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Spectrophotometric Determination of Paracetamol Drug via Charge-Transfer Complex Formation

Hadeel M. Dawood[1], Hassan T. Abdulsahib [1], Atared F. Hassan[1]
[1]Department of Chemistry, College of Science, University of Basrah, Basrah, Iraq
Email: hassan.abdulsahib@uobasrah.edu.iq

ABSTRACT
An Accurate, simple, rapid, inexpensive and sensitive method has been applied for the spectrophotometric determination of paracetamol, in bulk sample and dosage form, depending on the formed charge- transfer complex between cited drug and, Tetracyanoethylene (TCNE) as a chromogenic reagent. The formed complex shows absorbance maxima at 410 nm against reagent blank. The calibration graph is linear in the ranges of (1.0 - 22.0) $\mu g.mL^{-1}$ with detection limit of 0.195 $\mu g.mL^{-1}$. The results show the absence of interferences from the excipients on the determination of the drug. Therefore, the proposed method has been successfully applied for the determination of paracetamol in pharmaceutical preparations.

Keywords: Pharmaceutical, Spectrophotometric, paracetamol, Charge- transfer.
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1. Introduction

The molecule N-acetyl-p-aminophenol has the formula $C_8H_9NO_2$, and is known as paracetamol (acetaminophen). The figure 1 shows its chemical structure. [1] It melts at 168–172 degrees Celsius and has a molecular weight of 151.17 g mol-1. It is a white powder with fine crystals that dissolves somewhat in ether, ethylene chloride, and water. It dissolves better in alcohol. [2] Phenacetin is the source of the analgesic and antipyretic drug paracetamol. Because it doesn't cause the stomach disturbances that other analgesics like acetyl salicylic acid do, it is frequently utilized (alone or in combination with other active ingredients like caffeine) [3]. In addition, headache, muscle soreness, arthritis, backache, toothache, cold, and fever can all be treated with paracetamol.[4-6] Overdosing on paracetamol can have harmful consequences such fulminating hepatic necrosis, which results in roughly 450 fatalities annually in the United States.[7] Numerous techniques, such as HPLC [8], electrochemical approaches [9], chemiluminescence [10], spectrofluorimetric [11], flow injection [12], spectrophotometry [13], and many more, have been reported for the measurement of paracetamol in pharmaceutical formulations. Thus, it is evident that the development of straightforward techniques for the measurement of paracetamol is important for the pharmaceutical industry. Because of its simplicity, sensitivity, and range of applications, oxidative coupling organic reactions are now a well-established technique that, when employed to analyze pharmaceutical preparations (14), can be thought of as a favorable substitute for other commonly used techniques.

In contrast, visible spectrophotometry is considered as the most convenient analytical technique in most quality control and clinical laboratories, for the assay of different classes of drugs and metals in biological [14] and environmental samples [15] due to its simplicity, reproducibility, speed, less analysis time and reasonable sensitivity with significant economic advantages.

In the present work, we developed simple, sensitive, rapid, accurate and validated spectrophotometric method for the determination of paracetamol in pure form and pharmaceutical formulations.

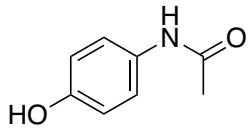

Figure 1: Structure of paracetamol

2. Experimental

UV visible Spectrophotometer (Biotech UV 9200,UK) was used with 1cm quartz cuvettes to record the UV spectra of paracetamol . A digital weighing balance (BL2105 Sartorius-Romania) was used for all preparations. pH meter (AD-1030 Adwa-Romania) was also used. All chemicals, solvents and reagents used in this work were of analytical reagent or pharmaceutical grade and all solutions were prepared fresh daily. Double distilled water was used throughout the investigation. The reference samples of paracetamol were obtained from

Al-Fayhaa, Iraq. Sodium Hydroxide pellets extra pure AR and HCL was purchased from BDH company. Paracetamol (500mg & 1000 mg) was purchased from local market. A 0.0755 gm of paracetamol was accurately weighed and dissolved in warm distilled water, which was then diluted to the mark with distilled water in a 50 ml volumetric flask to get 10-2 M . That solution was used as a stock solution. A 10-2 M TCNE solution, was prepared by dissolving 0.064 g of the TCNE in acetonitrile and then the solution was diluted to a final volume 50 mL with acetonitrile. Working solutions were freshly prepared by subsequent dilutions. This solution is prepared daily using red- glass volumetric flask because it is a light sensitive reagent.

2.1 General Recommended Procedure

Measured volumes of the standard stock solution of the drug containing appropriate amount of paracetamol were transferred into 10 mL calibrated flasks, 1 ml of 10-2 M TCNE solution was added to each, and then diluted to volume with acetonitrile. Absorbance measurements of resulting solutions were done at the wavelength of maximum absorption (410 nm) against reagent blank which prepared by the same manner, but without addition of paracetamol.

Analysis of paracetamol in Pharmaceutical Preparations

The content of 5 tablets were mixed well and a certain amount of fine powder was accurately weighted to give an equivalent to 200 mg for tablets and dissolve in 2 ml of 1 M NaOH and 150 mL of deionized water, swirled, left to stand for 90 mints and diluted to 200mL in a volumetric flask with acetonitrile. Working solutions were freshly prepared by subsequent dilutions with acetonitrile and analyzed by the recommended procedure.

3. Results and discussion

Spectrophotometric procedures are popular for their sensitivity in the assay of drugs and hence, charge-transfer complex formation has received considerable attention for the quantitative determination of many pharmaceutical compounds [16]. Paracetamol react with TCNE to give red color charge-transfer complex, which exhibits absorption maxima at 410 nm against its reagent blank, Figure2. The same bands may be attributed to the formation of TCNE radical anion, which probably resulted from the dissociation of the donor-acceptor complex in relatively high polar solvents like acetonitrile [17]. Therefore, in order to avoid the maximum interference from the reagent blank, the absorbance measurements were carried out at 420 nm in the subsequent work.

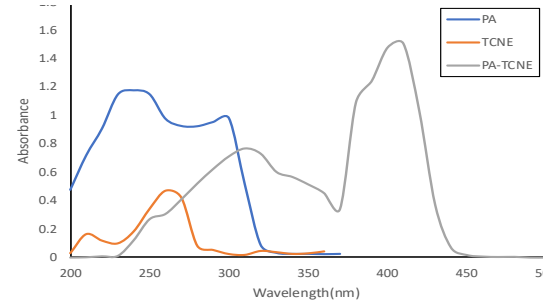

Figure 2: Absorption spectra for the reaction product of (10-3M) paracetamol against (10-3M) TCNE reagent blank solution.

3.1 Optimization of experimental variables

The experimental variables affecting the development and stabilities of charge-transfer complex formation were achieved through a number of preliminary experiments. Such factors include reagent volume, reaction time, pH and temperature. For this reason, a variable was modified while maintaining the other variables at their constant values, then by maintaining that variable at its optimized value, another was modified; all variables were optimized via this method.

3.2 Effect of Reagent Volume:

The influence of amount of the used reagent on the absorbance of paracetamol - TCNE complex is illustrated in, Figure 3. A 2mL of 10-2 M solution of TCNE was found to be optimum to develop the maximum color intensity for formed charge-transfer complex, after which no more increase in absorbance values was obtained; therefore, the cited amount of TCNE solution was used.

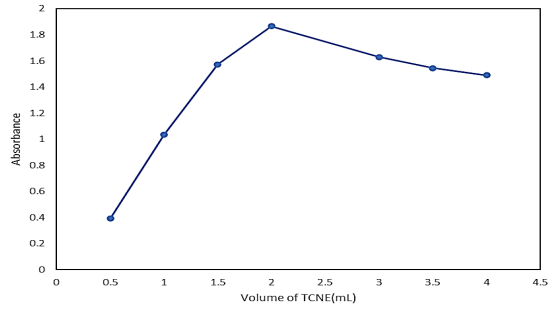

Figure 3: Effect of reagent volume on the absorbance of 10-3M paracetamol; 10-3M TCNE

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3.3 Effect of reaction time:

The optimum reaction time is determined by following the color development at ambient temperature (25 ± 2 °C). It was found that the reaction of paracetamol with TCNE, under the conditions of the study, is instantaneous, and the formed complex attained maximum absorbance immediately after mixing. The developed color remained strictly unaltered for at least 10 min. in dark place, Figure 4.

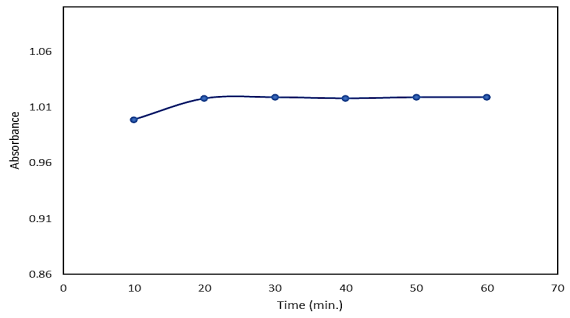


Figure 4: Effect of reaction time on the absorbance of 10-3M paracetamol; 10-3M TCNE.

is independent on the temperature of the medium up to 40 °C; hence the absorbance of the complex remains, approximately, constant. The value of the absorbance starts to decrease considerably when reaction temperature raised above 40 °C, this may be due to decomposition of the formed charge transfer complex. 25°C was chosen to be optimum, because the product attained maximum and constant absorbance, Figure 6.

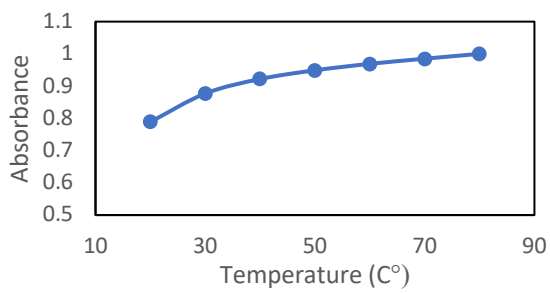


Figure 6: Effect of temperature on the absorbance of 10-3M paracetamol; 10-3M TCNE.

3.4 Effect of pH:

A preliminary study was conducted to demonstrate the effect of pH by monitoring the absorption of the colored product. It was found that adding of HCl or NaOH led to a decrease in absorption, so it was excluded in subsequent experiments, and all absorbance measurements were made at pH 7 as shown in Figure.5.

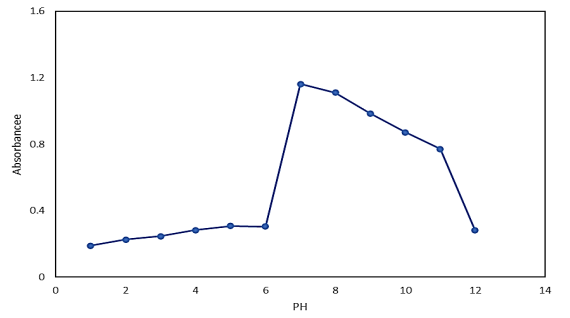


Figure 5: Effect of pH on the absorbance of 10-3M paracetamol; 10-3M TCNE.

3.6 Calibration Graph:

Employing the optimum experimental conditions, a linear calibration graph for the determination of paracetamol, by charge-transfer complex formation with TCNE, was obtained, Figure 7, which shows that Beer's law was obey in the concentration range of (1.0-22.0) µg. mL^{-1}, with a correlation coefficient (R2= 0.9986) and detection limit of 0.195 µg.mL-1.

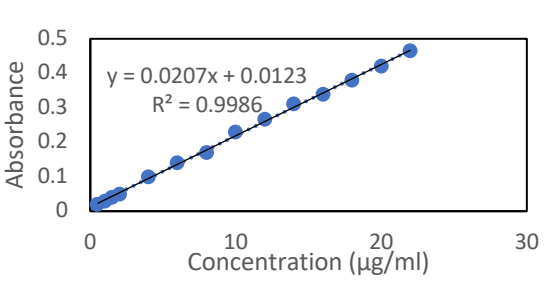


Figure 7: Calibration graph of paracetamol under optimum experimental conditions.

3.5 Effect of Temperature:

The optimum reaction temperature was determined by following the color development at ambient temperature in the range from (20 - 60 ± 2°C). It was found that the reaction between paracetamol and TCNE

3.7 Spectral Characteristics of the Proposed Method:

Under optimum experimental conditions of the proposed method, the regression plot showed linear dependence of absorbance signals on the concentrations of the studied drug in the range given. The regression

equations, correlation coefficients, molar absorptivity's, detection limits and sandell sensitivity in addition to other parameters are given in Table 1.

Table (1): Spectral characteristics and statistical data of the regression equation for determination of paracetamol via charge transfer formation.

Parameters	Value
Color	Yellow
Medium	pH 7
λ_{max}, nm	410
Beers law range (µg/ml)	1.0-22.0
LOD (µg/ml)	0.195
LOQ (µg/ml)	0.65
Ɛ (l . mole^{-1}. cm^{-1})	3129.074
Sandells sensitivity (µg/cm^2)	0.048
Intercept (a)	0.0123
Slope (b)	0.0207
Determination coefficient (R^2)	0.9986
RSD%	0.70

3.8 Stoichiometry of the Complex:

To propose a structure for the formed charge transfer complex between paracetamol and TCNE, two analytical procedures (Mole ratio and Job's of continuous variation method) were followed, Figures 8 and 9 respectively. The results, in both studies, showed that the complex is composed from TCNE and paracetamol with a ratio of 1:1 (TCNE: paracetamol).

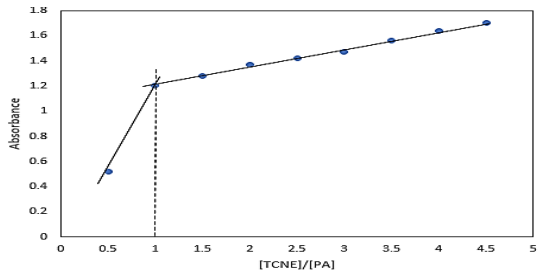


Fig. (8): Mole ratio of 10-3M paracetamol, 10-3M TCNE.

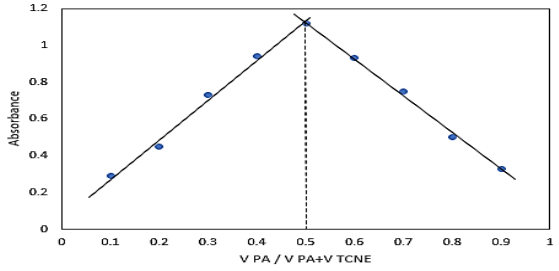
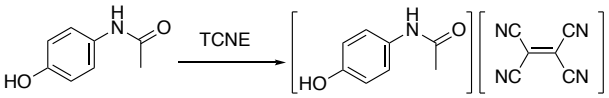


Fig. (9): Continuous variation of 10-3M paracetamol 10-3M TCNE.

The structure of the formed charge transfer complex can be represented as in Scheme 1. The mechanism of the reaction depends on the formation of an original donor-acceptor (DA) complex through the interaction between one of the nitrogen atoms of amine moieties in the acyclovir (as n-electron donor) and TCNE (as π-acceptor). Then, the dissociation of DA-complex may be promoted by the solvent, especially that with high ionizing power such as acetonitrile, where complete electron transfer from the donor to the acceptor moiety takes place. This is followed by formation of the TCNE radical anions as a predominant chromogen [18].



PA.TCNE

Scheme (1): Structure of the formed charge transfer complex

3.9 Accuracy and Precision:

The accuracy and precision of the proposed method was checked by analyzing three replicates of three different concentration levels of the drug (within Beer's law range). The accuracy was determined by calculating the recovery percentage (RE%), while the precision was tested by calculating the percentage relative standard deviation (%RSD). The results indicated good accuracy with reasonable precision of the proposed method, Table 2.

The proposed method was advantageous when compared statistically with other methods found in the literature in having good sensitivity and the results are shown in Table 3.

3.10 Interferences Study:

The results showed that no interferences were found in the presence of up to 100 , 500, 1000 µg of the studied excipients (Cellulose ,Microcrystalline , Sodium benzoate , Starch) in the determination of paracetamol.

3.11 Analysis of Dosage Forms:

The applicability of the proposed method for the determination of paracetamol in commercial dosage form (Tablets; PA-500 mg and PA-1000 mg) was examined by analyzing of their content of the active ingredient by the proposed method (charge-transfer complex formation). The results given in Table 4, reveal that the recoveries were in the range of, reflecting high

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Table (2): Evaluation of accuracy and precision for the determination of paracetamol by proposed procedure.

Conc. Of PA (taken) µg/ml	Conc. Of PA (added) µg/ml	Conc. Of PA (found) µg/ml	Recovery %	Range of recovery %	RSD %
	5	9.97	99.7		0.98
5	10	14.52	96.8	98.0	1.03
	15	19.50	97.5		1.07
	5	15.195	101.3		0.94
10	10	19.78	98.9	99.99	0.90
	15	24.94	99.77		0.88
	5	19.29	96.45		0.79
15	10	24.67	98.68	98.35	0.91
	15	29.98	99.93		0.75

Table (3): Analytical parameters for the analysis of paracetamol by the proposed and others methods.

Reagent used	λmax (nm)	$\varepsilon x10^4$/ $Lmol^{-1}cm^{-1}$	Beers law limits/µg ml^{-1}	Sandells sensitivity/µg cm^{-2}	Remarks	Ref.
8- hydroxyquinoline or 2-naphthol	470 or 490	1.9 or 2.46	2-10	7.9×10^{-3} Or 5.9×10^{-3}	------	16
1-napthol Or Resorcinol	505 or 485	1.68 or 2.86	0-10	9.0ng $ml^{-1}cm^{-2}$ Or 5.3ng $ml^{-1}cm^{-2}$	Color stability is <than 1 hour	17
Sodium bismuthate	550 or 560	77.27 Or 100.0	100-300 in HCl or 300-800 in CH3COOH	-------	Lack of Sandells sensitivity	18
2,4-dichloroaniline	490	3219.69	4-350	-------	Lack of application	19
Different solvents	243	------	1-30 mg L^{-1}	------	Less sensitive	20
Histidine	430	1.118	10-500 µg mL^{-1}	0.0135	Less selective	21
2,7-dihydroxy naphthalene	481	1.058	1-14	0.0142	-------	22
Proposed method 1,3-dinitrobenzene Or 2,4-dinitrophenyl hydrazine	429 or 430	1.965 Or 2.777	0.8-20.5 or 0.5-18.4	7.692×10^{-3} Or 5.698×10^{-3}	-------	
TCNE	410	3129.074	1.0-22.0	0.048	-------	This work

Table (4): Spectrophotometric determination of paracetamol in pharmaceutical preparations via charge-transfer complex formation with TCNE.

Pharmaceutical preparation	Amount taken (µg/ml)	PA content found (µg/ml) Direct method	Recovery (%)	RSD%	St.add. method	Recovery (%)	RSD%
PA-PA 500 mg	5.0	5.31	106.2	2.52	5.25	105.0	1.50
PA-DOLOVAS-1000mg	5.0	4.77	95.4	1.88	4.81	96.2	1.26

accuracy and precision of the proposed method as indicated by low percentage relative standard deviation value. The recommended method was compared with standard additions methods.

The standard addition method was applied to demonstrate the efficiency and success of the proposed spectrophotometric method for the determination of paracetamol in in the pharmaceutical preparations (Tablets; PA-500 mg and PA-1000 mg) , and its free from interferences, A comparison and evaluation between the proposed spectrophotometric method and the standard addition method were conducted to assess the accuracy and suitability of the analytical application, as illustrated in Figure 10 and 11, it is observed that the standard addition curve for paracetamol is parallel to the direct method curve, indicating the absence of interferences. Table 5 show the agreement of the standard addition method with the proposed method and which did not exceed the permissible values in terms of the analytical variables for both recovery % .This alignment between the standard addition method and the proposed method suggests satisfactory selectivity, indicating that the method is satisfactorily selective.

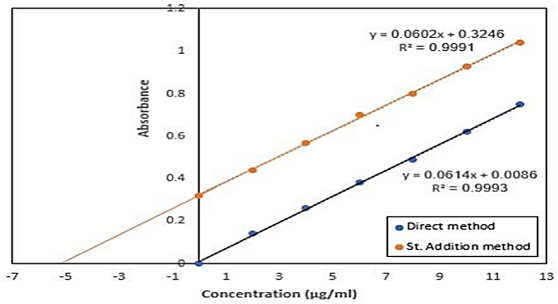

Figure 10: Paracetamol determination by proposed method and standard addition method PA-500 mg tablet solution.

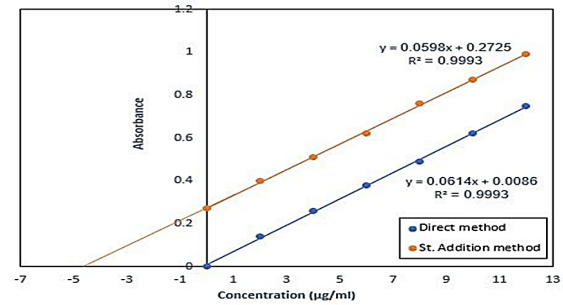

Figure 11: Paracetamol determination by proposed method and standard addition method PA-1000 mg tablet solution.

4. Conclusions

The utility of TCNE reagent for the spectrophotometric determination of paracetamol was established. The methodbased charge-transfer complex formation between the cited drug and TCNE as a chromogenic reagent. The proposed method was found to be accurate, simple and sensitive. It was satisfactorily applied to the determination of paracetamol in pharmaceutical product samples.

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6. Conflict of interest

Authors declare no conflict of interest

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