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Original Article

SPECTROPHOTOMETRIC METHODS FOR THE QUANTITATIVE DETERMINATION OF MEMANTINE HYDROCHLORIDE IN PURE FORM AND PHARMACEUTICAL FORMULATIONS

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ABSTRACT

Objective: Three simple, sensitive, accurate, and precise spectrophotometric methods have been developed and validated for the determination of Alzheimer's disease drug memantine HCl (MEM) in pure form and pharmaceutical formulations.

Methods: The method was based on the formation of charge transfer complex between MEM as n-electron donor and various π-acceptors quinalizarin (Quinz) in methanol, p-chloranilic acid (p-CA) and 7,7,8,8-tetracyanoquinodimethane (TCNQ) in acetonitrile as chromogenic reagents which showed an absorption maximum at 558, 532 and 840 nm using Quinz, p-CA and TCNQ, respectively. The optimization of the reaction conditions such as the type of solvent, reagent concentration and reaction time were investigated.

Results: Under the optimum conditions, beer's law is obeyed in the concentration ranges 4.0–24, 10–160 and 5.0–50 µg/mlusing Quinz, p-CA and TCNQ, respectively with good correlation coefficient ($r^2 \geq 0.9995$) and with a relative standard deviation (RSD% ≤ 1.11). For more accurate analysis, Ringbom optimum concentration ranges were found to be between 8.0–20, 15–140 and 10–45 µg/ml using Quinz, p-CA and TCNQ, respectively. The limits of detection were found to be 1.2, 2.70 and 1.45 µg/ml and the limits of quantification were found to be 4.0, 9.0 and 4.83 µg/ml for Quinz, p-CA and TCNQ, respectively. A Job's plot of the absorbance versus the molar ratio of MEM to each of the acceptors under consideration indicated (1:1) ratio.

Conclusion: The methods were successfully applied to the determination of MEM in its pharmaceutical formulations and the validity assessed by applying the standard addition technique. Results obtained by the proposed methods for the pure MEM and commercial tablets agreed well with those obtained by the reported method.

Keywords: Memantine HCl, Spectrophotometry, Quinalizarin, *p*-Chloranilic acid; 7,7,8,8-tetracyanoquinodimethane, Charge transfer reaction, Dosage forms

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INTRODUCTION

Memantine hydrochloride (MEM), chemically known as 1-amino-3,5-dimethyladamantane hydrochloride, is an adamantane derivative with a unique non-planar tricyclic saturated ring structure (fig. 1). It is a psychoanaleptic antidementia drug for the treatment of moderate to severe Alzheimers disease. Memantine is an amantadine derivative and antagonist of *N*-methyl-*D*-aspartate (NMDA) receptors. Memantine also has antagonistic activity at the type 3 serotonergic (5-HT3) receptor with a potency that is like that at the NMDA receptor, and lower antagonistic activity at the nicotinic acetylcholine receptor [1, 2].

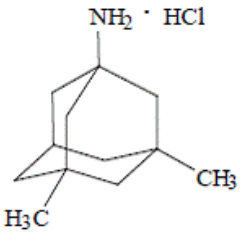


Fig. 1: The chemical structure of memantine hydrochloride (MEM)

Several methods for analysing MEM in pure drugs, pharmaceutical dosage forms, and biological samples have been described in the literature, including high performance liquid chromatography [3-5], liquid chromatography coupled with fluorescence detection [5-9] and mass spectrometry [10-13], gas chromatography with mass spectrometry (GC-MS) [14], potentiometry [15, 16], and spectrofluorimetric [17, 18]. These procedures, on the other hand, are costly, difficult to use for routine analysis, time consuming, and not available in most laboratories.

Only a few spectrophotometric techniques for determining MEM in pure and dose forms are available, according to a thorough literature search [18-29]. However, many of the methods mentioned above have one or more drawbacks, such as low sensitivity, the requirement for expensive solvents in addition to elaborate treatment, the necessity for time-consuming extraction operations, and the need for measurements.

Because of its simplicity and low cost, sensitivity and selectivity, high accuracy and precision, and broad availability and usefulness for pharmaceutical analysis, the specttrophotometric technique is widely used. The creation of brightly coloured charge transfer complexes, which absorb visible radiation, is often connected with molecular interactions between electron donors and acceptors [30]. Charge-transfer complexes with diverse acceptors have been reported using a variety of electron-donating chemicals [31-37].

We devised a simple, sensitive, fast, accurate, and verified spectrophotometric method for determining MEM in pure and dose forms in the current study. The suggested method entails the development of a charge transfer complex between MEM and several chromogenic reagents (Quinz, p-CA, and TCNQ).

MATERIALS AND METHODS

Apparatus

All absorption spectra were made using Varian UV–Vis spectrophotometer (Cary 100 Conc., Australia) equipped with 10 mm quartz cell was used for absorbance measurements. This

spectrophotometer has a wavelength accuracy of±0.2 nm with a scanning speed of 200 nm/min and a bandwidth of 2.0 nm in the wavelength range of 200–900 nm.

Materials and reagents

All employed chemicals and solvents (dimethyl sulfoxide, methanol, acetonitrile, acetone and ethanol) were of analytical-reagent grade and high-purified water was used throughout the study.

Pure MEM drug and pharmaceutical formulations

Pure sample of memantine HCl, (MEM), working standard, was kindly was kindly supplied by ADWIA Pharmaceuticals Community, El Obour City, Egypt. The commercial pharmaceutical formulations (Dementexa tablets labeled to contain 10 mg MEM per tablet, product of Pharaonia Pharmaceuticals, Alexandria, Egypt and Revmantine tablets, labeled to contain 10 mg MEM per tablet, product of EvaPharma, Egypt) were purchased from local market were subjected to the analytical procedure.

Preparation of stock standard solutions

A standard stock solution of MEM containing (400 and 100 µg/ml) or (1.0×10^{-3} mol/l) was prepared by dissolving an exact weight of pure MEM in 20 ml methanol for (Quinz) or acetonitrile for (p-CA or TCNQ) in a 100 ml calibrated flask and diluting to 100 ml with the same solvent to obtain the working concentration. The standard solution was kept in the refrigerator and found to be stable for at least one week if kept in a cool (<5 °C) and dark location.

Reagents

Quinalizarin 1,2,5,8-tetrahydroxy-anthraquinone (Quinz) (Sigma-Aldrich); chloranilic acid (p-CA), (Fluka, Switzerland) and 7,7,8,8-tetracyanoquinodimethane (TCNQ) (Aldrich Chem. Co., Milwaukee, USA) were used without purification. A stock solution 1.0 x 10^{-3} mol/l was made by dissolving the appropriate weight of the reagent in roughly 25 ml of methanol for (Quinz) or acetonitrile for (p-CA or TCNQ), then filling a 100 ml volumetric flask to the mark with the same solvent. At 4 °C, these solutions were stable for at least one week.

Procedures

Aliquot volumes (0.4-2.4 ml) or (0.5-5.0 ml) and (0.25-4.0 ml) of MEM standard working solutions (100 µg/ml) and (400 µg/ml) for (Quinz or TCNQ) and p-CA, respectively, were put into 10-ml calibrated flasks. 2.0 and 1.5 ml of (1.0 x 10^{-3} mol/l) (Quinz or p-CA) and TCNQ solution were added to each flask, respectively. The reaction mixture was then shaken to speed up the reaction, and the volume was topped up with methanol if Quinz was being used. When employing p-CA or TCNQ, the reaction mixture was combined and heated in a water bath at 60 °C for 10 min, then cooled and diluted with acetonitrile to a volume of up to 10 ml. Quinz, p-CA, and TCNQ had their absorbance measured at 558, 532, and 840 nm, respectively, against a reagent blank generated at the same time. By graphing the absorbance against the final concentration of MEM, the calibration graph was created. The regression equation for the appropriate variable was calculated.

Applications to pharmaceutical formulations (tablets)

The contents of ten tablets containing 10 mg MEM were coarsely ground and weighed properly using an agate mortar. In a 100 ml calibrated flask, a properly weighed quantity of the powder equivalent to 40 mg MEM was transferred and dissolved in 50 ml methanol for (Quinz) or acetonitrile for (p-CA or TCNQ). The flask's contents were shaken and sonicated for about 10 min, then thoroughly mixed and filtered using Whatman No.42 filter paper. The first portion of the filter was discarded, and the solution was then topped up with methanol to make a 400 g/ml stock solution. To acquire the working concentration ranges, this solution was further diluted with the same solvent as needed. The proposed procedures were applied to aliquots encompassing the working concentration ranges for each approach in a series of 10 ml volumetric flasks. Using the associated regression equations or calibration graphs, the nominal content of the tablets was determined.

Stoichiometric relationship

At the optimum wavelengths of maximal absorbance, the stoichiometric ratios of the charge transfer complexes produced between MEM and reagents were calculated using Job's method of continuous variation [38]. A 1.0×10^{-3} mol/l standard solution of MEM and a 1.0×10^{-3} mol/l mol/l solution of reagent were used in Job's method of continuous variation. A series of solutions were made, each with a total volume of 2.0 ml of medication and reagent. Following the above-mentioned processes, the reagents were combined in various amounts with the medication and diluted to volume in a 10-mL calibrated flask with methanol.

RESULTS AND DISCUSSION

Absorption spectra

The goal of this study is to create accurate, repeatable, and sufficiently sensitive spectrophotometric methods for determining MEM as an Alzheimer's disease medication in bulk powder and pharmaceutical formulations. In methanol or acetonitrile, the approach is based on the development of a charge-transfer complex between MEM as an electron donor and certain π-acceptors (Quinz). The radical anion (absorbing species) was produced in the medium immediately after mixing the reagents at optimum conditions, with maximal absorption at 558, 532, and 840 nm, respectively, using Quinz, p-CA, and TCNQ (fig. 2-4). As a result, these wavelengths were chosen for all subsequent measurements in order to achieve the best sensitivity possible with the presented methodologies.

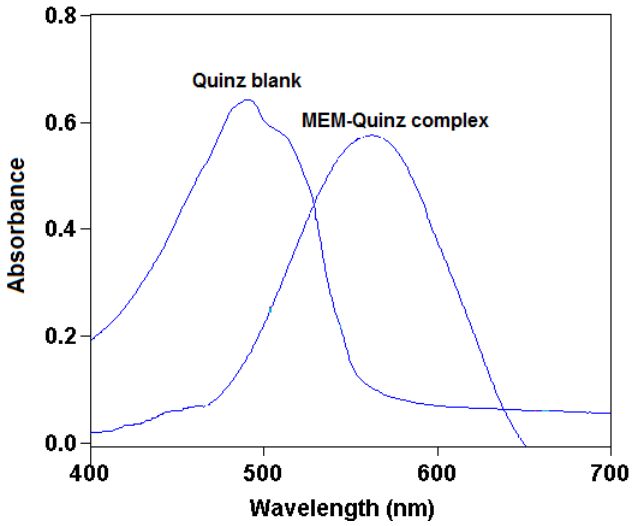


Fig. 2: Absorption spectra of Quinz and the reaction product of MEM (24 µg/ml) in methanol

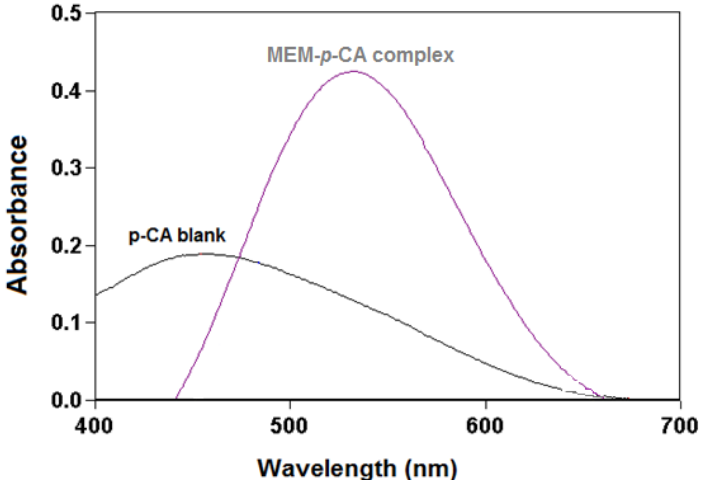


Fig. 3: Absorption spectra of *p*-CA and the reaction product of MEM (160 µg/ml) in acetonitrile

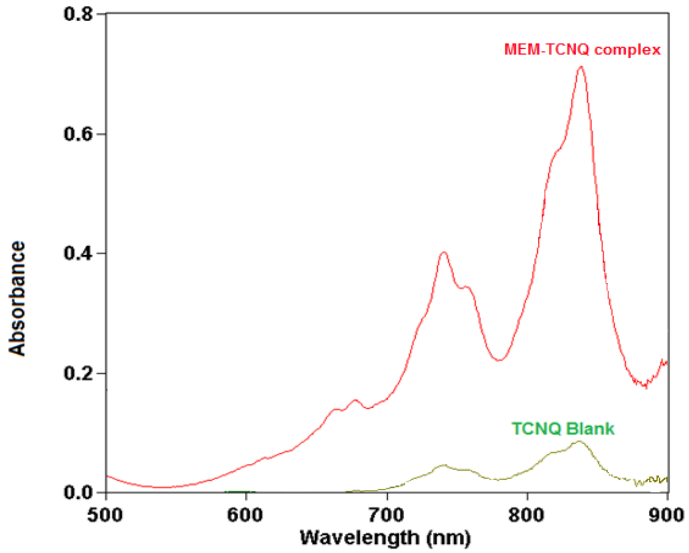


Fig. 4: Absorption spectra of TCNQ and the reaction product of MEM (50 µg/ml) in acetonitrile

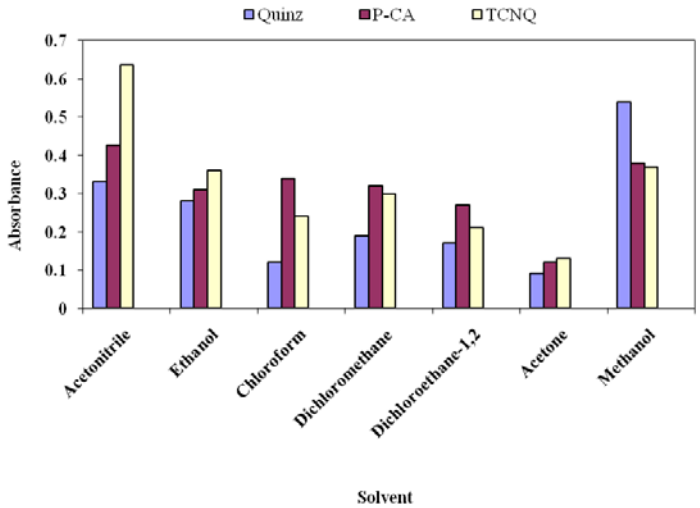
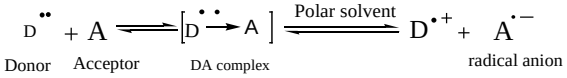


Fig. 5: Effect of different solvents on the charge transfer complex of MEM-reagent solution obtained against reagent blank solutions also prepared in each solvent

In polar solvents such as methanol or acetonitrile, complete electron transfer from the MEM (D), as an electron donor, to the acceptor moiety (A) takes place with the formation of intensely colored radical ions with high molar absorptivity values, according to the following scheme:



The dissociation of the (D–A) complex was promoted by the high ionizing power of the polar solvent and the resulting peaks in the absorption spectra of MEM-acceptor reaction mixtures were similar to the maxima of the radical anions of the acceptors ($Quinz^{-}$, $p\text{-}CA^{-}$ and $TCNQ^{-}$) obtained by the iodide reduction method [39].

Optimization of the reaction conditions

Effect of the solvent nature

Acetone, methanol, ethanol, methylene chloride, 1,2-dichloroethane, DMSO, acetonitrile, and chloroform were among the solvents tested. Because it has a high relative permittivity, acetonitrile was determined to be the optimum solvent for both p-CA and TCNQ, ensuring the highest yield of p-CA and TCNQ species (fig. 5). In methanol or ethanol, the production of $p\text{-}CA^{-}$ and $TCNQ^{-}$ radicals was possible, although the colour intensity was lower than in acetonitrile. Quinz found that methanol had the best sensitivity, despite the fact that DMSO and acetonitrile had the highest dielectric constants. This is likely due to methanol's ability to form stable hydrogen bonds with the radical anion. Then, for additional testing, methanol was chosen.

Effect of the reagent's concentration

The results for varying reagent concentrations revealed that 2.0 and 1.5 ml of (1.0×10^{-3} mol/l) (Quinz or p-CA) and TCNQ, respectively, are the best volumes for producing maximal and repeatable colour intensity for MEM in acetonitrile (fig. 6). Higher reagent concentrations had no effect on the colour intensity.

Effect of time and temperature

At room temperature (25±2 °C), the optimum reaction time was established by monitoring the colour intensity. Quinz with MEM allowed for complete colour development in an instant. For the p-CA and TCNQ complexes, complete colour development took 50 and 90 min, respectively. The complete colour development was attained by raising the temperature to 60±5 °C for 10 min using p-CA or TCNQ with MEM (fig. 7). Using Quinz, p-CA, and TCNQ, the colour remained steady for 10, 6.0, and 4.0 h, respectively.

Stoichiometric ratio

The stoichiometric ratio of the reactants was determined by Job's method of continuous variation [38]. Job's continuous variation graph for the reaction between MEM and Quinz, p-CA or TCNQ reagents shows that the interaction occurs between an equimolar solution of MEM and the reagents. The result indicated that the charge transfer complex was formed in the ratio of (1:1) (MEM: reagent) (fig. 8). Based on the literature data and our experimental results, tentative reaction mechanisms for MEM-TCNQ complex is proposed and given in scheme 1, respectively.

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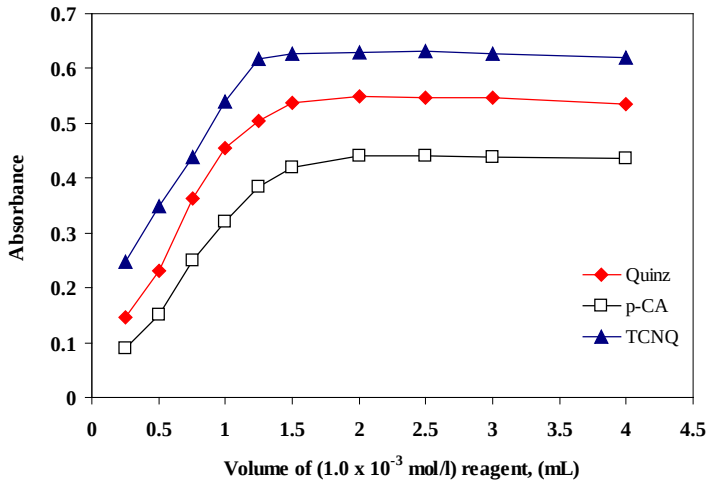


Fig. 6: Effect of reagent concentration on the absorbance of charge transfer complexes formed between MEM and acceptors (1.0×10^{-3} mol/l)

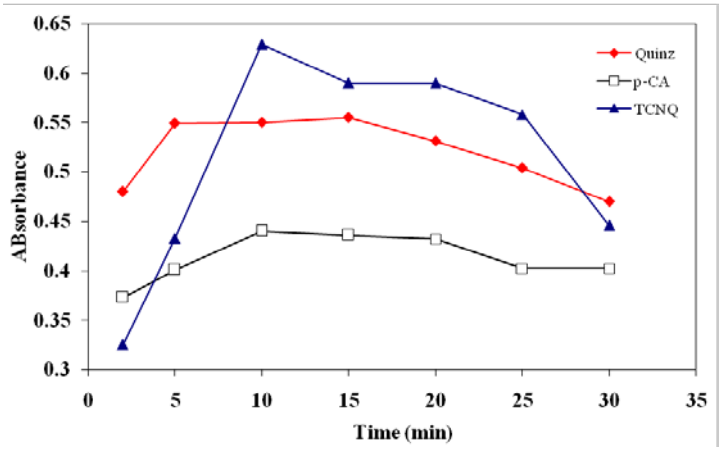


Fig. 7: Effect of time on the absorbance of charge transfer complexes formed between MEM and acceptors (1.0×10^{-3} mol/l)

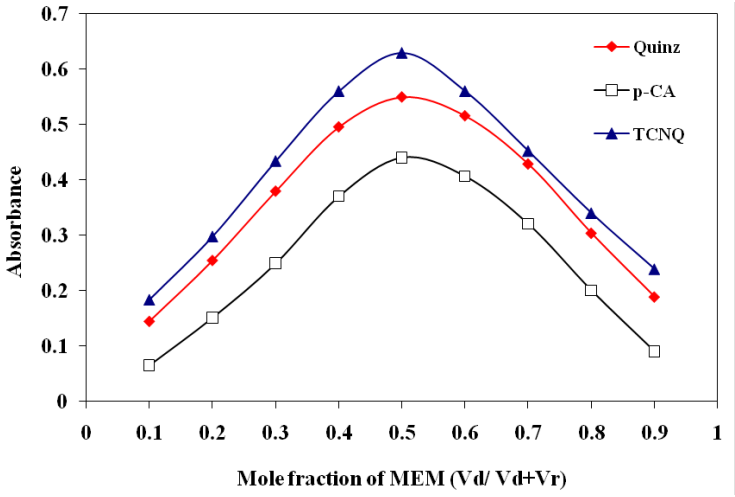
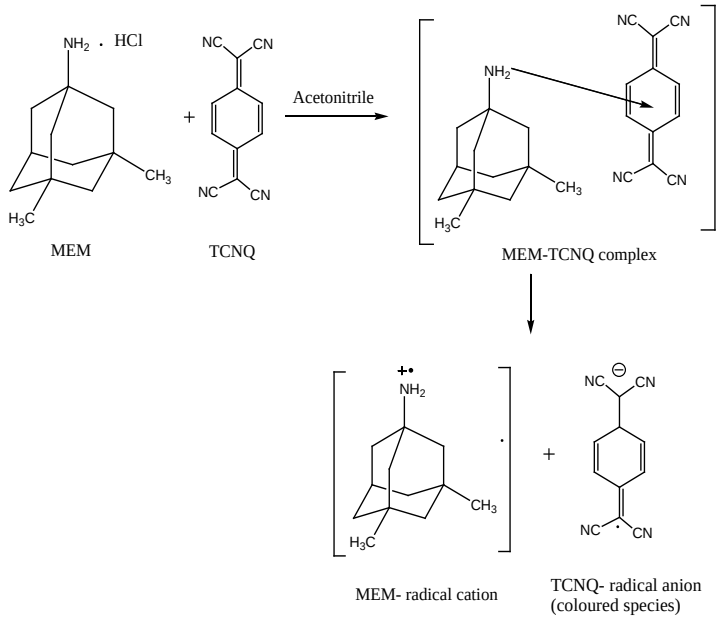


Fig. 8: Continuous variation plots for the reaction of MEM with Quinz, *p*-CA and TCNQ. λ= 558, 532 and 840 nm, respectively. Total molar concentration = 1.0 x 10^{-4} mol/l



Scheme 1: Proposed reaction pathway for the formation of charge transfer complex between MEM and TCNQ

Method of validation

The validity of the methods was tested regarding linearity, specificity, accuracy, repeatability and precision according to International Conference on Harmonization (ICH) guidelines [40].

Linearity, detection, and quantification limits

Using Quinz, p-CA, and TCNQ, the relationship between absorbance and concentration for MEM in the concentration ranges of 4.0–24, 10–160, and 5.0–50 µg/ml was relatively linear in the concentration ranges of 4.0–24, 10–160, and 5.0–50 µg/ml, respectively. The least-squares approach [41] was used to create the regression equations. The following equations resulted from a linear regression analysis of the data. A=-0.0084+0.0088C, r^2= 0.9996 for Quinz; A= 0.0029+0.0176C, r2= 0.9997 for p-CA; and A=-0.0065+0.0126C, r^2= 0.9995 for TCNQ, where A is the absorbance, C is the MEM concentration (µg/ml), and r^2 is the correlation coefficient. The minimum level at which the analyte can be reliably identified for MEM was used to calculate the limits of detection (LOD). The limit of quantification (LOQ) was determined by establishing the lowest concentration that can be measured with acceptable accuracy and precision [40, 42]. The results are shown in table 1. LOQ and LOD were calculated according to the following equations:

$$LOD = 3s/k$$

$$LOQ = 10\,s/k$$

Where *s* is the standard deviation of replicate determination values under the same conditions as for the sample analysis in the absence of the analyte and *k* is the sensitivity, namely the slope of the calibration graph. Using Quinz, p-CA, and TCNQ, the detection limits were found to be 1.20, 2.7, and 1.45 µg/ml, while the limit of quantization was determined to be 4.0, 9.0, and 4.83 µg/ml, respectively, according to the formula. Table 1 compares the percentage recoveries of pure MEM medication using the proposed procedures to those obtained using the published method [23]. Statistical analysis [42] was used to assess the validity of the proposed methods by comparing the findings obtained from the proposed methods to those obtained from the stated methods. There is no significant difference between the proposed and reported methods in terms of accuracy and precision when using the estimated Student's t-test and variance ratio F-test (table 1).

Table 1: Statistical analysis for determination of MEM using the proposed methods

Parameters	Quinz	*p*-CA	TCNQ
Wavelengths λ_{max} (nm)	558	532	840
Beer's law limits (µg/ml)	4.0-24	10-160	5.0-50
Ringbom optimum concentration range (µg/ml)	8.0-20	15-140	10-45
Molar absorptivity ε, (l/mol. cm) x 10^3	3.878	0.6809	2.599
Sandell·s sensitivity (ng/cm^2)	55.64	316.9	83.0
Regression equation [a]			
Slope (b)	0.0088	0.0176	0.0126
Intercept (a)	-0.0084	0.0029	-0.0065
Correlation coefficient (*r*)	0.9996	0.9997	0.9995
mean±SD[b]	99.70±0.60	99.20±0.90	99.30±1.10
Relative standard deviation, RSD%[b]	0.60	0.91	1.11
Relative error, RE%[b]	0.63	0.95	1.16
LOD (µg/ml)[c]	1.20	2.70	1.45
LOQ (µg/ml)[c]	4.0	9.0	4.83
Calculated *t*-value[d]	0.54	0.45	0.24
Calculated *F*-value [d]	2.01	1.12	1.67

[a]$A = a+b\,C$, where C is the concentration in µg/ml, A is the absorbance units, a is the intercept, b is the slope. [b]SD, standard deviation; RSD%, percentage relative standard deviation; RE%, percentage relative error. [c]LOD, limit of detection; LOQ, limit of quantification; ε, molar absorptivity. [d]The theoretical values of *t* and *F* at P= 0.05 are 2.571and 5.05, respectively, at confidence limit at 95% confidence level and five degrees of freedom (p= 0.05).

Accuracy and precision

Six repeat studies on pure drug solution at three distinct concentration levels were used to assess the methodologies' accuracy and precision (within the working range). The proposed spectrophotometric methods' precision and accuracy were calculated using percentage relative standard deviation (RSD%) and percentage relative error (RE%). In all situations, the relative standard deviation (RSD) was less than 2.0%, showing that the suggested approaches were repeatable. The proposed methodologies' level of precision was sufficient for MEM quality control analysis. The percentage relative error calculated using the following equation:

$$\%\ R.E. = \left[\frac{found - taken}{taken}\right] \times 100 \quad \text{..... Eqn. 3.}$$

The intra-day precision as percent relative error (RE%) and accuracy as percent relative error (RE%) results are found to be within-1.0-1.0% and 0.50–1.50%, respectively and the inter-day precision as percent relative error (RE%) and accuracy as percent relative error (RE%) results are found to be within-0.90-0.80% and 0.35-1.30%, respectively (table 2). The data proved good repeatability and reproducibility for the developed methods.

Ruggedness and robustness

Method ruggedness was expressed as the RSD and was also tested by applying the proposed methods to the assay of MEM using the same operational conditions but using three different instruments as well as three different anaysts. The inter-analysts RSD were in the range 0.50-2.60%, whereas the inter-instruments RSD ranged from 0.55-2.20% suggesting that the developed methods were rugged. The results are shown in table 3. This indicated the reliability of the proposed method during its routine application for the analysis of MEM. This demonstrated the proposed methods' reliability during normal application for MEM analysis, and hence the proposed spectrophotometric approaches are regarded robust. The proposed procedures were applied to the assay of MEM using the same operational settings but three separate instruments and three different anaysts, and their ruggedness was measured using the RSD. The RSD between analysts was 0.50-2.60%, while the RSD between instruments was 0.55-2.20%, indicating that the developed approaches were robust. Table 3 displays the results. This demonstrated the proposed method's dependability when used for MEM analysis on a regular basis.

Table 2: Evaluation of intra-day and inter-day precision and accuracy for MEM obtained by the proposed methods

Methods	Added (µg/ml)	Intra-day			
		Recovery %	Precision RSD %[a]	Accuracy RE %[a]	Confidence limit[b]
Quinz	5.0	99.20	0.65	-0.80	4.96±0.034
	10	99.50	0.90	-0.50	9.95±0.094
	15	100.50	1.50	0.50	15.08±0.24
p-CA	50	99.00	0.70	-1.0	49.50±0.36
	100	101.0	1.10	1.0	101.0±1.17
	150	99.10	1.30	-0.90	148.65±2.03
TCNQ	10	99.60	0.50	-0.40	9.96±0.052
	20	99.30	0.80	-0.70	19.86±0.167
	30	100.40	1.25	0.40	30.12±0.395
		Inter-day			
Quinz	5.0	99.40	0.40	-0.60	4.97±0.021
	10	100.80	0.70	0.80	10.80±0.074
	15	99.10	1.10	-0.90	14.87±0.172
p-CA	50	99.20	0.50	-0.80	49.60±0.26
	100	99.50	0.90	0.50	99.50±0.94
	150	100.70	1.20	0.70	151.05±1.90
TCNQ	10	99.30	0.35	-0.70	9.93±0.036
	20	100.60	0.65	0.60	20.12±0.137
	30	99.20	1.30	-0.80	29.76±0.41

[a]Mean of six determination, RSD%, percentage relative standard deviation; RE%, percentage relative error. [b]mean±standard error, Confidence limit at 95% confidence level and five degrees of freedom (t = 2.571).

Table 3: Results of method robustness and ruggedness (all values in RSD%) studies

Methods	Nominal amount concentration (µg/ml)	RSD%			
		Robustness		Ruggedness	
		Variable alerted [a]			
		Reagent volume (n=3)	Reaction time (n=3)	Different analysts (n=3)	Different instruments (n=3)
Quinz	5.0	0.80	0.70	0.50	0.75
	10	1.70	1.10	1.30	1.40
	15	2.10	1.90	1.80	2.0
p-CA	50	1.0	1.20	0.85	0.55
	100	1.20	1.60	1.50	1.60
	150	2.30	2.60	2.30	1.90
TCNQ	10	0.70	0.70	1.20	0.70
	20	1.40	1.30	1.70	1.20
	30	2.50	2.50	2.60	2.20

[a]Volume of reagent (1.0 x 10^{-3} mol/l) is (2.0±0.2 ml) for Quinz or p-CA and (1.5±0.1 ml) for TCNQ and reaction time is (10±2.0 min) (after adding reagent) were used.

Specificity and effect of excipients

By observing any interference from the common tablet's excipients, the specificity of the suggested technique was examined. By adding known amounts of pure MEM to a previously assessed tablet solution, the conventional addition procedure was used. By comparing the concentration of the spiking mixtures with the previously determined value, the recovery of the added MEM was computed. Table 4 shows that satisfactory findings were obtained, which were better than the published spectrophotometric methods. The high recovery values of the proposed methods revealed that the excipients did not interfere with the proposed methods, implying that the offered methods have a high selectivity.

Application of the proposed methods to pharmaceutical formulations

The presented methods were used to fig. out how much MEM is in medicinal formulations (Dementexa tablets, and Revmantine tablets, 10 mg MEM per tablet). According to ICH requirements [40], the method was assessed for linearity, specificity, accuracy, repeatability, and precision. The proposed methods' results were compared statistically to those obtained using the reference approach [23]. SD values for recovery were obtained. Statistical analysis of the results using the Student's t-test and the variance ratio F-test at a 95% confidence level revealed no significant differences in the accuracy and precision of the suggested and reference methods, respectively (table 5) [42]. This suggested that the examination of MEM in its formulations was done with similar precision and accuracy. These findings show that the proposed methods can be used to analyse MEM in various dosage forms with equivalent analytical performance.

Comparison between the proposed methods and some referenced methods

Table 6 shows comparison between the proposed spectrophotometric methods and other reported methods in the literature for the quantification of MEM in pharmaceutical formulations [18-29]. The proposed methods are new, simple, cost effective and selective spectrophotometric methods for the determination of MEM in pharmaceutical dosage forms. The reported methods are less selective, poor sensitivity, depending on critical experimental variables, few methods require a rigid pH control and tedious and time-consuming liquid–liquid extraction step; some other methods have a relatively narrow dynamic linear range, and/or use of expensive reagent or large amounts of organic solvents.

Table 4: Results of recovery experiments by standard addition method for the determination of MEM in tablets using the proposed methods

Method	Taken drug (µg/ml)	Pure drug added (µg/ml)	Dementexa tablets		Revmantine tablets	
			Total found (µg/ml)	Recovery[a] (%)±SD	Total found (µg/ml)	Recovery[a] (%)±SD
Quinz	8.0	4.0	11.88	99.00±0.57	11.84	98.70±0.50
		8.0	15.76	98.50±0.76	15.89	99.30±0.88
		12	19.84	99.20±0.80	20.14	100.70±1.50
p-CA	60	30	89.30	99.20±0.60	90.45	100.50±0.55
		60	121.0	100.80±0.90	119.30	99.40±0.80
		90	149.25	99.50±1.40	148.65	99.10±1.10
TCNQ	20	10	30.36	101.20±0.60	29.76	99.20±0.65
		20	39.64	99.10±0.70	40.36	100.90±0.90
		30	50.25	100.50±1.20	49.50	99.00±0.95

[a]Average of six determinations. SD; standard deviation.

Table 5: Results of analysis of tablets by the proposed methods for the determination of MEM and statistical comparison with the reported method [23]

Samples	Recovery (%)±SD[a]			
	Proposed methods			Reported method
	Quinz	*p*-CA	TCNQ	
Dementexa tablets	99.70±0.90	99.60±0.40	99.25±0.70	99.52±0.60
t-value[b]	0.37	0.25	0.65	
F-value[b]	2.50	2.25	1.36	
Revmantine tablets	99.70±0.85	99.10±0.54	99.50±0.83	99.30±0.74
t-value[b]	0.95	0.49	0.40	
F-value[b]	1.32	1.88	1.26	

[a]Average of six determinations±standard deviation. [b]The theoretical values of t and F are 2.571 and 5.05, respectively at confidence limit at 95% confidence level and five degrees of freedom (p = 0.05).

Table 6: Comparison between the proposed and report spectrophotometric methods for determination of MEM

Reagent	Wavelength (nm)	Beer's law (µg/ml)	Detection limits (µg/ml)	Molar absorpitivity (l/mol. cm)	References
4-chloro-7-nitro-2,1,3-benzoxadiazole (NBD-Cl)	476	5.0-70	1.101	ND	[18]
o-phthalaldehyde/N-acetyl-L-cysteine	340	5.050	0.858	ND	
Eosin	546	1.0-10	0.33	19249×10^4	[19]
2,4-Dinitrofluorobenzene	360	5.0-30	1.27	6301×10^4	
Bromothymol blue (BTB)	415	2.0-20	0.011	1.349×10^5	[20]
Solochrom black T (SBT)	510	5.0-25	0.022	1.299×10^5	
UV	291	10-30	2.516	ND	[21]
Bromocresol green (BCG)	420	3.0-18	1.03	ND	[22]
Picric acid	430	5.0-30	0.252	ND	
Bromophenol blue (BPB)	415	1.1-12.5	0.097	1.93×10^4	[23]
Bromocresol purple (BCP)	412	0.9-13.1	0.073	2.13×10^4	
Methyl orange (MO)	414	1.2-14	0.084	1.9×10^4	
1-Napthol	292	1.0-10	ND	ND	[24]
Bromocresol green (BCG)	415	4.0-12	ND	1.29×10^4	[25]
Bromothymol blue (BTB)	420	2.0-6.0	ND	1.988×10^4	
4-chloro-7-nitro-2,1,3-benzoxadiazole (NBD-Cl)	476	5.0-70	1.101	ND	[18]
o-phthalaldehyde/N-acetyl-L-cysteine	340	5.050	0.858	ND	
Folin-ciocalteau	760	4.0-12	ND	0.778×10^4	[26]
1,2-Napthaquinone-4-sulphonate (NQS)	460	7.5-17.5	ND	0.607×10^4	
Ninhydrin	595	0.4-19.3	0.011	1.12×10^4	[27]
$FeCl_3$	375	0.3-9.7	0.014	1.73×10^4	
Cerium (IV) sulphate/ Fe^{2+}	480	0.4-16.2	0.112	1.75×10^4	[28]
Chromotrope 2R (C2R)	528	0.1-8.3	0.056	2.1×10^4	
Rhodamine 6G (Rh6G)	525	0.2-11.4	0.098	1.89×10^4	
Rose bengal	576	2-20	0.476	ND	[29]
Quinz	558	4.0-24	1.20	3.878×10^3	The
P-CA	532	10-160	9.0	0.6809×10^3	proposed
TCNQ	840	5.0-50	11.45	2.599×10^3	work

ND: Not detected

CONCLUSION

MEM as an electron donor and several electron acceptors were studied in a charge-transfer complexation reaction. The coloured complexes were used to construct three spectrophotometric techniques for analysing MEM in pure form and dose forms that were easy, accurate, robust, economical, and sensitive with good precision and accuracy. The proposed approaches can be utilised as an alternative to the stated methods for determining tablets on a regular basis. This stimulates their usage in routine MEM analysis in quality control laboratories, and the processes are quite easy.

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AUTHORS CONTRIBUTIONS

Prof. Dr. Ragaa El Sheikh and Prof. Ayman A. Gouda has generated the research idea, interpreted the data and helped to draft the manuscript, helped in check spelling, reducing the plagiarism, interpreting the data, reviewed the manuscript and submit the manuscript for publication. Prof. Dr. Ali H. Amin has suggested the research idea and participated in the design of the study. Mr. Mohamed Ali, Ms. Basma M. Abdelnaby and Ms. Ghada M. Abdel Fattah were prepared the solutions, carried out the experiments, interpreted the data and helped to draft the manuscript.

CONFLICTS OF INTERESTS

The authors confirm that this article content has no conflict of interest.

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