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Cloud point extraction method for the sensitive determination of metoclopramide hydrochloride in pharmaceutical dosage forms

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ABSTRACT

In this work, a simple and very sensitive cloud point extraction (CPE) process was developed for the determination of trace amount of metoclopramide hydrochloride (MTH) in pharmaceutical dosage forms. The method is based on the extraction of the azo-dye results from the coupling reaction of diazotized MTH with *p*-coumaric acid (*p*-CA) using nonionic surfactant (Triton X-114). The extracted azo-dye in the surfactant rich phase was dissolved in ethanol and detected spectrophotometrically at λ_{max} 480 nm. The reaction was studied using both batch and CPE methods (with and without extraction) and a simple comparison between the two methods was performed. The conditions that may be affected by the extraction process and the sensitivity of methods were carefully studied. Using optimal conditions, the linearity of calibration curves was in the range of 0.4-13 and 0.05-4 $\mu\text{g/mL}$ and limits of detection of 0.044 and 0.028 $\mu\text{g/mL}$ of MTH for batch and CPE methods respectively. Average recoveries for samples were detected to be between 97-101 % for both methods, with the relative standard deviation (RSD %) best than 2.7 % and 4.5 % for both methods, respectively. The suggested methods were applied successfully for assay of MTH in commercial pharmaceutical tablets.

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INTRODUCTION

Metoclopramide hydrochloride (MTH), chemically named, 4-amino-5-chloro-N-(2-diethylaminoethyl)-2-methoxybenzamide monohydrochloride monohydrate, is a dopamine-receptor antagonist ([British Pharmacopoeia, 2001](#)). MTH is usually used as an anti-emetic and in treatment of diabetic gastric stasis, which causes symptoms, for instance, nausea,

heartburn, decreased appetite, vomiting, and prolonged fullness after eating. It is also used for its prokinetic and antiemetic properties in disorders of decreased gastrointestinal motility ([Mycek et al., 2000](#)). The literature reported different methods for determination of MTH using different techniques involving spectrofluorimetry ([Attia and Aboaly, 2010](#)), spectrophotometry ([Bilici et al., 2020](#)), colorimetry using oxygenated graphene quantum dots ([Sefidan and Eskandari, 2019](#)), LC-ESI-MS ([Yan et al., 2010](#)), Flow injection spectrometry ([Jia et al., 2010](#); [Al-Arfaj, 2004](#)), ultra-performance liquid chromatography ([Sowjanya et al., 2013](#)), voltammetry ([Farghaly et al., 2005](#)), and potentiometry ([Faridbod et al., 2009](#)). Most of the previously reported methods are sensitive but required expensive instrumental set up and time-consuming. In contrast, the spectrophotometric technique is still the technique of choice due to its cost-effectiveness and simplicity. MTH was determined using several spectrophotometric methods based on differ-

ent reactions such as redox reactions, ion-pair complex formation (Abdel-Gawad and El-Guindi, 1995), diazotization coupling reactions (Revanasiddappa and Veena, 2006; Qassam *et al.*, 2013), charge transfer reactions (El-Gendy, 1992) and Schiff-base complex formation (Devi *et al.*, 2016). Cloud point extraction, as a separation and extraction technique, is still provided attractive features in routine analysis of different compounds using surfactants rather than organic solvents. CPE is dependent on a well-known surfactant phenomenon. Adopting uses the micelles systems for extraction and preconcentration has attracted large attention because of its agreement with the principle of green chemistry. CPE offers many advantages over conventional extraction methods, such as simplicity, uses aqueous medium rather than large amounts of toxic organic solvents and obtained a higher efficiency with a large preconcentration factor. CPE involved subsequent steps, involved the solubilization of the analytes in surfactant micelles and then clouding by heat and finally separation of two phases for analysis (Gouda *et al.*, 2016).

In the present work, a diazotization reaction of MTH with a new reagent (*p*-coumaric acid) was adopted for sensitive assay of trace amounts of MTH in dosage forms. The formation of azo-dye was determined spectrophotometrically using both batch and CPE methods (with and without extraction). The proposed CPE method was simple, very sensitive for the accurate assay of trace amount of MTH in its pharmaceutical applications.

EXPERIMENTAL

Apparatus

A digital single-beam spectrophotometer (Shimadzu UV-VIS 1260/Kyoto-Japan) was used for all absorption spectra and absorbance measurements of the samples supplied with matched quartz cells (Cecil, 1 cm path length and 50 μL internal volume). A thermostatic water bath expert (England) was used of the CPE process. For separation two phases, a centrifuge (Hettich, EBA 21 model) with 50 mL calibrated centrifuge tubes were used.

Reagents and materials

All the reagents used in this work were of analytical grade. MTH (purity 99.9%) and excipients were supplied from the state company for drug industries (SDI/Samara-Iraq). Pharmaceutical tablets containing MTH were obtained from local pharmacies and subjected to the method of analysis: Actavis[®] 10mg-metoclopramide hydrochloride/UK and Meclodine[®]- 5 mg metoclopramide

hydrochloride-SDI/Iraq. All reagents used in this study were of analytical reagent grade.

MTH stock standard solution 1000 ($\mu\text{g}/\text{mL}$)

To prepare this solution, 0.1000 g of standard MTH was dissolved in 100 mL distilled water. Working standard solutions were obtained from simple dilution of the MTH stock solution with distilled water.

Sodium nitrite solution (2.82×10^{-3} M)

In 250 mL volumetric flask, 0.0487 g of sodium nitrite (Merck) was dissolved in distilled water and diluted to the mark with the same solvent.

Hydrochloric acid solution (1 M)

Prepared by appropriate volume of concentrated hydrochloric acid (35.4% w/w) with distilled water in 250 mL volumetric flask.

p-Coumaric acid solution (5×10^{-3} M)

Prepared by dissolving 0.0820 g of the reagent in 5 mL ethanol then diluted to the mark in 100 mL volumetric flask with distilled water.

Ammonium hydroxide solution (2 M)

An appropriate volume of concentrated ammonium hydroxide (28-30% w/w) was diluted with distilled water in a 250 mL volumetric flask.

Triton X-114 (10% v/v)

The solution was prepared by dissolving 10 mL of surfactant (purity > 99.9%, Fluka) in 100 mL distilled water.

Preparation solution of pharmaceutical forms (500 $\mu\text{g}/\text{mL}$)

An accurately weighed amount of 10 finely powdered tablets (Actavic[®] or Meclodine[®]) of MTH equivalent to 50 mg of the pure drug was dissolved in distilled water and filtered into a 100 mL volumetric flask. Then the filtrate was washed and the volume was completed to the mark with distilled water. Diluted working solutions were obtained from simple dilution of the stock solution. Three different concentrations of each pharmaceuticals solution were analyzed in four replicate using both spectrophotometric procedures with and without extraction).

General batch procedure (without extraction)

Into 10 mL volumetric flasks increasing volumes (0.04-1.3 mL) of 100 $\mu\text{g}/\text{mL}$ of MTH were transferred. Then an equimolar of NaNO_2 solution (2.82×10^{-4} M) and 0.2 mL of 1M hydrochloric acid solution were added with cooling the contents to 10 $^\circ\text{C}$. The contents of flasks were shaken well and subsequently, 0.8 mL of *p*-CA (5×10^{-3} M) and 1.6 mL of ammonium hydroxide (2 M) were added. The flasks

Table 1: Optimum conditions for estimation of MTH with and without extraction

Variable	Studied range	Optimum values	
		Batch	CPE
Concentration of HCl (M)	0.01-0.16	0.02	0.04
Concentration of p-CA (mM)	0.04-0.6	0.4	0.2
Concentration of NH ₄ OH (M)	0.04-0.4	0.32	0.24
Concentration of Triton X-114 (%(v/v))	0.5 –1.5	—	1.0
Temperature (°C)	40-80	—	70
Incubation time (min)	10-40	—	30

Table 2: Analytical characteristics of the batch and CPE methods

Parameter	Value	
	Batch	CPE
λ_{\max} (nm)	480	480
Regression equation	$y=0.1032x - 0.0268$	$y=0.2712x + 0.0464$
Correlation coefficient, r	0.9975	0.9972
Beer's law limits ($\mu\text{g}/\text{mL}$)	0.4 – 13	0.05-4
Molar absorptivity, ϵ (L/mol cm)	3.17×10^4	8.13×10^4
Sandell 's sensitivity ($\mu\text{g}/\text{cm}^2$)	9.45×10^{-3}	3.69×10^{-3}
Limit of detection, LOD ($\mu\text{g}/\text{mL}$)	0.044	0.028
Limit of quantification, LOQ ($\mu\text{g}/\text{mL}$)	0.133	0.085
Slope, b (mL/ μg)	0.1032	0.2712
Intercept, a	-0.0268	0.0464
$S_{y/x}$	0.0279	0.0344
S_b	0.0020	0.0082
S_a	0.0157	0.0149
Stability of the dye product (min)	180	180
Molar ratio (D:R)	1:1	1:1
Preconcentration factor	10	–
Enrichment factor	3	–

Table 3: Accuracy and precision for suggested methods

Method	Conc. of MTH ($\mu\text{g}/\text{mL}$)		Recovery%	Erel%	RSD% (n=4)
	Present	Found			
Batch	2	1.96	98.00	-2.00	1.44
	4	3.84	96.00	-4.00	4.23
	8	7.69	96.13	-3.88	2.70
CPE	0.5	0.51	102.00	2.00	4.06
	1	1.02	102.00	2.00	3.98
	3	3.01	100.33	0.33	4.59

Table 4: Application of the suggested and official methods in the estimation of MTH in pharmaceutical tablets

Dosage form	Proposed methods					HPLC method
	Conc.($\mu\text{g}/\text{mL}$)		Batch	Mean Rec.(%)	RSD (%)*	Mean Rec.(%)
	Taken	Found	Rec. (%)*			
Mecloidine [®]	1	1.03	103.00	102.28	4.51	101.50
Tablets	2	2.01	100.50		4.78	
(5 mg)	3	3.10	103.33		3.14	
Actavis [®]	1	0.98	98.00	98.22	0.76	98.50
Tablets	2	1.98	99.00		2.57	
(10 mg)	3	2.93	97.67		2.27	
MTH (pure form)				96.71		100.00
t (2.447)**	0.523					
F (9.277)**	3.688					

Dosage form	Proposed methods				HPLC method	
	Conc.($\mu\text{g}/\text{mL}$)		CPE	Mean Rec.(%)	RSD (%)*	Mean Rec.(%)
	Taken	Found	Rec. (%)*			
Mecloidine [®]	1	1.00	100.00	101.61	5.01	101.50
Tablets	2	2.07	103.50		4.47	
(5 mg)	3	3.04	101.33		3.75	
Actavis [®]	1	0.93	93.00	96.50	1.18	98.50
Tablets	2	1.97	98.50		2.73	
(10 mg)	3	2.94	98.00		3.23	
MTH (pure form)				101.44		100.00
t (2.447)**	0.084					
F (9.277)**	3.744					

* Average of four determinations; ** theoretical value; conc., concentration; RSD = relative standard deviation.

were diluted and left for 10 min for further spectrophotometric detection at 480 nm.

General extraction procedure (CPE)

Into a series of 10 mL volumetric flasks, an increasing volume (0.02-1.6 mL) of 25 $\mu\text{g}/\text{mL}$ of MTH was transferred, followed by equimolar of sodium nitrite solution (7.05×10^{-5} M) and 0.4 mL of 1M hydrochloric acid solution. The whole flasks were cooled in an ice-bath to 10 °C. After shaking the contents of flasks, a 0.4 mL of *p*-CA (5×10^{-3} M), 1.2 mL ammonium hydroxide (2 M) and 1 mL of Triton X-114 (10% v/v) were added, mixed and diluted to mark with distilled water. The resultant solution was transferred to a 10 mL centrifuging tube and equilibrated at 70 °C for 30 min in the thermostatic bath. Separation of the phases was accomplished by centrifugation at (4000 rpm for 10 min) and thereafter cooled in an ice bath to facilitate the separation process. Then the aqueous phase was decanted by inverting the tube and the surfactant-rich phase (contains the azo-dye) was dissolved with 1 mL of

ethanol and detected spectrophotometrically at 480 nm against a reagent blank.

3. Results and discussion

Absorption spectra and mechanism of the reaction

The absorption spectra of the azo-dye resultant by coupling of diazotized MTH and *p*-CA in the presence of the ammonium hydroxide was shown in (Figure 1a). Absorption spectra of the azo-dye product and the blank were recorded between 300 and 700 nm. The maximum absorption band located at 480 nm, indicating the formation of a complex between diazotized MTH drug and *p*-CA reagent. To be sure of the reaction mechanism, the molar ratio of the reactants (MTH and *p*-CA) was estimated using a continuous variation method (Job's method) (Hargis, 1998). The results referred to as a 1:1 ratio product (MTH: *p*-CA) is produced (Figure 1 b). The mechanism of reaction summarized by diazotized MTH compound in the first step (using NaNO_2/HCl)

followed by coupling in the presence of ammonium hydroxide, as shown in Scheme 1.

According to data obtained from Job's method, the conditional stability constant of the orange-colored azo-dye was calculated using the following equation ((Berger, 1977).

K_f

$$= \frac{A/A_m}{(1 - A/A_m)^{n+1} C^n n^n}$$

A and A_m are referred to the highest value of absorbance and the absorbance analogous to the intersection of the two tangents of the Job's method curve, respectively (Figure 1b), n symbol is the stoichiometric constant. C is the concentration of MTH at the maximum absorbance. The calculated K_f was equal to 2.84×10^5 L/mole, indicates to the stability of the product. Gibbs free energy (ΔG) was estimated by the following equation: $\Delta G = -2.303 RT \log K_f$ (R , 8.314 J/mol deg and T , 298 K). The negative value of calculated ΔG (-13.509 kJ/mole) refers to the spontaneously of the suggested reaction.

Optimization of batch and CPE methods

To obtain full advantage of the methods and increase the sensitivity of the colored product, the effects of all conditions that affect the sensitivity of product results from suggested reaction (with and without extraction), were studied. Different experimental parameters such as the reagent concentrations and reaction conditions were studied through changing one variable with the time and keeping the others unchanging. A $4 \mu\text{g/mL}$ of MTH was used for studying all chemical conditions, with measuring absorbance at 480 nm against the blank.

Optimization of chemical parameters

Effect of concentration of hydrochloric acid

The suggested reaction depends on the diazotization of MTH and the diazotization reaction usually carried out in acidic medium and hydrochloric acid is the best choice. The effect of concentration of hydrochloric acid was studied using series of concentrations range of 0.01-0.16 M. The results indicated that 0.02 and 0.04 M (0.2 and 0.4 mL of 1 M of hydrochloric acid in 10 mL final volume) gave the maximum analytical signal for batch and CPE methods respectively (Figure 2).

Effect of concentration of *p*-coumaric acid

The -CA is a new reagent used for coupling reactions. The effect of the reagent concentration on the formation of the azo-dye product was examined for both methods using different concentrations in the range of 4×10^{-5} to 6×10^{-4} M *p*-CA. (Figure 3)

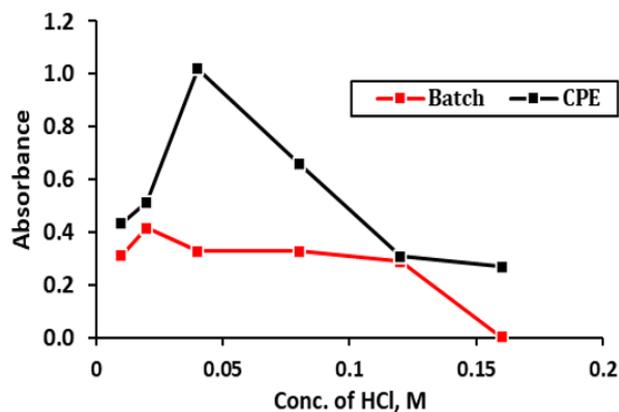


Figure 2: Effect of concentration of hydrochloric acid for determination $4 \mu\text{g/mL}$ of MTH (conditions for CPE: Temp. 60°C ; incubation time, 30 min; Triton X-114 (10%v/v), 1 ml; *p*-CA, 0.2 mM)

illustrated to increase absorbance with the increasing concentration of -CA and reached a maximum at 4×10^{-4} and 2×10^{-4} M (i.e., 0.8 and 0.4 mL of 5×10^{-3} M in 10 mL final volume) for batch and CPE methods respectively, then slightly decreases. Therefore, the previously mention concentrations of -CA were selected as the optimum and used for the next experiments.

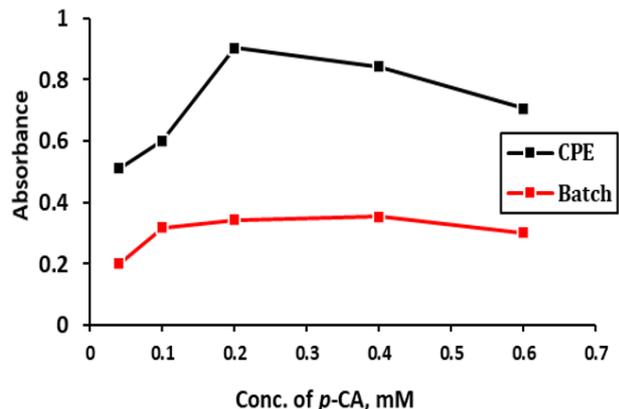


Figure 3: Study the effect of concentration of reagent (conditions for CPE: Temp. 60°C ; incubation time, 30 min; Triton X-114 (10%v/v), 1 ml; HCl, 0.04 M)

Effect of concentration of ammonium hydroxide solution

Due to the phenolic nature of the *p*-CA reagent, the reaction medium preferred to be alkaline to increase the reactivity of reactants and facilitate the coupling reaction. Different alkalies, such as NaOH, NH_4OH , and Na_2CO_3 , were examined to determine the best alkaline medium, but their effect on the sensitivity of azo-dye was less than that of ammonium hydroxide; as a result, the latter was used during the study.

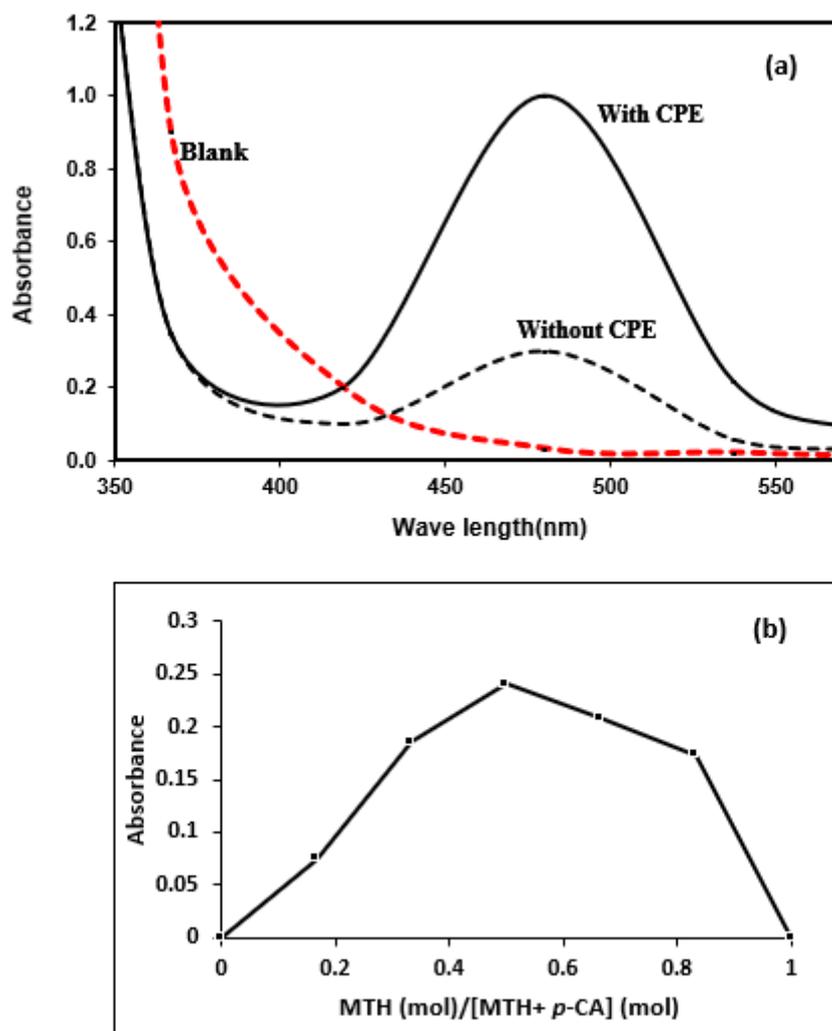


Figure 1: (a) Absorption spectra of 4 µg/ml of MTH treated with and without CPE measured against reagent blank, and the blank; (b) Job's method of the reaction between MTH and p-CA.

The effect of different concentrations (0.04-0.4 M) of ammonium hydroxide on the formation of azo-dye was investigated. It was found that 0.32 and 0.24 M of base gave a maximum absorbance for batch and CPE methods, respectively (Figure 4).

Optimization of the CPE method

Effect of Triton X-114 concentration

The concentration of the surfactant plays an important role in the CPE procedure. The amount of surfactant usually influences the extraction efficiency besides the volume of the surfactant-rich phase. The optimal concentration of Triton X-114 was studied using concentrations range of 0.5 -1.5% (v/v). As can be seen in (Figure 5), the absorbance of extracted azo-dye was increased with increase of Triton X-114 concentration up to 1% (v/v), reaching the area of little variation, which is maybe illustrated to complete extraction. Therefore, a concentration of 1% (v/v) was selected for further use.

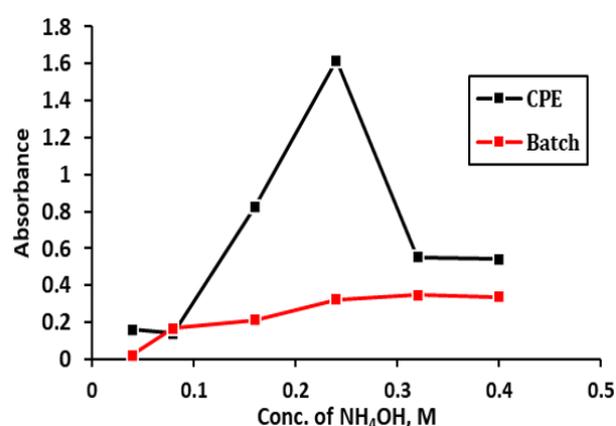
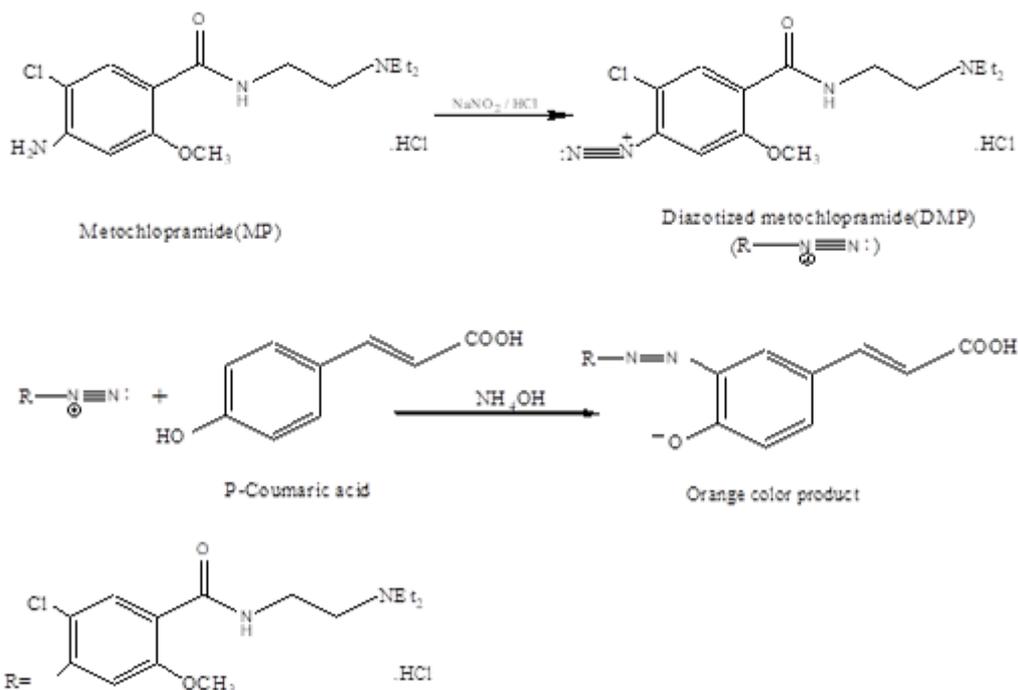


Figure 4: Effect of the concentration of NH₄OH solution

Effect of temperature and time of extraction

To obtain a successful separation, optimal equilibrium temperature and extraction time should be



Scheme 1: Proposed mechanism of the reaction

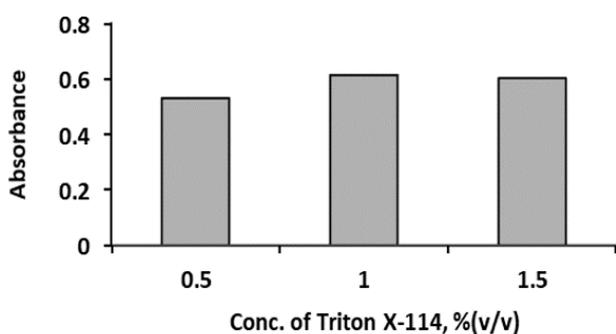


Figure 5: Effect of concentration of Triton X-114 (Conditions: 2 $\mu\text{g}/\text{ml}$ of MTH; Temp. 60 $^{\circ}\text{C}$; incubation time, 30min; p-CA,0.2 mM; NH_4OH , 0.24 M)

studied carefully. The effect of temperature on the extraction of the azo-dye product was estimated in the range from 40 to 80 $^{\circ}\text{C}$ at incubation time for 30 min were applied. Maximum absorbance for the extracted product was obtained at 70 $^{\circ}\text{C}$ (Figure 6) and then decreased, so the equilibration temperature of 70 $^{\circ}\text{C}$ was selected for all experiments.

The incubation time usually affected on extraction efficiency and the equilibrium between two phases. Therefore optimal required time was studied in the range of 10-40 min at 70 $^{\circ}\text{C}$. The results in (Figure 7) illustrated that the incubation time of 30 min was adequate to accomplish quantitative extraction. The centrifugation time does not have a significant effect on the absorbance of the product. This variable was

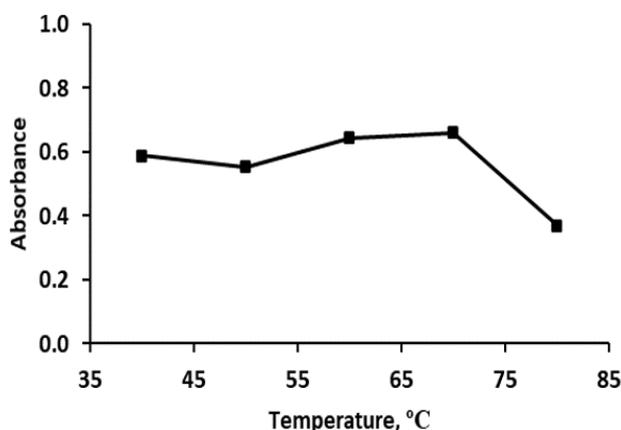


Figure 6: Effect of temperature (Conditions: 2 $\mu\text{g}/\text{mL}$ of MTH; incubation time, 30 min; p-CA,0.2 mM; NH_4OH , 0.24 M; Triton X-114, 1% (v/v))

determined in the range of 2-10 min, and complete separation of two phases was accomplished at 5.0 min, so this period time was selected as optimum time.

Summarized of optimum conditions

All the studied variables that affected on intensity and stability of the product for both methods with their optimum values are summarized in (Table 1).

Analytical figures of merit

Using the optimized conditions (Table 1) for assay of MTH with and without extraction, the calibration curves for both methods were constructed. The lin-

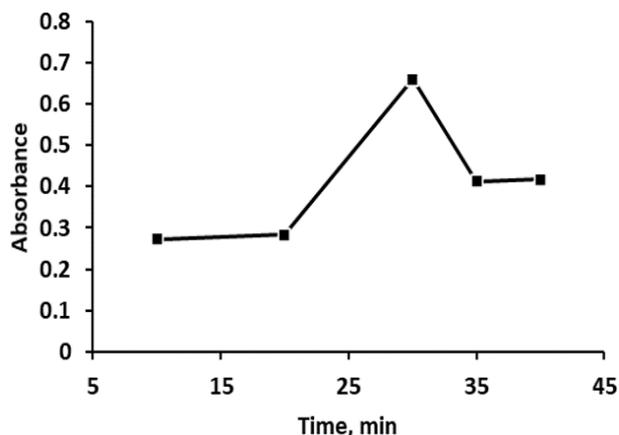


Figure 7: Effect of separation time (Conditions: 2 $\mu\text{g/mL}$ of MTH; p-CA, 0.2 mM; NH_4OH , 0.24 M; Triton X-114, 1% (v/v); Temp., 70 $^\circ\text{C}$)

earity ranges were 0.4-13 and 0.05-4 $\mu\text{g/mL}$ of MTH for batch and CPE methods, respectively. According to the least-square method, the regression equations for both methods were derived and the analytical figures of merits such as slope, intercept correlation coefficient, and molar absorptivity values were summarized in (Table 2). The values of the limit of detection, $\text{LOD}=3\text{SD}/b$ (where SD the standard deviation of 10 replicate of the blank and b the slope of the calibration graph) of 0.04 and 0.02 $\mu\text{g/mL}$ for batch and CPE methods respectively indicated the sensitivity of both methods. Also, the small values of the standard deviation of the residual ($S_{y/x}$), intercept (S_a), and slope (S_b) indicated the little scattering of points of the calibration curve and the precision of the present methods. The enrichment factor value (defined as the ratio of the slope of the calibration curve of the analyte with extraction to the slope of the calibration curve of the analyte without extraction) was estimated to be 3, while the pre-concentration factor (considered from the ratio of the volume aqueous solution to the volume of the surfactant-rich phase) was 10.

Accuracy and precision

To investigate the reliability and accuracy of the suggested methods, the intra-day precision test was performed for three different concentrations of MTH solutions analyzed by two suggested methods (with and without extraction) in four replicates. The acceptable values of relative error and relative standard deviation listed in (Table 3) indicated the accuracy and repeatability of the proposed methods.

Study of interferences

In order to investigate the usefulness of the methods in the assay of MTH in different pharmaceutical forms, the effect of some common excipients (starch, polyvinylpyrrolidone, magnesium stearate, and lac-

tose) which often added to MTH in dosage forms for manufacturing purposes, were examined. Tenfold of each excipient (20 $\mu\text{g/mL}$) was added to the solution containing 2 $\mu\text{g/mL}$ of MTH with applying the general procedures of batch and CPE methods. The percentage recoveries values attained were ranged between 97-101%, indicating no significant effect of interference was observed in the assay of MTH in its dosage forms.

Analytical applications

The suggested methods were applied to assay the MTH in two pharmaceutical tablets containing MTH as an active ingredient (Table 4). To assess the applicability and competence of proposed methods, the attained results were compared with those attained from applying the official method (HPLC method) (British Pharmacopoeia, 2001). The statistical comparison between methods was performed using two common tests (*t*- and *F*-tests at a confidence level of 95%) (Miller and Miller, 1993). The calculated *t*- and *F* values were less than the tabulated one, indicated the absence of any significant variation in accuracy and precision between the methods used for the assay of MTH in its pharmaceutical tablets.

CONCLUSIONS

Although the literature involved several methods for assay of MTH, however development a simple, very sensitive and cost-effectiveness method is still gaining a lot of attention. MTH is determined in pharmaceutical forms with and without extraction using batch and cloud point extraction procedures. A CPE using a non-ionic surfactant has been used for selective separation of azo-dye formation as a result of a diazotization reaction for MTH. A combination of CPE with UV-Vis spectrophotometry offered an easy and low-cost method for estimation of MTH without requiring toxic solvents or sophisticated techniques such as GC-MS, capillary electrophoresis and HPLC. Suggested procedures successfully applied for the determination of MTH in pharmaceutical tablets with acceptable accuracy and repeatability.

Conflict of Interest

None.

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None.

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