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Novel Green Method for the Spectrophotometric Determination of Metoclopramide Hydrochloride in Pharmaceutical Formulations

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Abstract: A less environmentally harmful reagent, 2-tert-Butyl-4-methoxyphenol (BHA), is used to evaluate Metoclopramide hydrochloride (MCP.H) by simple, rapid, sensitive, accurate and precise spectrophotometric method, through azo coupling reaction between metoclopramide hydrochloride medicine and it's pharmaceutical preparation by utilizing BHA as a reagent, (MCP.H) azo-dye formed shows the higher absorption peak at 504 nm. Absorbance- concentration relation is linear over the range from 20 to 280 µg / 5 mL, (i.e. 4-56 ppm) with a good sensitivity (molar absorptivity $0.26x10^4$ $L.mol^{-1}.cm^{-1}$); good precision (RSD better than 0.844 %) and high accuracy (relative error less than + 0.4%), Sandell's sensitivity index is -0.1293 $\mu g.cm^{-2}$, the calculated limit of detection (LOD) is 0.0658 µg/mL and the evaluated limit of quantitation (LOQ) is 0.2193 µg/mL. The application has had successful results for the assay of metoclopramide hydrochloride in dosage forms of tablets and injection.

Keywords: Butylated hydroxyanisole, metoclopramide hydrochloride, spectrophotometry friendly environment.

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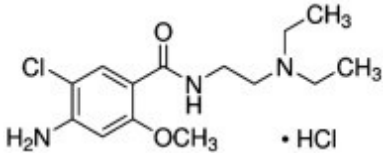
1. INTRODUCTION

Metoclopramide hydrochloride (MCP.H), [4-amino-5-chloro-N-[2-diethylaminoethyl]-2-methoxybenza-mide hydrochloride], (Sketch 1), is used as an anti - vomiting agent in the treatment of certain types of queasiness and emeticing as well as to increase gastrointestinal motility (1). Oral forms of the drug are rapidly absorbed in the gastrointestinal tract, therefore they are not suitable for administration to children or elderly patients after surgery, as vomiting is often performed before absorption in the gastrointestinal tract (2). Taking the medicine causes some side effects, including dry mouth, insomnia, and changes in arterial blood pressure (3).

A survey of the literature reported that metoclopramide hydrochloride was estimated under optimal conditions by different spectropho-tometric methods and using various chemical reagents, such as: azo-dye coupling (3-11), oxidative coupling (12-14), Schiff base Reaction (15), and charge transfer complex (16). A number of researchers were able to estimate (MCP.H) by using other spectrophotometric methods such as UV, colored ion–pair complex, oxidation, reduction reaction and nucleophilic substitution reaction, in the presence of chemical reagents and under various optimal condition (17-20), diverse HPLC methods (21-25), Fluorescent analysis (26), and Glassy carbon electrode (GCE) were also used (27).



Sketch 1: $C_{14}H_{23}Cl_2N_3O_2.HCl$ M.wt. = 336.26 g/mol.

Currently, the recent methodological development in analytical chemistry gave rise to a plethora of improved and durable versions of an environ-mentally friendly approach (28), some of these concepts are safe compounds (29). As a result, this study describes a simple, sensitive and environ-

mentally friendly spectrophotometric method for assay of (MCP.H), using 2-tert-Butyl-4-methoxyphenol (BHA), a synthetic antioxidant as a safer reagent. (30).

2. EXPERIMENTAL

2.1 Apparatus

A JASCOV-630 UV-VIS (Tokyo, Japan) double beam spectrophotometer was used for all spectral and absorbance measurements with matched of 1.0 cm path length glass cells. ABS 120-4 Kern & Sohn GmbH used for weighing the samples.

2.2. The reagents

All the reagents used were of analytical-reagent grade. MCP.H stock standard solution 500 µg/mL: prepared by dissolving 0.05 g of pure MCP.H (NDI-Iraq) in distilled water and diluting to the marked in 100 mL volumetric flask using the same solvent. The stock solution was properly diluted to create the working solution 200 µg/mL. The prepared solutions were transferred to a dark bottle and kept in a cooled place which are stable for one month at least.

Sodium nitrite stock solution 1 × 10^{-2} M: was prepared by dissolving 0.0690 g of sodium nitrite in distilled water and diluting to the mark into a 100 mL volumetric flask. The stock solution was properly diluted to create 5.94 ×10^{-4} M working solution.

Butylated hydroxyanisole (BHA) reagent solution 5.54 ×10^{-4} M : was prepared by dissolving 0.0101 g of reagent (Miavit / Germany) in distilled water and diluting to the marked in 100 mL volumetric flask. The produced solutions, which can be used for at least two weeks, were transferred to a dark bottle and kept in a cool location.

2.2.1. MCP.H Tablet solution (200 µg / mL)

The average weight of 10 Metoclopramide tablets Bp 10 mg (Flamingo Pharma, UK), was ground and mixed well. A portion of this powder, equivalent to 0.0200 g, accurately weighed. then was dissolved in warm distilled water and filtered it, the residue was washed and the same of solvent completed to the mark 100 mL in volumetric flask.

2.2.2. Injection solution (200 µg / mL)

Using a 100 mL volumetric flask, 4 mL of METOCOL Injection 10 mg/ 2 mL (Pioneer, Iraq) were taken, and the volume was then increased to the proper amount with distilled water.

2.2.3. General procedure for calibration

In a series of 5 mL calibrated flasks, an aliquot of a standard solution (200 µg/mL = 5.94 × 10^{-4} M) containing 0.1–1.4 mL of MCP.H was added. Equimolar sodium nitrite solution (5.94 × 10^{-4} M) was added to this solution, and 0.2 mL of a 1 M hydrochloric acid solution was used to correct the pH. The mixture was vigorously shaken, wait for 5 minutes to complete the diazotization step. Then, 1 mL of BHA (5.54 × 10^{-4} M) and 0.25 mL of 0.5 M sodium carbonate solutions were added. The mixture was thoroughly mixed and waited for between 2- 5 minutes before being diluted to the proper concentration with distilled water. The colored azo dye's absorbance at 504 nm against the equivalent reagent.

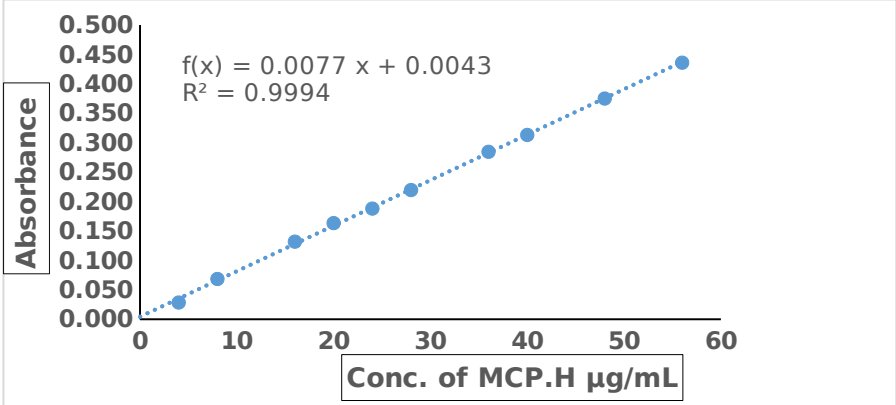


Figure 1: Standard curve for estimating MCP.H.

Figure 1 shows a good linearity over the range of the concentration between 4 to 56 µg/mL with good sensitivity in which that the molar absorptivity is 0.26 x 10^4 L / mol.cm and sensitivity index of Sandell is 0.1293 µg/cm^2.

3. RESULTS AND DISCUSSION

3.1. Study of the optimum conditions

3.1.1. Choosing of the acid

A number of different acids with the concentration of 1.0 M and an amount of 0.25 mL was used in this study. The results are shown in Table 1. As shown in Table 1. the maximum intensity of the colored product's absorptions occurs when 1 M hydrochloric acid is fixed in the following experiments.

Table 1: Choosing the appropriate acid type.

Type of acid	λ_{max}	Absorbance
H_3PO_4	509	0.1304
HCl	504	0.1502
H_2SO_4	508	0.0989
HNO_3	Turbid	Turbid
CH_3COOH	510	0.0723

3.2. Effect of Different Volumes of 1 M Hydrochloric Acid Solution

Different volumes (0.1-0.4 mL) of 1.0 M hydrochloric acid were added to the reaction medium 5 mL volumetric flask. Figure 2 found that 0.1 mL was turbid, and after 0.2 mL of hydrochloric acid the absorbance of the colored azo dye product decreases with the increase of acid amount added. So 0.2 mL of 1 M hydrochloric acid was chosen.

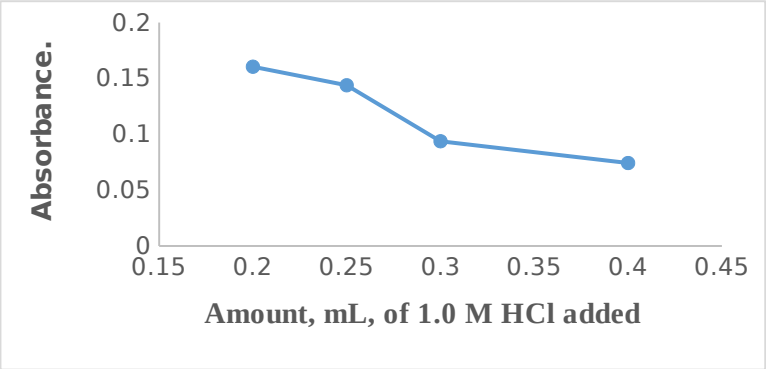


Figure 2: Effect of different volumes of 1 M hydrochloric acid solution.

3.3. Choosing the Base

Several alkaline solutions (potassium hydroxide, sodium bicarbonate, sodium carbonate and sodium hydroxide) with a concentration of 0.5 M were investigated. Sodium carbonate was choice which considered as a best alkaline medium for producing maximal absorbance of the red azo dye and was chosen. Figure 3 illustrates the results.

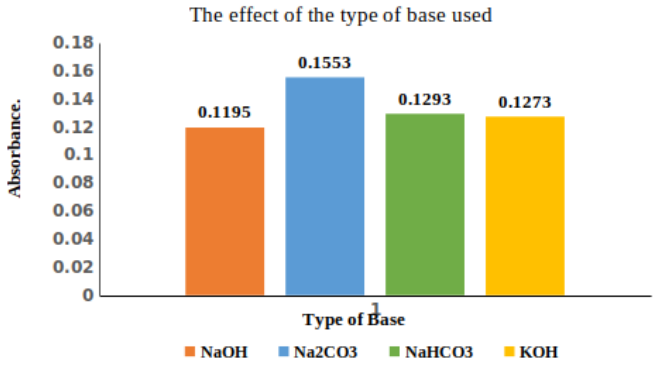


Figure 3: Choosing the appropriate of base type.

3.4. Effect of Different Amount of 0.5 M Sodium Carbonate

Different volumes (0.1 - 0.5 mL) of 0.5 M sodium carbonate solution were added to the reaction medium, Figure 4 found that 0.5 mL was turbid and 0.3 mL was enough to obtain the maximum absorbance, which was utilized in all future studies.

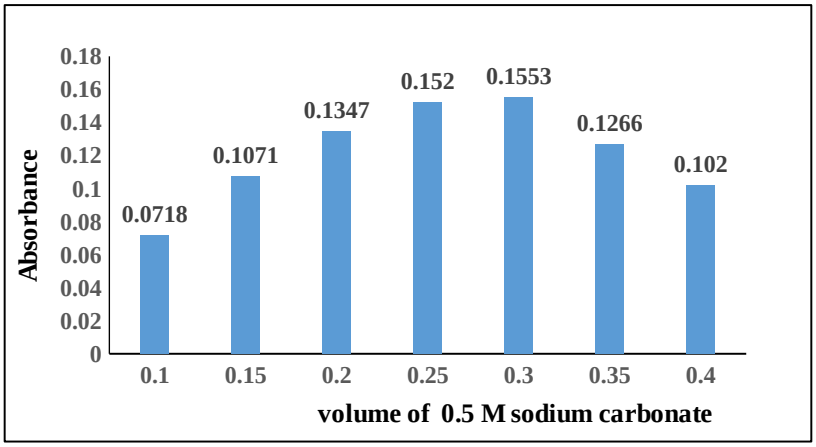


Figure 4: Effect of different amount of 0.5M sodium carbonate.

3.5. Effect of BHA Reagent Amount

The effect of changing volumes 0.5-1.5 mL of 5.54 $\times 10^{-4}$ M BHA coupling agent, studied against different concentrations of MCP.H, which was evident that the absorbance increases with increasing BHA concentration, the determination coefficient of measured absorbances has been evaluated. Table 2 shows that 1 mL of 5.54 $\times 10^{-4}$ M of the coupling agent solution gives the best results.

Table 2: Effect of BHA reagent amount.

mL of 5.54 $\times 10^{-4}$ M reagent	Absorbance / µg of MCP.H						
	36	**32**	**28**	**24**	**20**	**12**	**R^2**
0.5	0.237	0.236	0.212	0.176	0.148	0.093	0.9702
0.75	0.266	0.249	0.215	0.176	0.147	0.097	0.9915
1.0	**0.287**	**0.251**	**0.224**	**0.189**	**0.155**	**0.094**	**0.9991**
1.25	0.286	0.243	0.221	0.188	0.159	0.099	0.9961
1.5	0.286	0.246	0.221	0.181	0.152	0.094	0.9964

3.6. Study of the Effect of Surfactants

1 mL of anionic sodium dodecyl sulfate (SDS), cationic cetylpyridinium chloride (CPC), cetyl trimethyl ammonium bromide (CTAB), and neutral iso-octylphenoxy-poly ethoxy ethanol (Triton X-100) were used to examine the impact of surfactants on absorption intensity. The use of surfactant was disregarded because the inclusion of SDS resulted in turbid solution and the addition of CPC reduces absorption intensity, while the addition of CTAB and Triton X-100 had no effect on absorption intensity.

3.7. Study of the Effect of Temperature

The effect of different temperature between 0°C to 40°C was studied, on the diazotization and coupling reaction show that the absorbance of the azo dye remains constant in the 25°C but decrease at lower than room temperature and higher than 30°C. Therefore, it has been recommended to carry out reaction at room temperature (25°C).

3.8. Stability of the Azo Dye Product

Following the mixing of the chemicals, the stability of the colored dye was investigated for 1 hour using 20 and 40 g/mL shows that the colored product maintains its stability for at least 55 minutes. See Table 3.

3.9. Final Absorption Spectrum

The BHA-MCP.H product's absorption spectra were plotted under the optimum reaction conditions obtained in Fig. 5 that a reddish orange colored compound had a maximum absorption at 504 nm versus blank.

Table 3: Stability of the azo dye product.

Time, min	Absorbance / µg of DMCPH per mL	
	20	**40**
0	0.1638	0.3113
5	0.1644	0.3077
10	0.1646	0.3053
15	0.1632	0.3085
20	0.1615	0.3062
25	0.1628	0.3056
30	0.1604	0.3057
35	0.1593	0.3059
40	0.1586	0.3046
45	0.1588	0.3019
50	0.1575	0.2998
55	0.1560	0.2965
60	0.1553	0.2967

3.10. Accuracy and Precision of the Suggested Method

The accuracy and precision of the suggested method were tested by analyzing of three different concentration (20, 36, 48) µg/mL with four replicates. The low relative error and low percentage relative standard deviation were summarized in Table 4. These values indicate the high accuracy and precision of the proposed method.

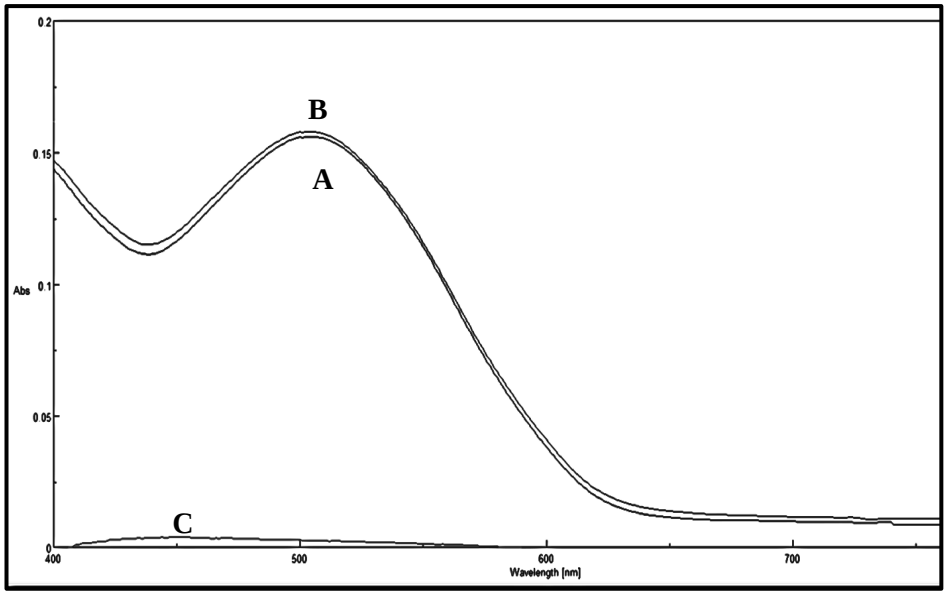


Figure 5: Final Absorption of spectra of (A) MCP.H (20 µg/mL) with BHA versus blank and (B) MCP.H with BHA versus distilled water (C) Blank versus distilled water.

Table 4: Accuracy and precision of the suggested method.

Amount of MCP.H µg/mL	Recovery, %*	Relative error, %*	Relative standard deviation, %*
20	100.12	+0.12	0.902
36	99.09	- 0.90	1.08
48	99.63	- 0.36	0.551

*Average of four determinations.

3.11. The Nature of the Dye

The stoichiometry of the product was studied applying the continuous variation method (Job's method). The results obtained in Figure 6 shows that a 2:1 azo dye was formed between diazotized MPC.H and BHA. The scheme below shows the proposed mechanism for the azo dye structure.

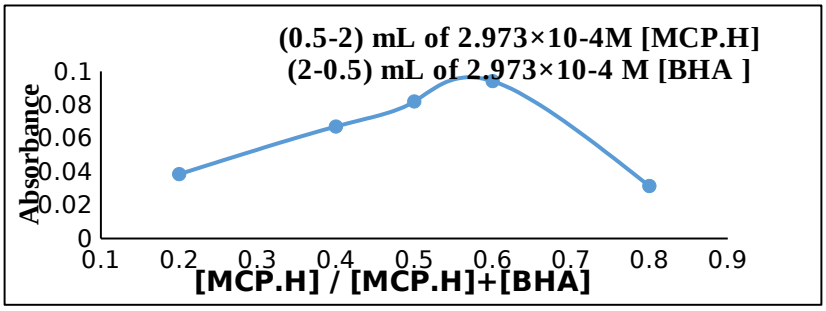
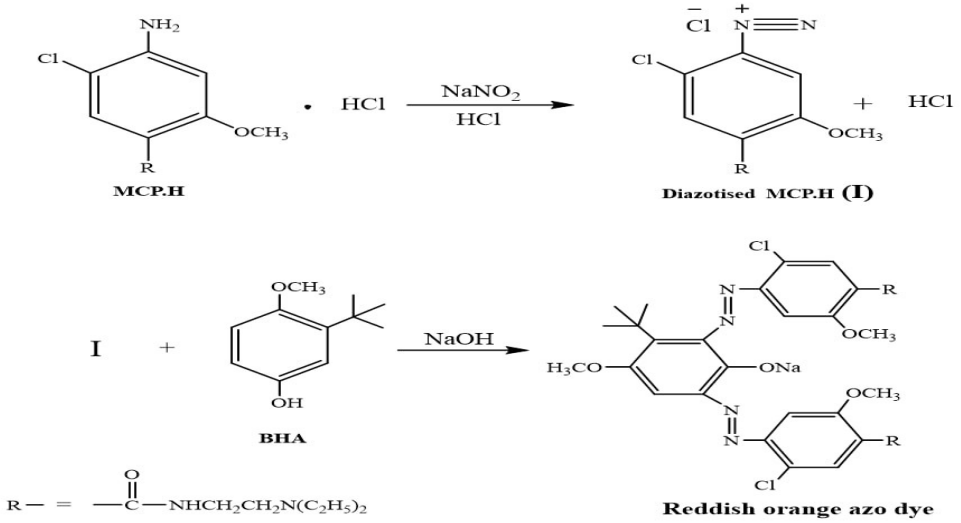


Figure 6: Continuous variation method.



Scheme 2: The suggested mechanism for MCP.H and BHA azo dye.

The azo dye's stability constant in aqueous solution was calculated and found to be 3.0379 $\times 10^{12}$ (31).

Table 5: Summary of optical characteristics and statistical data for the proposed method.

Parameter	Optimum conditions
Reagent	BHA
Linearity range, (µg mL^{-1})	4-56
Molar absorptivity, ($L.mol^{-1}. cm^{-1}$)	0.26×10^4
Sandel's Index, (µg. cm^2)	0.1293
λ_{max}, (nm)	504
Acid	HCl
Base	Sodium carbonate
LOD,(µg.mL^{-1})*	0.0658
LOQ, (µg.mL^{-1})*	0.2193
Average recovery, (%)**	99.6
RSD**	0.844
Correlation coefficient	0.9994
Medium	Aqueous
Solvent	Water

* Average of ten determinations.
**Average of four determinations of blank.

3.12. Effect of Interferences

Table 6 visions the effects of a few typical excipients associated with MCP.H in pharmaceutical preparations. The study shows that these additives has no negative effects on the efficiency of the suggested procedure.

3.13. Application Part

In order of demonstrate the applicability of the suggested method to the determination of MCP.H, on the form of tablets and injections, with three different concentrations, the results are summarized in Table 7. The assay results were indicating a good applicability of the of proposed method**.**

Table 6: Effect of excipients for MCP.H assay.

Excipients (1000 µg/mL)	Recovery (%) of 20 µg/ mL MCP.H per µg/ mL of excipient added		
	50	100	300
Lactose	98.59	100.51	101.3
Glucose	99.23	99.62	100.64
Starch	100.26	101.73	100.06

Table 7: Assay of MCP.H in pharmaceutical preparations using the proposed method.

µg MCP.H / mL	SDZ Present (µg)	SDZ Found (µg)	Relative Error (%) *	Recovery (%) *	RSD (%) *
Metoclopramide tablets Bp 10 mg (Flamingo pharma, UK)	20	20.16	0.826	100.82	1.40
	36	35.97	-0.052	99.94	0.80
	48	48.09	+0.219	100.2	1.06
METOCOL Injection 10 mg / 2 mL (Pioneer, Iraq)	20	20.04	+0.244	100.24	1.29
	36	36.12	+0.360	100.36	0.22
	48	47.83	-0.339	99.66	0.74

*Average of four determinations.

3.14. Evaluation of the proposed method's results

To elucidate that there is no interference with the additives employed in the pharmaceutical manufactures, the drug content of tablet and injection preparations was also estimated using the standard addition method, for 20 and 32 ppm of the two MCP.H pharmaceutical preparations solution separately and adding various concentrations of the standard MCP.H solution under the condition that the maximum extent of the estimate in the calibration curve is not override. Figure 7A,B and Table 8 shows the results (32).

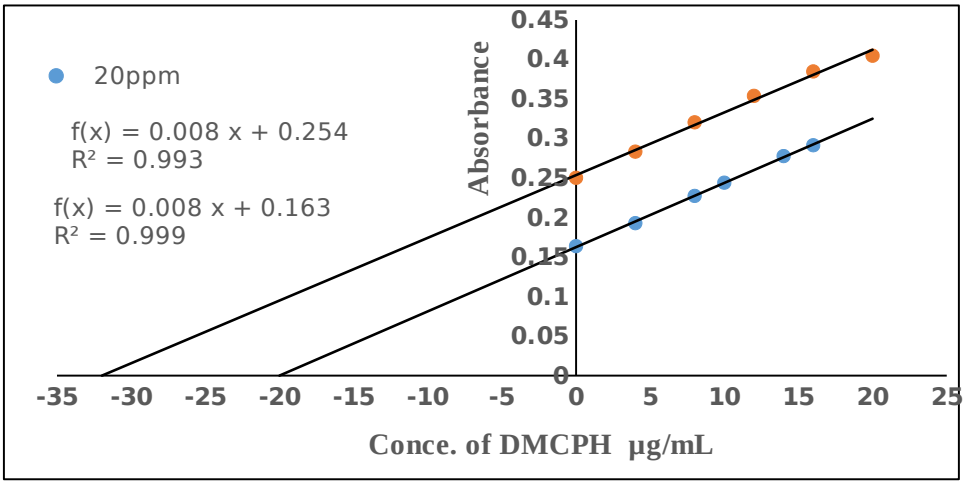


Figure 7A: Plot of standard addition method to estimate MCP.H in tablet.

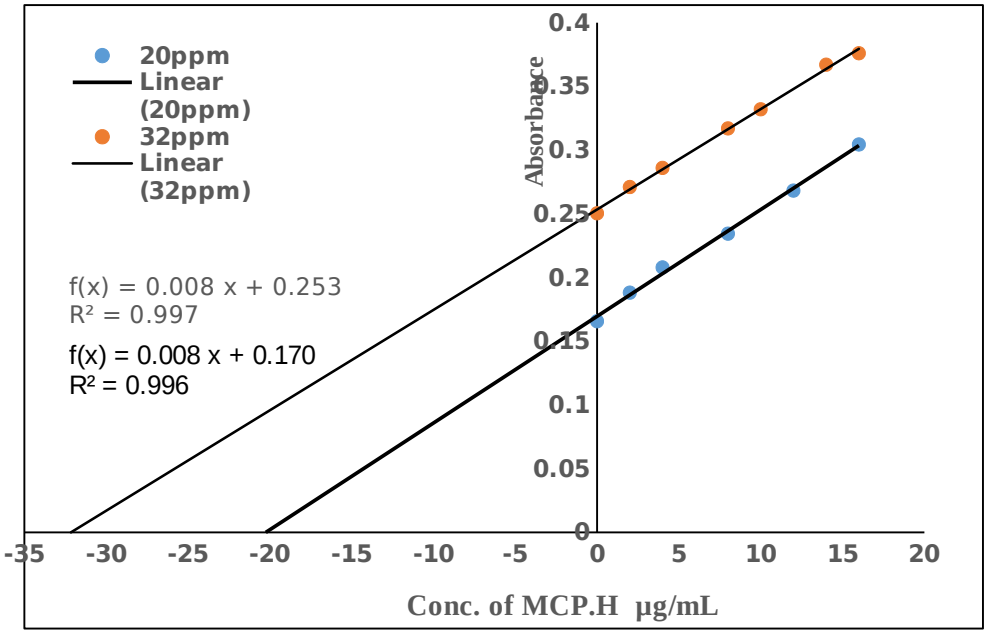


Figure 7B: Plot of standard addition method to estimate MCP.H in injection.

Table 8: Standard addition method to estimate MCP.H.

Pharmaceutical preparation	MCP.H Present (µg)	MCP.H measured (µg)	Recovery (%)*	Relative error, %*
METOCOL Injection 10 mg / 2 mL (Pioneer, Iraq)	20	20.17	100.85	+ 0.85
	32	32.07	100.22	+ 0.22
Metoclopramide tablets Bp 10 mg (Flamingo pharma, UK)	20	20.06	100.30	+ 0.30
	32	32.17	100.35	+ 0.35

*Average of four determinations.

3.15. Statistical Agreement t-test

The present method and the British Pharmacopeia one (based on potentiometric titration of pure medication with 0.1 M sodium hydroxide) at the 95 percent confidence level with 4 degrees of freedom were applied simultaneously for the t-test calculation (33). The value was compared with statistical Tables for four degrees of freedom at 95 percent validation level. The estimated t-test value (1.1255) was below the threshold of t 2.776 = (n_1 + n_2 - 2 = 2). These are confirming that, in terms of precision and accuracy in the determination of MCP.H in tablets, there are no appreciable discrepancies between the suggested approach and British Pharmacopeia's method.

Table 9: Comparison of the suggested method with the literature's method.

Parameters	**Present method**	**Literature method Ref. #34**
Reagent	BHA	p-Nitroaniline
λmax, (nm)	504	513
Temperature °C	Room Temp.	Room Temp.
Medium	Aqueous	Aqueous
Linearity range, (µg mL^{-1})	4-56	0.2-25
Molar absorptivity, L / mol.cm)	0.26×10^4	0.23×10^4
Sandell's Index, (µg.cm^2)	0.1293	0.1462
Nature of dye product Drug: Reagent	2:1	1:1
Average recovery,(%)	99.6	----
LOD, (µg.mL^{-1})	0.0658	0.182
LOQ, (µg.mL^{-1})	0.2193	0.553
Color of azo dye	Reddish-orange	Red
Application of the method	Tablet & Injection	Tablet & Injection

The results are shown in Table 9. The proposed method is not less important, of higher quality, and more sensitive than methods found in the literature. It does not require organic solvents; it can also be used to prepare pharmaceuticals with satisfactory results.

4. CONCLUSION

For the determination of metoclopramide hydrochloride in pharmaceutical preparations (administered as tablets or injections), an environmentally friendly method was used, in addition of being easy, sensitive and highly accurate, through its reaction with non toxic reagent (BHA), and free of organic solvents. In addition the method did not need any separation steps.

5. ACKNOWLEDGMENTS

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