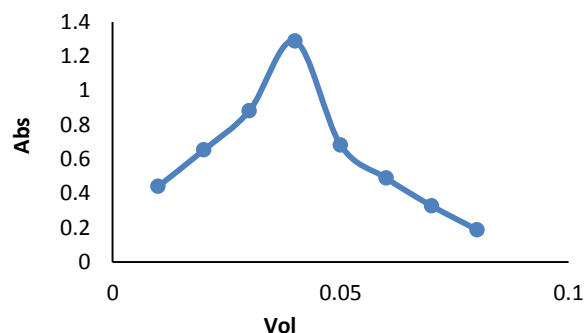


Figure 3. impact of HCL amount on the colored product formation.[conditions: MCP $3 \mu\text{g mL}^{-1}$); 0.02 ml NaNO_2 (0.1 M); reaction time (5 min); 0.2 ml of sulphamic acid (1%); 0.005 ml 1-Naphthol ($1000 \mu\text{g mL}^{-1}$); 0.005 ml of NaOH (0.1M); 1 ml of TX-114 (1.0%); CP temperature (55°C); incubation time (25 min).

Effect of NaNO_2 concentration

The absorption spectrum of cloud point layer was recorded at different amount (0.01-0.06) ml of 0.1 M NaNO_2 . Figure 4 shows the best absorption was recorded with 0.03 ml of NaNO_2 solution and used in further experiments.

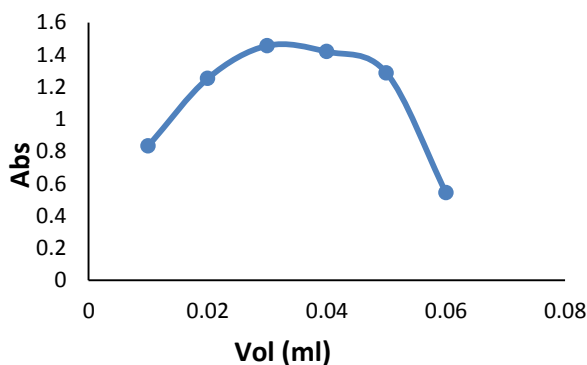


Figure 4. impact of NaNO_2 amount on colored product formation .[conditions: MCP $3 \mu\text{g mL}^{-1}$); 0.04 ml HCL(0.1M); reaction time (5 min); 0.2 ml of sulphamic acid (1%); 0.005 ml 1-Naphthol ($1000 \mu\text{g mL}^{-1}$); 0.005 ml of NaOH (0.1M); 1 ml of TX-114 (1.0%); CP temperature (55°C); incubation time (25 min).

Effect of sulfamic acid concentration

The next attempt was to optimize the concentration of sulfamic acid. Figure 5 shows the significant increase in absorption signal was reached at 0.3 ml of sulfamic acid which indicate the excess of nitrous oxide acid was removed from the solution and the date was collected using different sulfamic acid volume (0.05-0.45) ml at highest absorption signal at 550 nm.

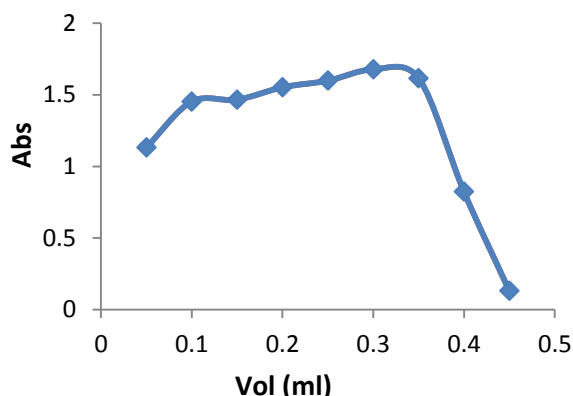


Figure 5. effect of Sulphamic acid concentration on the formation the colored product[conditions: MCP $3\mu\text{g mL}^{-1}$]; 0.04 ml HCL(0.1M);0.03 ml NaNO_2 (0.1M); reaction time (5 min);; 0.005 ml 1-Naphthol ($1000\ \mu\text{g mL}^{-1}$);0.005 ml of NaOH (0.1M); 1 ml of TX-114 (1.0%); CP temperature ($55\ ^\circ\text{C}$); incubation time (25 min).

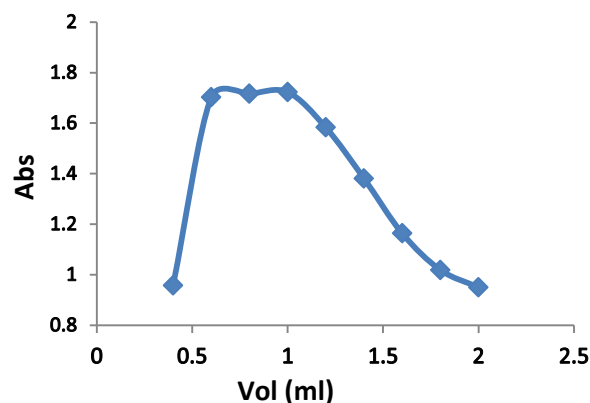


Figure 7. impact of NaOH concentration on the dye-azo formation.[conditions: MCP $3\mu\text{g mL}^{-1}$]; 0.04 ml HCL(0.1M);0.03 ml NaNO_2 (0.1M); 0.3 ml of sulphamic acid (1%); reaction time (5 min);0.4ml 1-Naphthol ($1000\ \mu\text{g mL}^{-1}$); 1 ml of TX-114 (1.0%); CP temperature ($55\ ^\circ\text{C}$); incubation time (25 min).

Effect of 1-Nanaphthol concentration

Several volumes were used for this purpose including (0.05-0.5) ml of 1-Naphthol. Figure 6 shows the experimental results and the best absorption was obtained at 0.4 ml of 1-Naphthol then our further studies focused on 0.3 ml.

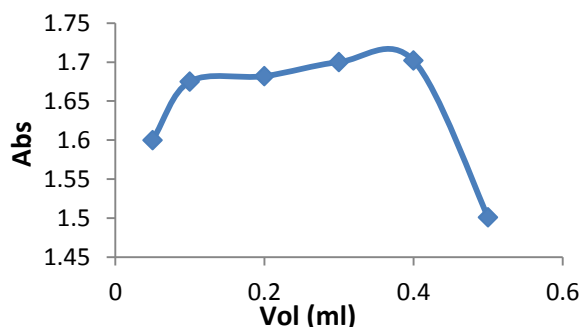


Figure 6. effect of 1-Naphthol concentration on the formation the colored product[conditions: MCP $3\mu\text{g mL}^{-1}$]; 0.04 ml HCL(0.1M);0.03 ml NaNO_2 (0.1M); 0.3 ml of sulphamic acid (1%); reaction time (5 min);0.005 ml of NaOH (0.1M); 1 ml of TX-114 (1.0%); CP temperature ($55\ ^\circ\text{C}$); incubation time (25 min).

Effect of NaOH concentration

The impact concentration of NaOH was investigated using different volumes (0.4-2) ml. Studies for the optimization of NaOH concentration revealed that the optimum volume was 1 mL of 0.1 M NaOH gives maximum absorption signal of the colored products between MCP and 1-Naphthol as displayed in Fig. 7.

Effect of Triton X-114 amount

The influence of variation of Triton X-114 amount on the absorbance signal of the colored products depicted in Fig (8). Different volumes range of Triton X-114 (0.2-1.2) ml (10% v/v) were used in this study at previously optimum conditions. Figure 8 shows the absorbance of colored product increases with increases of Triton X-114 volume up to 0.6 ml and then unexpectedly decreased at higher volume. As a result, 0.6 ml of 10% (v/v) Triton X-114 was utilized as the optimal volume in this study. This result is in agreement with reference which emphasize the amount of the TX-114 as an extracting medium plays a crucial role for the extraction efficiency by minimizing the phase volume ratio (V_s/V_a), as result, the pre-concentration factor of the CPE procedure was improved.

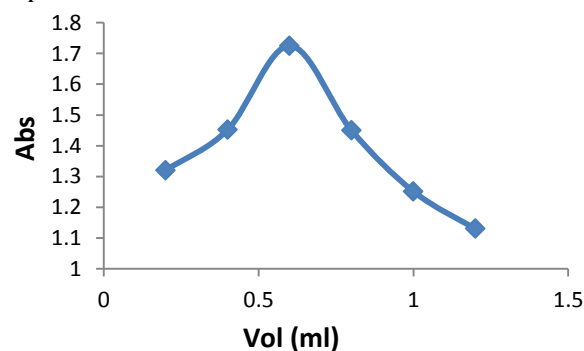


Figure 8. impact of Triton X-114 concentration on the formation the colored product. [conditions: MCP $3\mu\text{g mL}^{-1}$]; 0.04 ml HCL(0.1M); 0.03 ml NaNO_2 (0.1M); 0.3 ml of sulphamic acid (1%); reaction time (5 min);0.4ml 1-Naphthol ($1000\ \mu\text{g mL}^{-1}$); 1 ml of NaOH(0.1M); CP temperature ($55\ ^\circ\text{C}$); incubation time (25 min).

Effect of the temperature

Figure 9 summarize the behavior of the absorption signal of the colored product as a function of temperature was clearly observed at various temperature range from 50°C to 80 °C. The experimental results appeared that the absorbance signal started to increase from 50°C up to 65 °C. At higher temperature than 65 °C, a sudden decrease in absorption signal has occurred which most probably due to thermal decomposition and instability of the colored products. Increasing in surfactant-rich phase volume is compatible with spread of micelles in aqueous solution, which lead to decreasing in the extraction efficiency (23,24).

Further studies were then carried out with 65 °C of temperature to ensure the complete separation of the colored product.

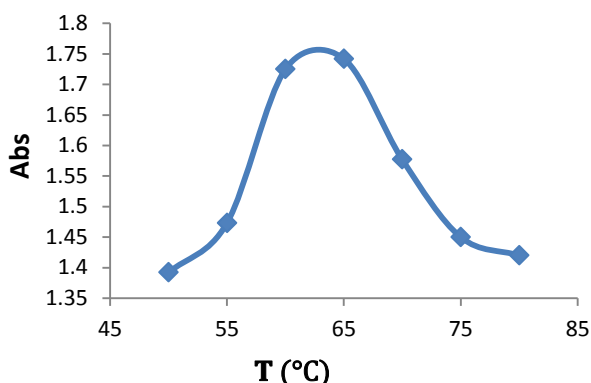


Figure 9. effect of temperature on the formation the colored product [conditions: MCP 3µg mL⁻¹]; 0.04 ml HCL(0.1M);0.03 ml NaNO₂ (0.1M); 0.3 ml of sulphamic acid (1%); reaction time (5 min);0.4ml 1-Naphthol (1000 µg mL⁻¹ ; 1 ml of NaOH(0.1M); incubation time (25 min).

Effect of the incubation time

The expected behavior between the absorption signal of the colored product and different heating times (10- 40) min at cloud point temperature of 65 °C was clearly observed. The results shown in Fig. 10 described the best absorption signal was achieved at 25 min then up to 25 min the absorption of the colored product gradually decreased. It was also noted that the centrifugation speed and time of 20 min at 35000 rpm were suitable to separate two phases.

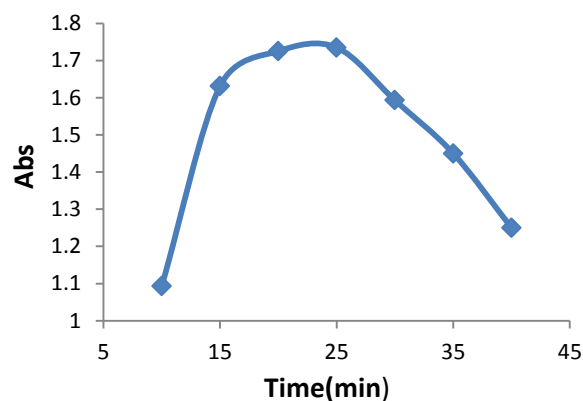


Figure 10. impact the incubation time on the formation the colored product [conditions: MCP 3µg mL⁻¹]; 0.04 ml HCL(0.1M);0.03 ml NaNO₂ (0.1M); 0.3 ml of sulphamic acid (1%); reaction time (5 min);0.4ml 1-Naphthol (1000 µg mL⁻¹; 1 ml of NaOH(0.1M); CP temperature (65 °C).

Stoichiometry of the reaction

The mole-ratio method used in order to find the composition of azo dye between MCP and 1-Naphthol in alkaline medium in which the amount of MCP is held constant, while the amount of the 1-Naphthol is varied. Absorbance is monitored at a wavelength where the azo dye absorbs. Figure 11 represent the mole-ratio plot of azo dye between MCP and 1-Naphthol in alkaline medium. The results obtained shows a ≈ 1:2 drug to reagent (1-Naphthol: MCP) was formed. Therefore, based on the mole ratio results the proposed reaction path for the formation azo dye can assumed as shown in Fig. 12.

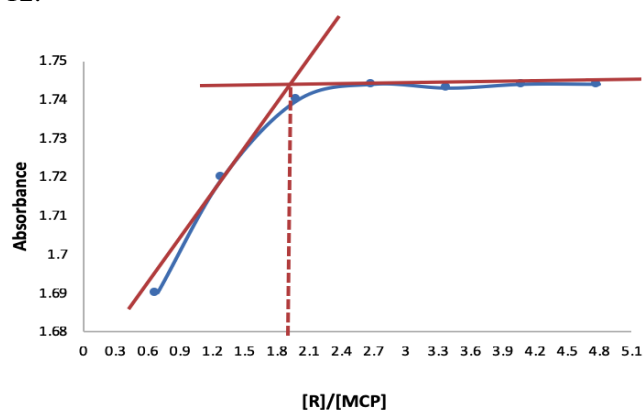


Figure 11. Mole ratio plot of MCP/1-Naphthol

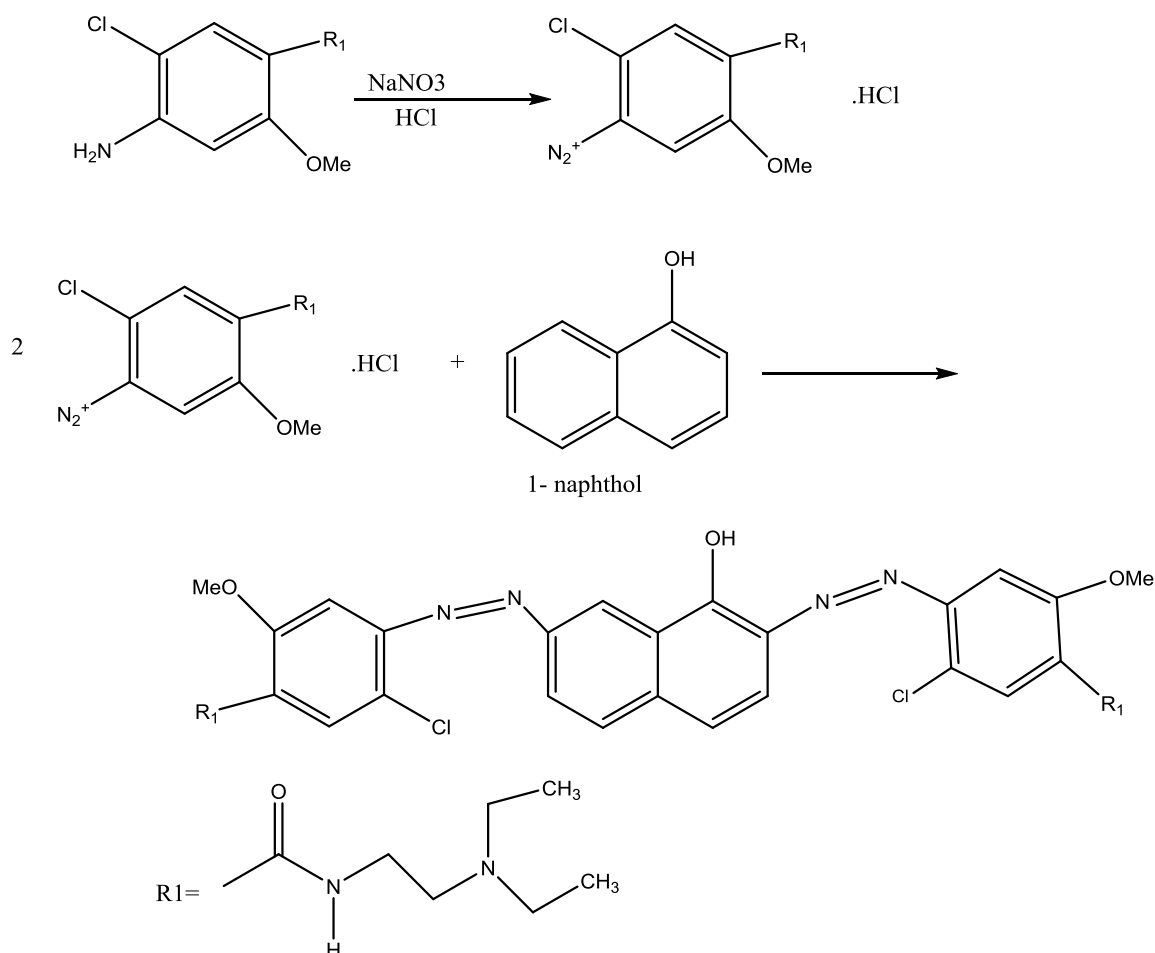


Figure 12. A reaction mechanism path between MCP and 1-Naphthol in alkaline medium.

Analytical figures of merit

Table (1) summarize the analytical characteristics of the optimized method, including regression equation, linear range, molar absorptivity, correlation coefficient, limits of detection, enrichment factor and extraction recovery. Calibration curve for the assay of MCP drug by its reaction with 1-Naphthol reagent was constructed by plotting the absorbance (at λ_{max} of 550nm) as a function of the corresponding concentrations as showed in Fig. 13. All linear dynamic range were based on the average

intensities(n=3) of nine MCP concentrations. Limits of detection (LOD) and limits of quantitation (LOQ) were calculated according to the formula $LOD=3 SB / m$ and $LOQ = 10 SB / m$; where SB is the standard deviation of the average blank signal and m is the slope the calibration curve. The (RSD) value at middle linear concentrations were excellent. This fact demonstrates that the pre-concentration procedure with CPE does not deteriorate significantly the precision of measurements.

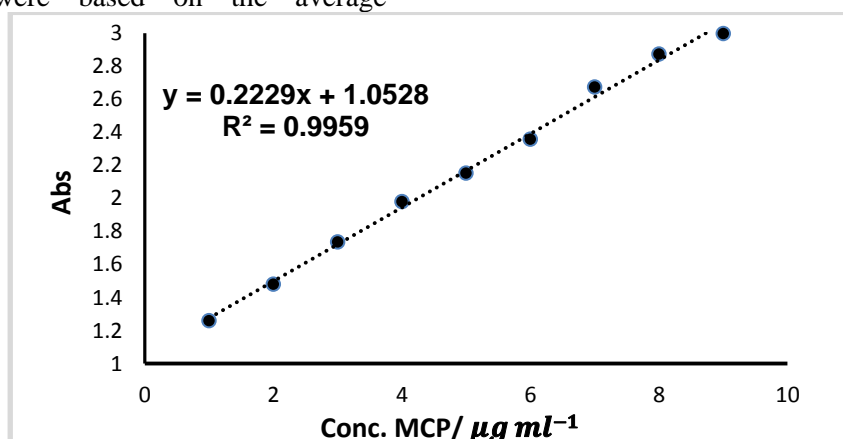


Figure 13. Calibration curve for determination MCP drug by using 1-Naphthol as conjugation reagent

Table 1. Analytical characteristics of the proposed method.

Parameter	Proposed method
Product colour	Dark purple
Wavelength (nm)	550
Linear Regression equation	$y=0.2229x+1.0528$
Correlation coefficient (r)	0.9959
LDR ($\mu\text{g mL}^{-1}$)	1-9
Reproducibility (RSD %)	0.89
Molar absorptivity ($\text{L.mol}^{-1}.\text{cm}^{-1}$)	1.7333×10^5
LOD ($\mu\text{g mL}^{-1}$)	0.10
LOQ ($\mu\text{g mL}^{-1}$)	0.34
SS ($\mu\text{g cm}^{-2}$) $\times 10^{-12}$	1.729
Composition of the coloured product	1:2
Enrichment factor	31.84
Preconcentration	33.3
Recovery (%)	99.10

LOD=Limit of Detection, LOQ= Limit of Quantitation, SS= Sandell's sensitivity, LDR= Linear Dynamic Range

Accuracy and Precision Study

To check the precision and accuracy of the proposed method a pure MCP solutions containing three different concentration within the linear rang [$1,3$ and $5\mu\text{g mL}^{-1}$] for MCP standard solutions were analyzed in three replicates. Table (2) summarized the results obtained from this study. The relative standard deviation and the percent recovery can be considered to be satisfactory.

Table 2. Precision and accuracy of the proposed method.

MCP mg mL^{-1}				
Taken	Found	SD	RSD%	Rec%
1	0.9950	0.0055	0.55	99.50
3	3.0785	0.0301	0.96	103.77
5	4.937	0.0169	0.34	98.74

Analysis of MCP in pharmaceutical injections

Determination of MCP has been tested by the suggested method on three brands commercially available pharmaceutical injections from various countries containing 10 mg/2 ml metoclopramide as an effective ingredient. All the samples were undergoing to the proposed CPE procedure as described earlier then MCP drug determined spectrophotometrically at 550 nm for three replicate measurements. Table (3) summarized the results obtained from the investigations which indicated no interfere with the determination and the proposed methods have good selectivity. Calculated t values for determination MCP using CPE method in various pharmaceuticals injections at 95% confidence interval are lower than t-tabulated that mean there is no systematic or random error at 95% confidence level (25). Table (4) summarized the statistical analysis data.

Table 3. Determination of MCP content in some pharmaceutical injections using the proposed method.

Pharmaceutical injection name	Concentration of MCP ($\mu\text{g/mL}$)			
	Taken	Found	Rec (%)	RSD%
METAMID (IBN HAYYAN PHARM (Syrian)	1	0.9699	96.99	0.98
	3	2.9731	99.10	0.44
	5	4.9253	98.50	0.45
(GLAND PHRMALIMITED(Indian)	1	0.9729	97.29	0.17
	3	2.9758	99.09	0.21
	5	4.9208	98.41	0.28
HAMELNAHARMACEUTICALS, GMBH LANGES FELD 13, (Germany)	1	0.9812	97.56	0.18
	3	3.1233	104.11	0.10
	5	4.9283	98.56	0.25

Table 4. Statistical comparison with quoted values for MCP drug determination in pharmaceutical injections by the suggested method

Pharmaceutical injection name	MCP content in proposed method ($\text{mg}/2\text{ml}$)	$t = (x - \mu) / \sqrt{n/s}$ between proposed method against demand value at 95% C.I.	RSD %
METAMID, IBN HAYYAN PHARM (Syrian)	9.80	$t_{\text{cal}} = 1.13$ $1.13 < 4.303$	2.90
	9.54		
	10.10		
	9.81 ± 0.28		
GLAND PHRMALIMITED (Indian)	9.81	$t_{\text{cal}} = 0.85$ $0.85 < 4.303$	3.27
	10.2		
	9.56		
	9.85 ± 0.32		
(HAMELNAHARMACEUTICALS, GMBH LANGES FELD 13, (Germany)	9.72	$t_{\text{cal}} = 0.28$ $0.28 < 4.303$	3.26
	9.76		
	10.3		
	9.92 ± 0.32		

t-tabulated value (4.303), N=3, degrees of freedom(n-1).

Conclusions:

Cloud point extraction combined with spectrophotometric technique provide a rapid and cost-effective producer for determination of MCP in pharmaceutical products as well as toxic solvent extraction has been avoided by using small amount (500 μ L per sample) of solvent which make proposed method environmentally friendly. The recovery results and all statistical factors clearly point to the accuracy and reproducibility of this method, which mean the current method can be selected as a good spectrophotometric method.

Conflicts of Interest: None.

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استخلاص نقطة السحب طريقه لتركيز وتقدير ميتوكلوبراميد باستخدام تقنية التحليل الطيفي

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الخلاصة:

في هذه المقالة نقدم طريقه بسيطة وانتقائية لفصل وتقدير الطيفي لكميات ضئيلة من ميتاكلوروبراميد في المنتجات الصيدلانية باستخدام تقنيه استخلاص نقطه السحب. وتعتمد هذي الطريقة على استخلاص ميتاكلوروبراميد في محيط قاعدي باستخدام تريتنون-114 الغير ايوني لتكوين صبغه بنفسجية داكنة. تحت الظروف المثلى منحني المعايرة خطيا ضمن المدى 0.34-9 ملغم/مل وقيمته معامل الارتباط 0.9959. معدل الاسترجاع للنماذج يتراوح بين 96.99-104.11%. والانحراف المعياري النسبي 0.89% وكانت الامتصاصية المولارية 1.733×10^5 . استخدام حجوم قليلة من المذيبات العضوية (500ميكروليتر لكل عينه) يجعل من الطريقة الاستخلاص صديقه للبيئة وفعاله من حيث التكلفة. تم تطبيق الطريقة المقترحة لتقدير الدواء في المستحضرات الصيدلانية.

الكلمات المفتاحية: استخلاص نقطه السحب، الكشف عن هيدروكلوريد ميتوكلوبراميد، 1-نافثول، منتجات دوائية، قياس الطيف الضوئي.