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# Micro Spectrophotometric Determination and Cloud Point Extraction of Metoclopramide with 4-Nitro Phenol in Pure Form and Pharmaceutical Drugs

**Noora Saad Mubder, Esraa Amer Kadhim*, Israa H. Ibraheem, Hawraa Mahmood, Saadiyah Ahmed Dhahir and Dr. Haider Al-Neshmi**
Department of Chemistry, College of Science, University of Baghdad, Baghdad, Iraq
*Email: Esraa.kadhim@csw.uobaghdad.edu.iq

**Abstract:** An eco-friendly procedure was developed for the detection of drug metoclopramide in pharmaceutical samples. It is a rapid and useful spectrophotometric method suggested for the determination of metoclopramide (MCP) with or without using cloud point extraction technique in pure form and pharmaceutical preparation. The first method was based on diazotization of the metoclopramide drug by sodium nitrite at 5 ºC, followed by coupling with 4-nitrophenol in a basic medium to form a purple colored product. To achieve this goal, all experimental variables for target analytes were previously optimized. The product was stabilized and its absorption measured at 440 nm. Beer's law obeyed in the concentration range of (1-12) µg·ml-1. Sandell's sensitivity was (0.02 )µg·cm-1, the detection limit was(0.0561 ) µg·ml-1, and the limit of Quantitation was(0.0782 ) µg·ml-1.The second method was the cloud point extraction (CPE) using Triton X-114 as a surfactant. Beer's law obeyed in the concentration range of (1-12) µg·ml-1. Sandell's sensitivity was(0.0163 ) µg·cm-1, the detection limit was(0.0331 ) µg·ml-1, and the limit of quantitation was(0.054 ) µg·ml-1. All variables including the reagent concentration, reaction time, color, stability period, and mole ratio were studied to optimize the reaction conditions. The mole ratio for the composition of the product is (1:1). Both methods were effectively useful for the determination of metoclopramide in a pharmaceutical dosage form. The attained results were in good agreement with the official and other methods in the literature.
Keywords: Micro spectrophotometric, cloud point extraction, metoclopramide, 4-nitro phenol

## Introduction:

Metoclopramide hydrochloride (Figure. 1) is Benzamide, 4-amino-5-chloro-N-[2(diethylamino) ethyl]-2methoxy-, monohydrochloride, monohydrate; 4-Amino5chloro-N-[2-(diethylamino) ethyl]-o-anisamide monohydrochloride monohydrochloride monohydrate [1]. MCP is a substituted benzamide and is commonly used as an anti-emetic in the management of some forms of nausea and vomiting and for enhancing the upper gastrointestinal tract's motility [2]. MCP reduces stomach acid reflux by strengthening the lower esophagus sphincter. Also, MCP accelerates stomach emptying of liquid and solid meals into small intestines. Furthermore, rapid emptying of meals helps to decrease stomach acid and other contents reflux into the esophagus [3]. Lastly, it is also used to alleviate chemotherapy-induced emesis [4].

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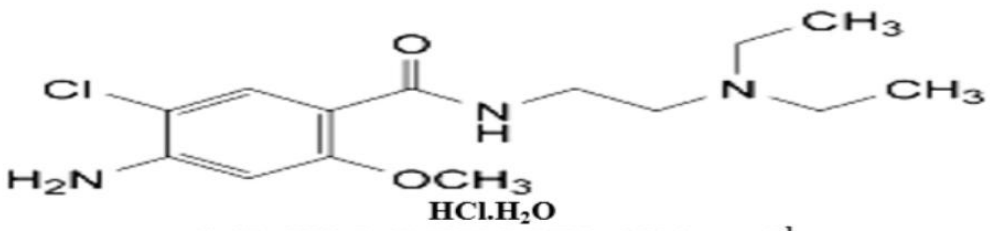


$C_{14}H_{22}ClN_3O_2.HCl.H_2O$ MW= 354.3 g.mol$^{-1}$

**Figure 1: Chemical Structure of Metoclopramide hydrochloride.**

The literature search revealed that various methods have been reported for the estimation of Metoclopramide hydrochloride. These include potentiometric titration method [4], visible spectrophotometric [5-8], potentiometric [9], spectrofluorimetric [10], flow-injection chemiluminescent [11], LC-ESIMS [12], HPLC [13], and quenched continuous fluorescence.[14]. Although these methods have valid sensitivity, they are not devoid of matrix interferences. These interferences may result from certain medications additives present in pharmaceuticals, perhaps, to help through their involvement in the diazotization coupling reaction.

Diazonium salts are important raw materials for the production of some aromatic compounds, drugs, dyes, and other organic compounds. These salts are valuable in the analytic process as they have electrolytic properties that enable them to combine with other high-density electronic compounds such as phenols and amino acids [15]. Also, they are consisting of colored compounds which are useful in estimating very small amounts of organic compounds, light absorption, or polygraphy by measuring current propagation. Cloud point extraction (CPE) is based on the phase behavior of non-ionic surfactants in an aqueous solution [16], which offers phase separation after an increase in temperature or the addition of a salting-out agent [17]. Separation and pre-concentration based on (CPE) are becoming important and practical applications of surfactant in analytical chemistry [18]. This study focuses on developing an easy a sensitive method to determine MCP. The experimental conditions are free of heating and environmentally friendly due to the small amounts of chemicals are used [19].

## Materials and Methods:

### Instruments:

UV-Vis spectrophotometer: SHIMADZU, Double beam UV-Vis, model UV-1800 made in Japan. The range of wavelength (190-1100) nm, quartz cell with 1cm path., Water Bath: A thermostat water bath, Memmert, made in Germany, Electric Balance: Sartorius (0.0000), made in Germany, Centrifuge, Triup International Corp. TRIU 800 Centrifuge, made in Korea & PH meter: HANNA, PH meter, HI 83141.

### Preparation Standard Solutions

All reagents and materials used in this work were of high purity materials. Distilled water was used to dissolve and prepare solutions. A stock solution of Metoclopramide hydrochloride (MCP) 1000µg. ml-1 was prepared by dissolving 0.1gm in a small amount of distilled water then completed to100ml by distilled water. A stock solution of reagent [4-nitro phenol] 1000µg. ml-1 was prepared by dissolving 0.1gm in a small amount of distilled water

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then diluting to the mark in a 100ml volumetric flask by distilled water. (1%) Sodium nitrite solution was prepared by dissolving 1g from NaNO2 in distilled water and diluting to the mark in a 100 ml volumetric flask. (1%) The sulfamic acid solution was prepared by dissolving 1g from H3NSO3 with distilled water 100 ml.1M from Phosphoric acid, Nitric acid, Sulphuric acid, Hydrochloric acid, and Acetic acid were prepared by proper dilution.1 M of sodium hydroxide (BDH), sodium carbonate (BDH), potassium hydroxide (Riedel De-Haenag, Germany), and ammonium solution was prepared by dissolving an appropriate amount in distilled water. (10% V/V) Different surfactants [TritonX-100, TritonX-114, Tween 20, Tween 80, STAP, SDS] was prepared by diluting 10 ml with distilled to
100 ml volumetric flask.

**General Procedure for Azo Coupling:**

The prepared Azo Coupling product is added in a volumetric flask (10ml) in an ice bath, Metoclopramide hydrochloride (MCP) 1ml of (1000 gμ ml-1), 1ml for hydrochloric acid, 1ml for sodium nitrate (1%), 1ml for sulphamic acid (1%), 1ml for 4- nitrophenol (1000 gμ ml-1), at last 1ml is added for sodium hydroxide and the volume is completed by distilled water. Then absorbance is measured by UV-VIS. Absorption spectra with maximum wavelength are shown in fig.2

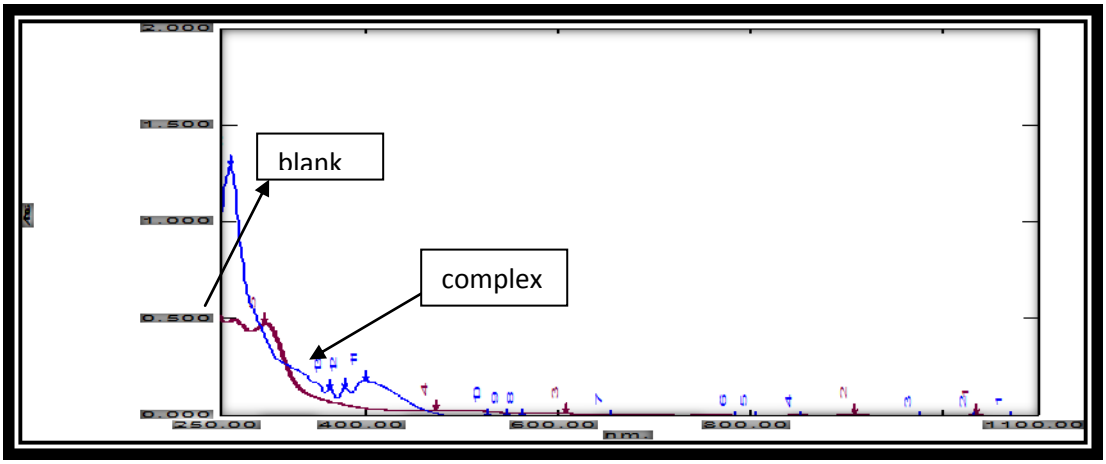


**Figure 2 : spectra of MCP**

**General procedure for CPE:**

A typical experiment of cloud point includes the following steps: taking a volumetric flask (10ml) and use the optimum condition of azo coupling. Add 1ml of surfactant (10%) and complete the volume with distilled water. The content of the volumetric flask is transferred to a centrifuge test tube. Then, the mixture is placed in a water bath for 20 minutes at 60 oC and separated by centrifugation for 25 minutes at 4000 rpm. The test tube is put in an ice bath to increase the viscosity of micelles layer for one minute. After that, it is easily separated. The separated sediments are dissolved by 2ml of ethanol, and its absorption spectrum are recorded in Fig. 2.

**General Procedure for Azo Coupling:**

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The prepared Azo Coupling product is added in a volumetric flask of (10ml) in an ice bath. One ml of Metoclopramide hydrochloride (MCP) (1000 gμ ml-1), 1ml of hydrochloric acid, 1ml of sodium nitrate (1%), 1ml of sulphamic acid (1%), 1ml of 4- nitrophenol (1000 gμ ml-1), and at last 1ml of sodium hydroxide are mixed in the volumetric flask. The volume is completed by distilled water. Then absorbance is measured by UV-VIS. Absorption spectra with maximum wavelength are shown in fig.2

**Results and Discussion:**

**First Methods: Spectrophotometric Determination of Sulphadimidine Sodium (MCP) by Oxidation Coupling Reactions. Optimization Parameters for Reaction**.

All of the factors, that influence the absorbance of azo dye products, are optimized to improve the sensitivity and detection limit for the determination of the drug. All optimization was worked under wavelength at 440 nm.

**Effect of Acid Type:**

In this study, 1 M of different acids [HCl, H2SO4, H3PO4, and CH3COOH] are used. The same procedure that [ 1ml of drug MCP, 1 ml of each acids, 1ml of NaNO2, 1ml of H3NSO3, 1ml 4- nitrophenol, and 1ml of KOH] are mixed in a 10mL volumetric flask. The volume is completed by distilled water to form the diazonium salt. After that, the absorbance is measured at a maximum wavelength for the drug. It is clear from this study that the acetic acid gives higher absorbance for MCP. This acid is a few of uses in subsequent experiments as shown in Fig .3.

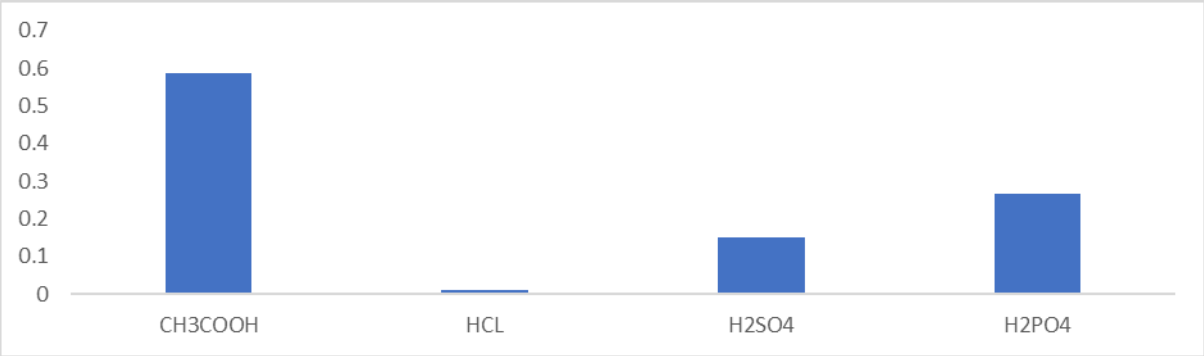


**Figure 3. The absorbance of different acid**s.

**Effect of Optimum Volume of 1M Acetic Acid**

The same addition for MCP is [1ml drug, with varying volumes of 1ml CH3COOH from (0.1-1) ml, 1 ml of NaNO2, 1ml of H3NSO3, 1ml of 4- nitrophenol, and 1ml of KOH in a 10 ml volumetric flask. The volume is completed by distilling water. Then, the absorbance is measured and the optimum volume for higher absorbance that fixed for sequence experiment 0.3 ml as shown in Fig. 4.

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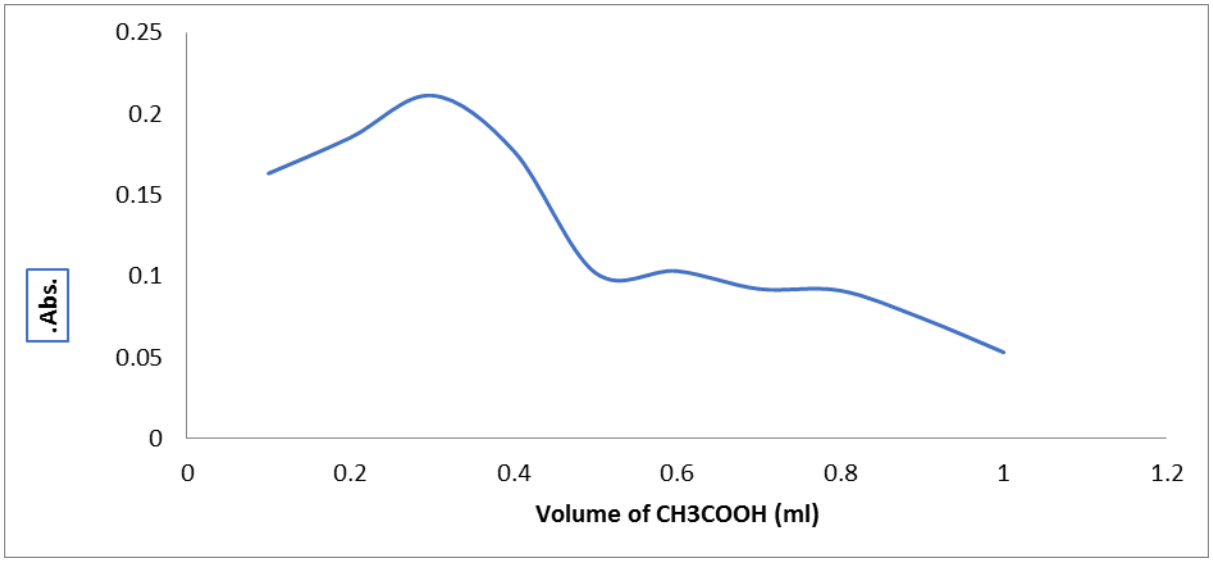


**Figure 4. The Volume of 1 M CH3COOH ml with MCP**

It is obvious that absorbance increases with increasing the volume of acid. Suddenly, the absorbance decreases because the primary amine becomes inactive [20].

**Effect of Base Type**

This experiment using different basics [NaOH, KOH, NH4OH, NaHCO3] and that follow the addition [1ml MCP, 0.3ml CH3COOH, 1ml NaNO2, 1ml H3NSO3, 1ml 4- nitrophenol, and 1ml of each base] in a 10 ml volumetric flask. Then maximal absorbance for the base is KOH as shown in Figure 5.

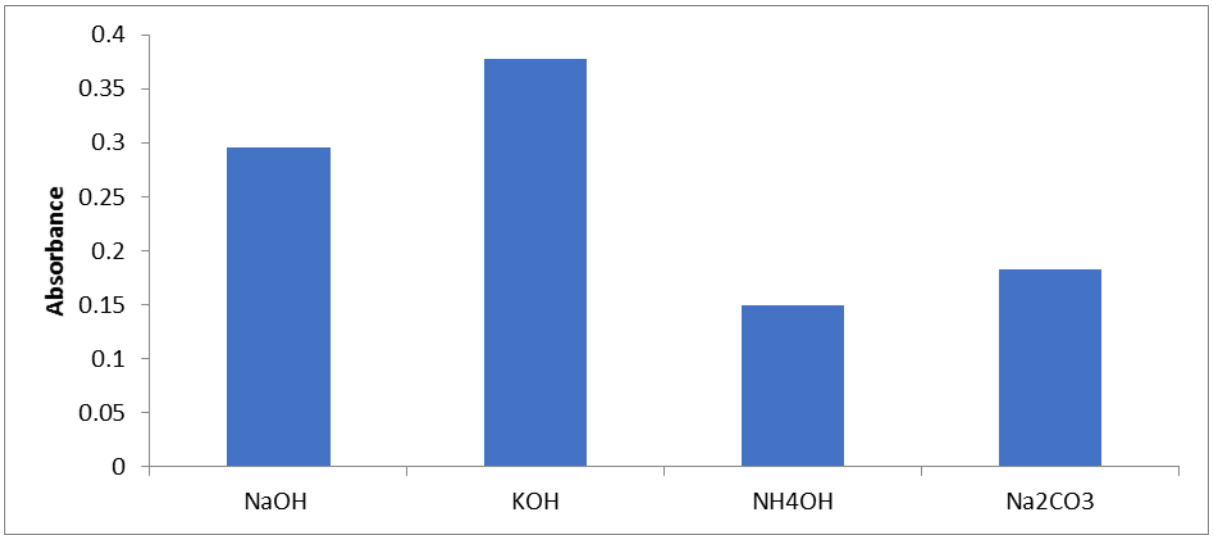


**Figure 5. The absorbance different base with MCP**.

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**Effect of Optimum Volume of KOH**

The same addition for MCP is [1ml drug, 0.3 ml CH3COOH, 1 ml NaNO2, 1ml H3NSO3, 1ml 4- nitrophenol, and (0.1-1) ml of KOH in a10 ml volumetric flask. The volume is completed by distilled water. Then, the absorbance and the optimum volume for higher absorbance that fixed at 0.3ml for sequence experiment are measured as shown in Fig. 6.

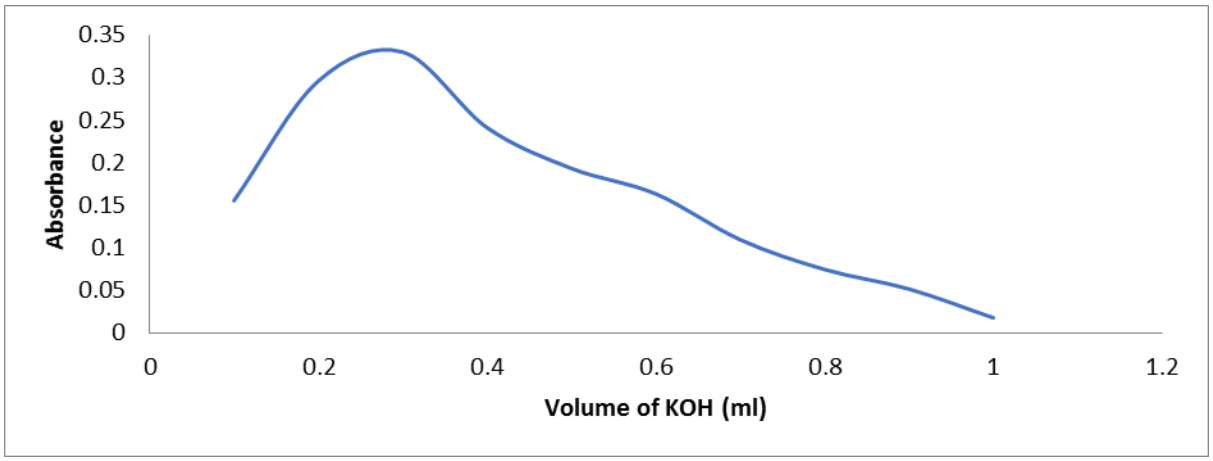


**Figure 6. Different Volume of KOH with MCP**

It is evident that absorbance increases with increasing the volume of KOH. Suddenly, the absorbance decreases because the decomposition happens when increased basicity and formation diazotization may couple and agree with previous studies [21].

**Effect of Optimum Volume of 1% Sodium nitrite.**

The same additions [1ml for MCP, 0.3 ml CH3COOH with a varying volume of 1% NaNO2 from (0.1-1) ml, 1ml H3NSO3, 1ml 4- nitrophenol, and 0.3 ml KOH have put in a 10ml volumetric flask and the higher absorbance of optimum volume fixed at 0.6 ml for sequence experiment, as shown in Fig.7.

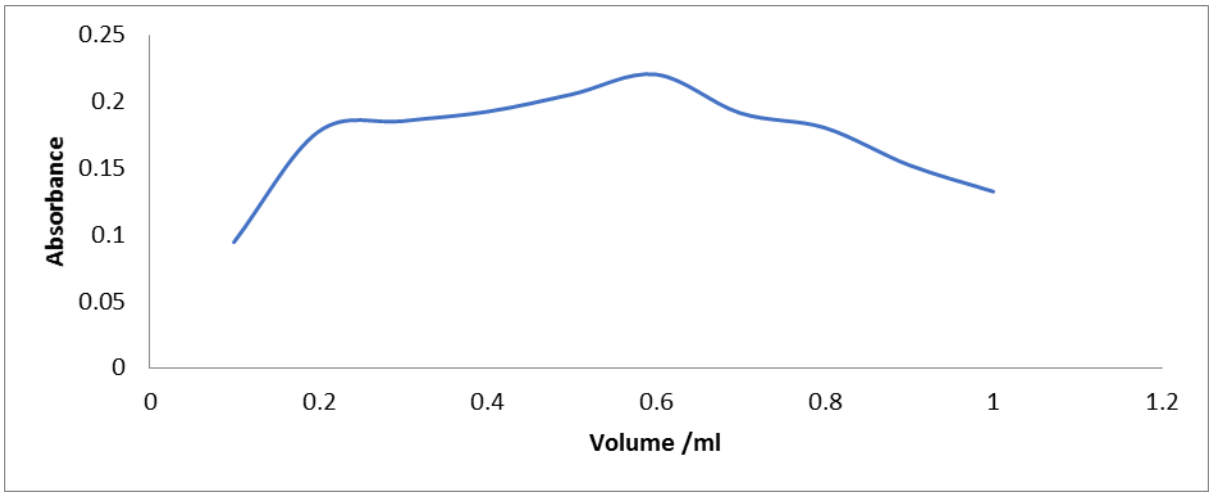


**Figure 7. Absorbance of 1% NaNO2 / ml**

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It is clear that the absorbance increases with increasing the volume of NaNO2, but the signals decrease because the nitrate was toxic because of a high rate of pollutants affecting diazonium salt [22].

**Effect of Optimum Volume of 1% Sulphamic acid.**

The same additions [1ml for MCP, 0.3 ml CH3COOH, 0.6ml NaNO2 with a varying volume of 1% H3NSO3 from (0.1-1) ml, 1ml 4- nitrophenol, and 0.3 ml KOH have put in a volumetric flask 10 ml and the higher absorbance of the optimum volume is fixed at 0.1 ml for sequence experiment as shown in Fig. 8.

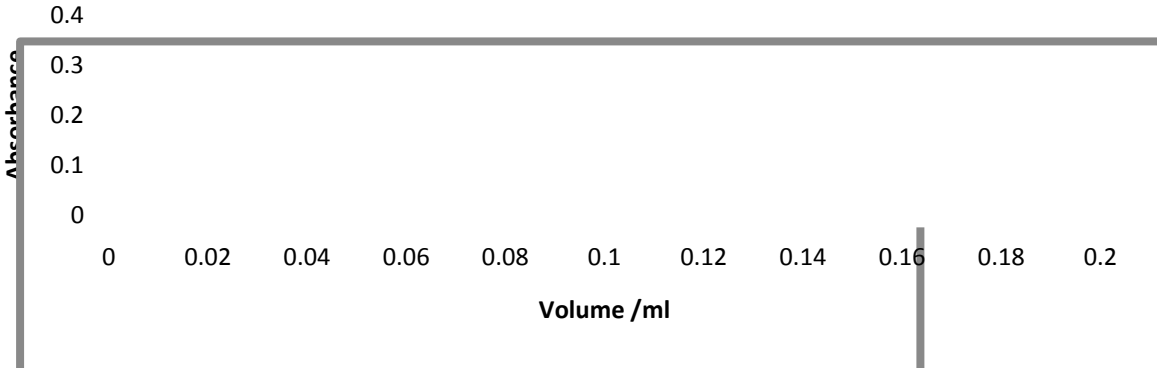


**Figure 8. The volume of 1% H3NSO3**

In this graph, it is clear that the absorbance increases with increasing the volume of Sulphamic acid but the signals decrease suddenly because this volume of sulphamic acid is used to removes nitrite and escape nitrogen gas [21].

**Effect of Optimum Volume of (100 µg mL-1) Reagent**

The same additions [1ml for MCP,0.3 ml CH3COOH, 0.6ml NaNO2,0.1ml H3NSO3, with varying volume from (0.2-2) ml 4- nitrophenol and 0.3 ml KOH have put in volumetric flask 10 ml and the higher absorbance of optimum volume 0.8 ml at maximum wavelength is fixed for sequence experiment as shown in Fig.9.

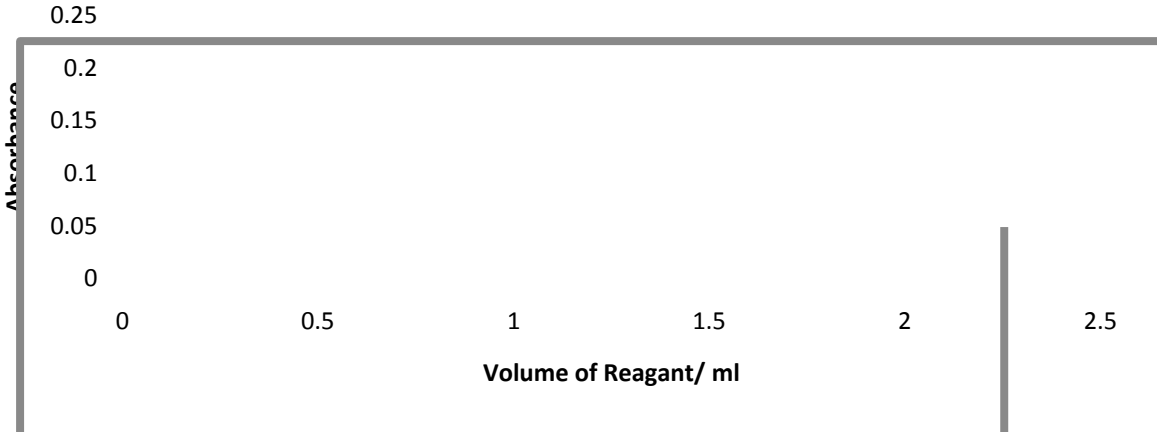


**Figure 9. volume of reagent /ml with MCP**.

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The absorbance increases with increasing the volume of the reagent but suddenly decreases because this is the required volume for coupling with MCP.

**Effect of Reaction Time on the Stability of the Product**

The optimum volumes are going to be applied for the color product of MCP [1ml MCP,0.3ml CH3COOH, 0.6ml NaNO2, 0.1 ml H3NSO3, 0.8ml 4- nitrophenol, 0.3ml KOH] in a volumetric flask 10 ml. The stability of the product is one of the important factors that diazotization reaction depends on, so the time needed is (0-55) minutes Then the absorbance is measured and the high reader at a high maximum wavelength is taken and recorded. The time of the product remains stable for MCP is 55 minutes show in Fig. 10.

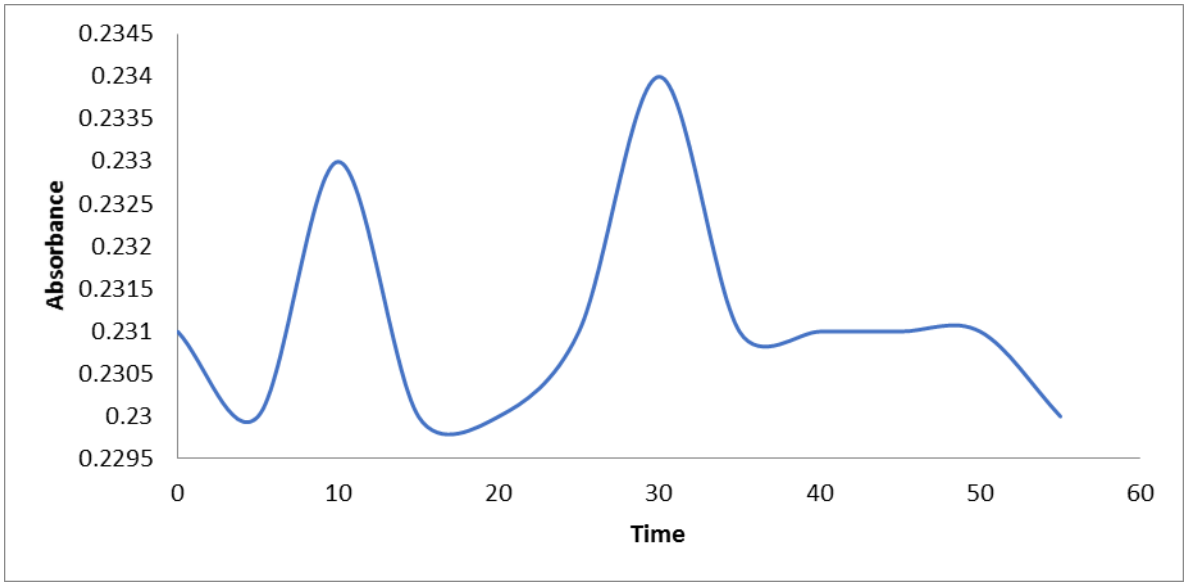


**Figure 10. Time stability color /minutes of MCP.**

**Effect of the Order of Addition**

In this study, the effect of the sequence of addition with optimum volumes depends on the same procedure is applied. The absorbance is measured and recorded in Table 9. R: 4-nitrophenol H: acid (CH3COOH), N: NaNO2, S: H2NSO3, D: Drug (MCP), B: Base (KOH). The best addition is order two because it gives the upper absorbance as shown in Fig. 11.

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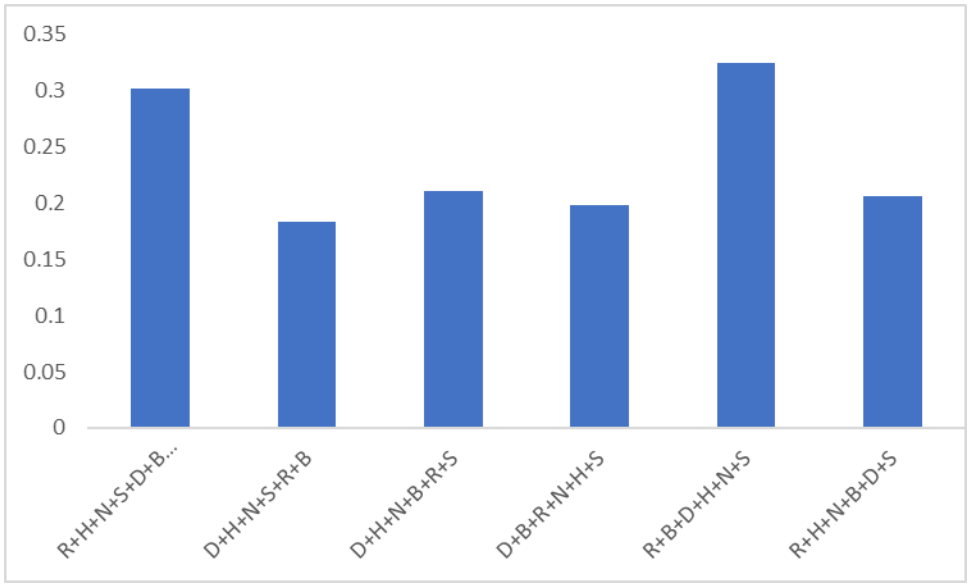


**Figure (11): Different addition with MCP**

**Stoichiometric Determination of Product Continuous Variation Method [23]**

A series of different volumes of reagent and drug were prepared (0.1-0.9) ml, with concentration (4x10-4 M) in a volumetric flask of 10 ml. The additions are in optimal condition and the volume is complete by distilled water (10 ml). Then absorbance is measured by UV-VIS at λ max =440 nm. The stoichiometric ratio between reagent[R] and drug [D] result in 1:1 as shown in Fig .1.

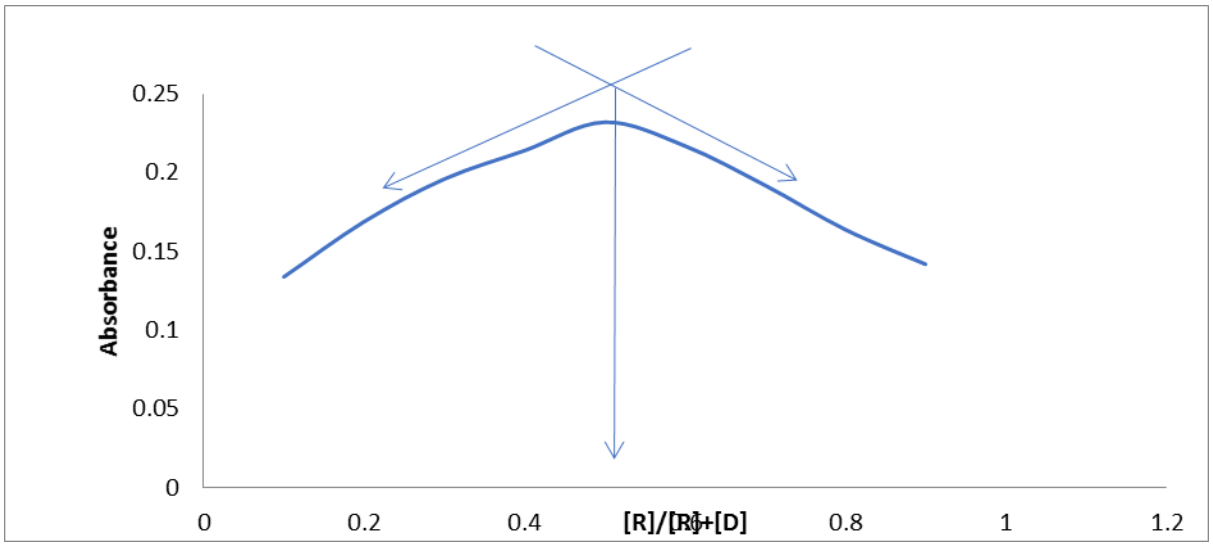


**Figure 12. Continuous Variation method of MCP**

**Mole Ratio Method**

In this method, the volume of the drug is fixed at 1 ml with concentration (4x10-4M), and the volume of reagent changes (0.1-1 ml). The optimum of addition is completed by distilled water in a volumetric flask of 10 ml and the absorbance is measured by UV-VIS at λ max

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=440 nm. The stoichiometric ratio between reagent[R] and drug [D] result in 1:1 shown in Fig 13.

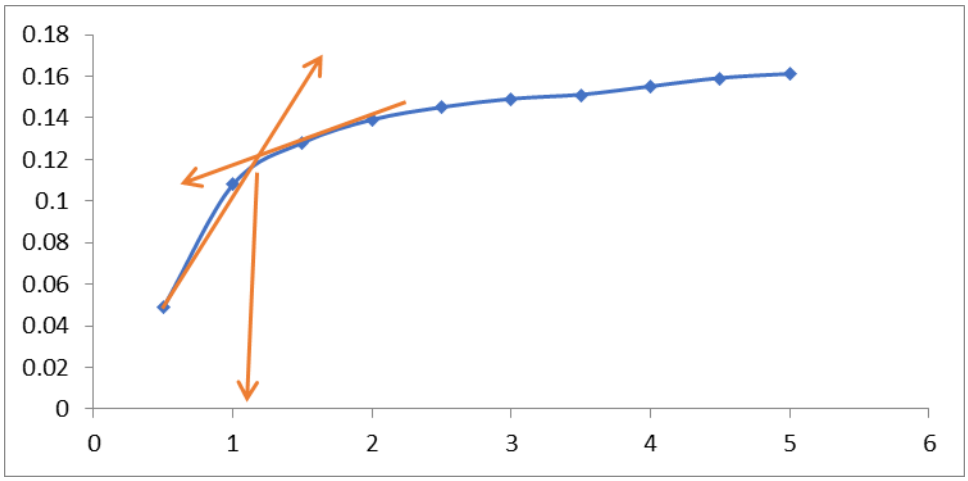


**Figure 13. Mole Ratio Method of MCP.**

**Calibration Curve for a complex of MCP - 4- Nitro phenol**

In this study, the solution is prepared in volumetric flask 10 ml containing increasing concentration of MCP (1-12) µg mL-1 by taken [0.3 ml CH3COOH, 0.6 ml NaNO2, 0.1 ml H2NSO3, 0.8 ml 4-nitro phenol, 0.3 ml KOH]. The volume is completed by distilled water and the absorbance is measured by UV-VIS at maximum wavelength against a blank solution prepares in the same condition without the drug. Linear calibration graph is established by plotting the absorbance against the concentration of MCP, it found (1-12) µg mL-1 obeys Bear Law. The molar absorption coefficient of a product equals (L.mol-1.cm-1) and Sandell's sensitivity (µg mL-2). The result is shown in Fig 14.

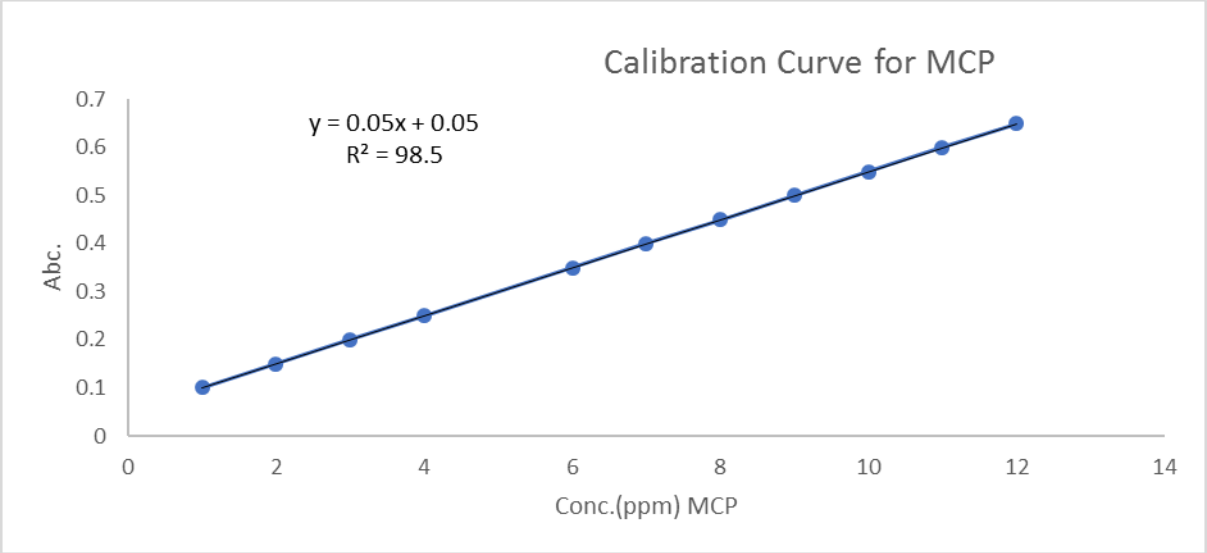


**Figure 14. Calibration Curve of MCP.**

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**Accuracy and precision**

To test the proposed method in term of freedom from systematic errors for the detection of MCP drug, accuracy was determined via the spiking three blank samples with 15, 20, and 25 µg mL-1 of MCP taking from the drug Metoclopramide hydrochloride BP (5000 µgmL-1) solution produced by Sanofi Pharmaceutical Industry –France and containing only chloride and water as additives. The three spiked samples were subjected to the general CPE procedure for MCP. The results were displays in Table 11, revealed that a good accuracy in term of percent recovery can be achieved within the range of 98.95±1.09%, due to the absence of systematic errors. Meanwhile, each spiked sample was repeated five times for precision testing in terms of %RSD and found in the range between 0.04 and 0.661%, indicative of good precision.

**Table 11. The accuracy and precision of the proposed method for the determination of MCP.**

| Amount of MCP taken, µgmL-1 | Amount of MCP found, µg mL-1 | Recovery % | Erel % | Mean Rec.±ts/√n, % | RSD % (n=5) |
|---|---|---|---|---|---|
| 10 | 9.88 | 99.20 | -0.800 | 98.95±1.09 | 0.661 |
| 20 | 19.84 | 99.20 | -0.800 | | 0.330 |
| 30 | 29.61 | 98.44 | -1.56 | | 0.040 |

**Application**

The proposed method is applied to [Plasil 10 mg France] injection that contains (10mg) from Metoclopramide in12ml). The result is good and summarized in Table (12).

**Table 12. Determination of MCP in pharmaceutical formulation by the proposed method**

| Amount of MCP taken, µgmL-1 | Amount of MCP found, µg mL-1 | Recovery % | Average Recovery % | Erel % | Average Erel% | RSD % |
|---|---|---|---|---|---|---|
| 12 | 11.9728 | 99.773 | 98.474 | -0.2266 | -1.5253 | 0.4134 |
| 9 | 9.0090 | 100.1 | | 0.1 | | 0.5982 |
| 6 | 5.8765 | 97.94 | | -2.058 | | 0.6678 |

**Second Method: Spectrophotometric Determination of Metoclopramide (MCP) with using Cloud Point Extraction Technique.**

**Effect Type of Surfactant with MCP**

The surfactant plays a vital role in the cloud point extraction process. The basic practical depends on micelles for extraction. The solution contains [1ml MCP,0.3ml CH3COOH, 0.6ml NaNO2, 0.1 ml H3NSO3, 0.8ml 4- nitrophenol, 0.3ml KOH] and 1ml of each

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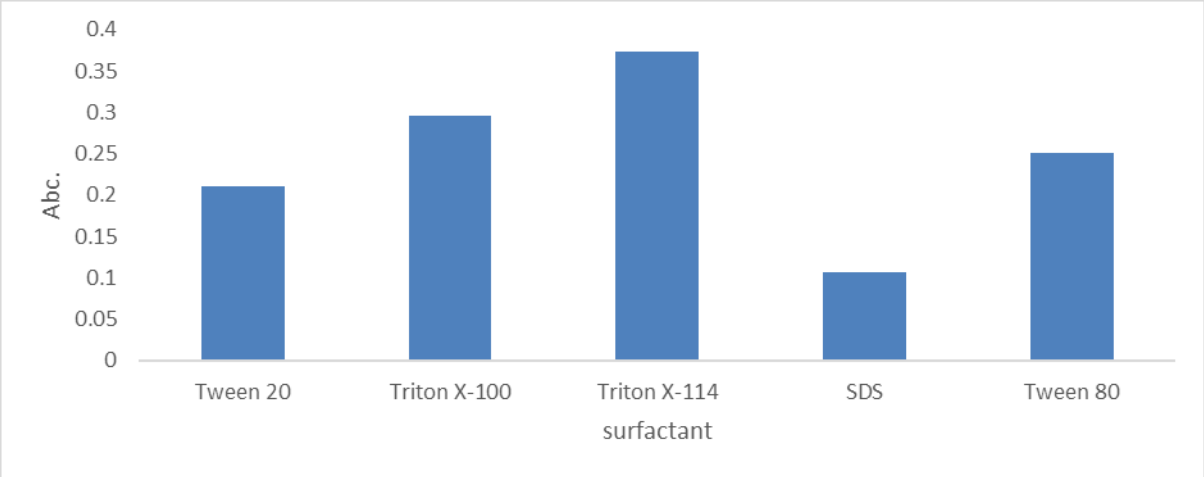
surfactant added in volumetric flask 10 ml and the volume is completed by distilled water at 60° C for 20 minutes then separated by centrifugation at 4000rpm for 20 minutes, that separated and dissolved in 2 ml ethanol and measured by UV-VIS at λmax=440 nm and the result shown in Table13. It is clear from this result that the surfactant Triton X-114 increases the absorbance and efficiency of cloud point extraction (24) shown in Fig.15.

**Figure 15. Effect of different Surfactant with MCP.**




**Effect of Triton X-114 Volume**

The solution contains the former addition and uses varying volumes of 10% Triton X-114 in a volumetric flask of 10 ml and completes the mark by distilled water. It is heated at 60 °C for 20 minutes to form cloud point and separated by centrifugation at 4000rpm for 20 minutes, 2ml ethanol will be added and measured by UV-VIS at λmax=440nm. The absorbance increases with the increasing volume of Triton X-114 with an effect on the efficiency of extraction (25). Suddenly this absorbance decreases below the optimum volume due to micelles catch enough amount of hydrophobic product. The best volume of Triton X114 is 1.6 ml as shown in Fig. 16.

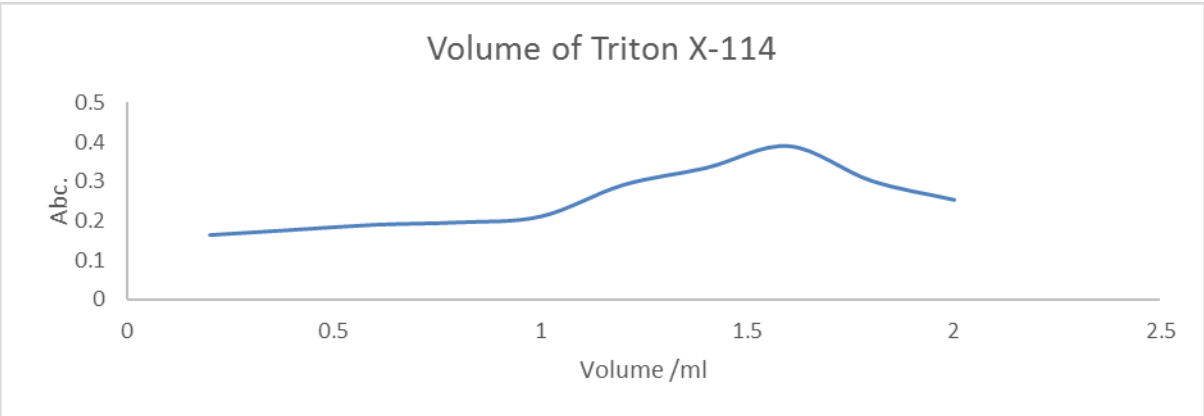



**Figure 16. The volume of TritonX-114 with MCP**

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**Effect of Equilibrium Temperature**

In series of 10 ml that contain [1ml MCP,0.3ml CH3COOH, 0.6ml NaNO2, 0.1 ml H3NSO3, 0.8ml 4- nitrophenol, 0.3ml KOH1.6 ml Triton X114] in a volumetric flask 10 ml then complete to the mark by distilled water. The varied temperature (35-70 °C) for 20 minutes to form cloud point and separated by centrifugation at 4000rpm for 20 minutes, 2ml ethanol will be added and measured by UV-VIS at λmax =440 nm and recorded as shown in Fig. 17. The result recorded that the best temperature is 55 °C as shown in Fig.16.

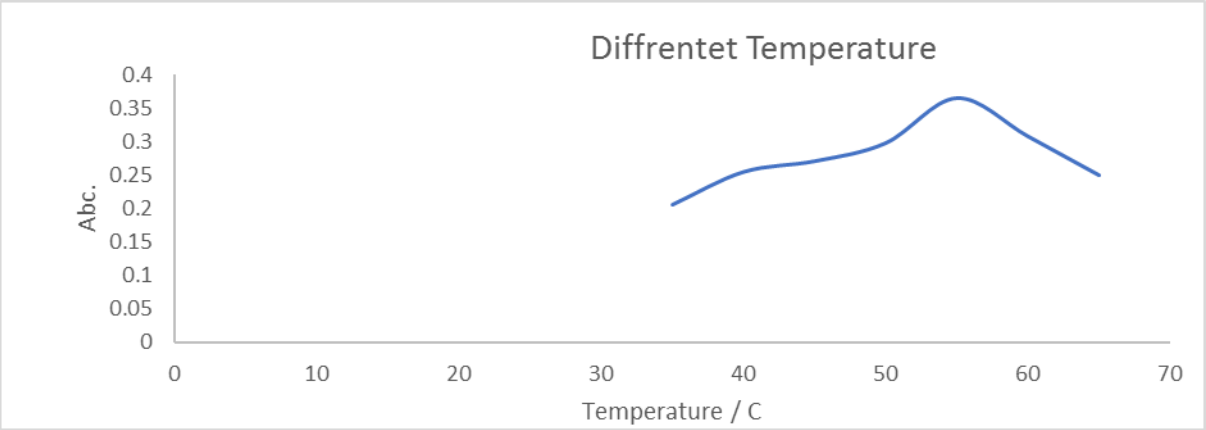


**Figure 16. Different Temperature/° C with Effect of Incubation Time.**

**Effect of Incubation Time**

The solution contains [1ml MCP,0.3ml CH3COOH, 0.6ml NaNO2, 0.1 ml H3NSO3, 0.8ml 4- nitrophenol, 0.3ml KOH1.6 ml Triton X114] is prepared in volumetric flask 10 ml and the volume is complete by distilled water at temperature 55 °C and the incubation time for(5-40minutes) to form cloud point and separated by centrifugation at 4000rpm for 20 minutes, 2ml ethanol will be added and measured by UV-VIS at λ max =440 nm. The best incubation time is 25 minutes as shown in Fig. 17.

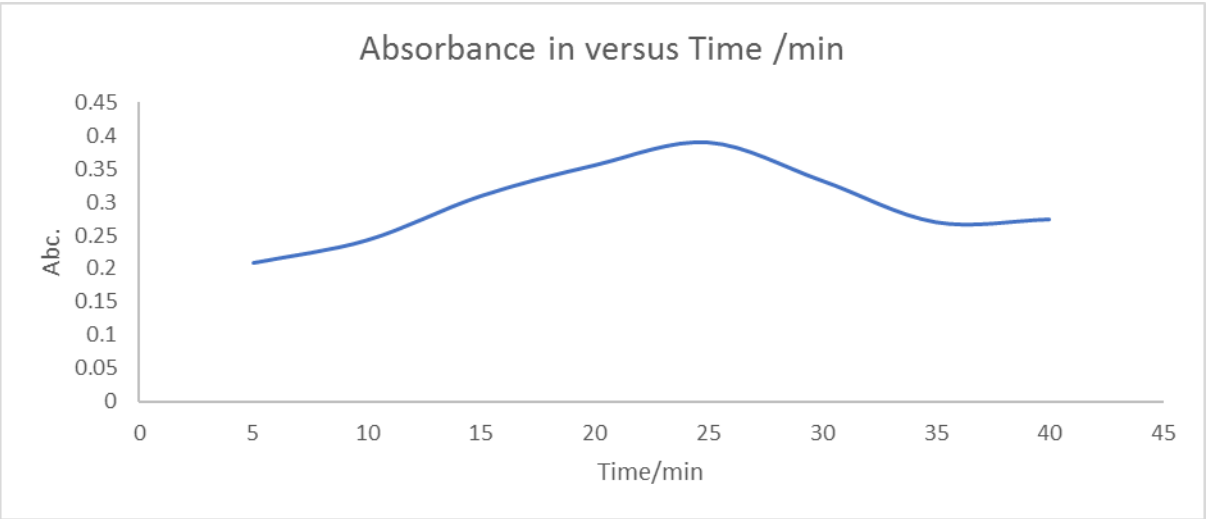


**Figure 17. The absorbance of different incubation times.**

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**Preparation of Calibration Curve in CPE**

The prepared solution prepared increasing concentration (1-12 µg mL-1) by taking [0.3ml CH3COOH, 0.6ml NaNO2, 0.1 ml H3NSO3, 0.8ml 4- nitrophenol, 0.3ml KOH1.6 ml Triton X114], and in volumetric flask 10 ml the volume is completed by distilled water at temperature 55oC and the incubation time for(25minutes) to form cloud point and separated by centrifugation at 4000rpm for 20 minutes, 2ml ethanol will be added and measured by UV-VIS at λ max=440 nm and show the result in Fig (18).

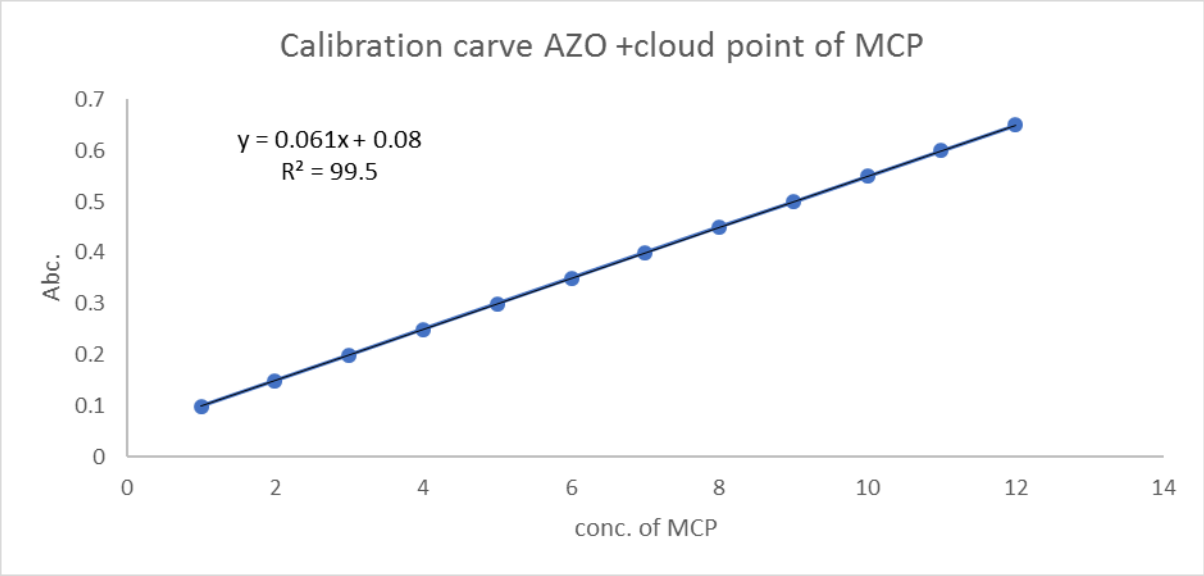


**Figure 18. Calibration Curve AZO + Cloud Point of MCP.**

**Accuracy and Precision Test**

To test the proposed method in term of freedom from systematic errors for the detection of MCP, table 17 show the accuracy and precision for MCP with CPE, which are studied at different concentrations (15,20,25). This result has good accuracy and precision as is shown in Table 17.

**Table 17. The accuracy and precision of the proposed method for the determination of MCP.**

| Amount of MCP taken, µg mL | Amount of MCP found, µg mL-1 | Recovery % | Erel % | Mean Rec.±ts/√n, % | RSD % (n=5) |
|---|---|---|---|---|---|
| 15 | 14.88 | 99.20 | -0.800 | 98.95±1.09 | 0.661 |
| 20 | 19.84 | 99.20 | -0.800 | | 0.330 |
| 25 | 24.61 | 98.44 | -1.56 | | 0.040 |

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**Conclusion:**

This study has shown that it is possible to a mutual estimate of the reactants involved in any chemical reaction by using a combined CPE-spectrophotometry method is kindliness with high sensitivity, better recovery, and extraction efficiency. Cloud point extraction is a simple, safe, and useful pre-concentration technique to determine MCP. It became clear from this study that it is possible to consider the MCP drug as a chemical organic reagent cheaply available. It can be used in the complexation of reagents other than 4- nitrophenol. It gives a good RSD and a low limit of detection.

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