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Determination of Paracetamol and Tramadol Hydrochloride in Pharmaceutical Preparations Using Green UV Method

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ABSTRACT

A simple, precise, and friendly environmental method for the determination of paracetamol and tramadol hydrochloride in pharmaceutical preparations has been worked out. The method is based on the determination of paracetamol at 242 nm and replaces its concentration in a multicomponent system equation for determination of both paracetamol and tramadol at 227 nm. Beer's law for paracetamol was obeyed over the concentration range 8-25 ppm at 242 nm and 4-16 ppm at 227 nm ,for tramadol it is obeyed over the range 2-14 ppm at 227 nm, water is used as a solvent for dissolution. The method is applicable to the determination of paracetamol and tramadol in their pharmaceutical preparations without prior separation steps from excipients as well as for determination of paracetamol in the presence of tramadol. The average recoveries for determination of mentioned drugs were 94.20-100.14%, and the average relative standard deviation of the method was better than ± 0.646%.

Keywords: Paracetamol - Tramadol combination, Green UV, Multicomponent system.

تقدير الباراسيتامول وهيدروكلوريد الترامادول في مستحضراتهما الصيدلانية بطريقة خضراء طيفية

الملخص

تم تقدير الباراسيتامول وهيدروكلوريد الترامادول في مستحضراتهما الصيدلانية بطريقة طيفية باستخدام طريقة مأمونة وسهلة وذات مضبوطية عالية. تعتمد الطريقة على إذابة المستحضر في الماء وتقدير الباراسيتامول عند طـول مـوجي 242 نانوميتر ثم ايجاد تركيز الترامادول عند طول موجي 227 نانوميتر باستخدام معادلة الامتصاص لنموذج متعدد المكونات. اظهر الباراسيتامول خضوعا لقانون بيير لمدى من التراكيز 8-25 جزء/ مليون عنـد الطـول المـوجي 242 نـانوميتر ولمـدى 4 -16جزء / مليون عند الطول الموجي 227 نانوميتر في حين اظهر الترامادول خضوعاً لقانون بيير لمدى مـن التراكيـز 2-14 جزء / مليون عند الطول الموجي 227 نانوميتر. اظهرت الطريقة قابلية تطبيق للادوية المذكورة فـي مستحـضراتهما الصيدلانيـة وكذلك تقديـر الباراسـيتامول بوجود الترامادول. كان معدل نـسبة الاسـترجاع لتقـدير الأدويـة المـذكورة 94.20- 100.14% وكان معدل الانحراف القياسي النسبي للطريقة أفضل من0.646 ± %.

INTRODUCTION

Paracetamol is N-acetyl-p-aminophenol (Sweetman, 2009), it is one of the most popular drugs over the counter analgesics and antipyretics (Moffat *et al*., 2005). It has low toxicity and high therapeutic index (Shah, 2010).

Tramadol is a synthetic codein analogue used as a non-steroidal anti-inflammatory drug with a good analgesic effect (Lipman *et al*., 2004), it is used in chronic and acute pain syndromes caused

by cancer itself or cancer treatment (Desai and Grossberg, 2010). Taking doses simultaneously or larger than therapeutic can lead to addiction (Naga *et al*., 2010).

An orally administration of combined tablet of paracetamol and tramadol provides effective analgesia in patients with moderate to severe acute pain and those chronic painful conditions (Clellan and Scott, 2003). A combination tablet of paracetamol and tramadol hydrochloride contains 37.5 mg of tramadol plus paracetamol 325 mg (Moffat *et al.*, 2005).

Many colorimetric methods for determination of paracetamol are reported (Filik, *et al*., 2005 ; Al-Ghabsha *et al*., 2005 ; Yanyan *et al*., 2011). All these methods are based on using organic, oxidizing, and or complexing reagents wheras methods for determination of tramadol based on chromatographic procedures involve different toxic solvents as a mobile phase (Kmetec and Roskar, 2006 ; Kartinasari *et al*., 2012 ; Zaheer *et al*., 2011; Belal *et al*., 2008).

A simultaneous determination of tramadol hydrochloride and paracetamol in bulk and marketed product has been developed. The method is based on the determination of tramadol hydrochloride at 270.5 nm and paracetamol at 243.5 nm in methanol. Tramadol and paracetamol obey linearity within the concentration range of 2.5-15 μg/ml and 3-15μg/ml. The % RSD is less than 2%. The percentage recoveries values of drug were between 99-103% (Shukla *et al*., 2011).

Another simultaneous estimation of tramadol hydrochloride and paracetamol in two component tablet dosage form has been developed utilizing the concept of internal standard addition. The method is based on determination of tramadol hydrochloride at 270.5 nm and paracetamol at 243.5 nm in distilled water. Tramadol hydrochloride and paracetamol at their respective λ_{max} 270.5 nm and 243.5 nm show linearity in the concentration range of 20-100 μg/ml and 3-15 μg/ml, respectively (Charg and Dhabale, 2010).

The primary goal of green chemistry and technology is to reduce the environmental impact of chemical processes and chemical manufacturing while simultaneously enhancing the overall process performance (Anish *et al*., 2012). In the side of technique, UV is the least environment harmful technique (Ulrich, 2009), while in the side of chemicals, water, without doubt, is the most acceptable in terms of cost and environmental impact and of course, running the reaction without any organic reagent is of the same importance (Paul and Mary, 2002). Nowadays, it is well understood that we must make every possible effort to protect the environment (Giusy, 2012).

This article suggests a simple UV spectrophotometric method for the simultaneous determination of paracetamol and tramadol using water as a solvent and eliminates the role of organic reagent.

EXPERIMENTAL

Materials

Paracetamol powder was provided from the State Company for Drug Industries and Medical Appliances (NDI), Nineveh–Iraq and used without further purification.

Tramadol ampoule (50 mg/ml) from Merckle GmbH, Blaueren, (Mepha), Germany.

A stock solution containing 100 ppm of pure drugs was prepared by dissolving accurately weighed (0.0100 g) of drug in about 30 ml of distilled water and diluted up to 100 ml with distilled water .

Apparatus

A shimadzu UV-1650 pc double beam spectrophotometer with 1-cm quartz cells have been used for scanning spectra.

UV Cecil single beam spectrophotometer (model CE1021, 10 000 series, Cambridge, England) with 1- cm quartz cells have been used for spectrophotometric measurements

Selection of analytical wavelength

Stock solutions of drugs were prepared in water separately. UV spectrum of 25 μg ml^{-1} of each individual drug was taken, and Fig. (1) shows that the maximum absorption of tramadol is at 227, and 272 nm; paracetamol has absorbance in these wavelengths also, but paracetamol exhibits a maximum absorbance at 242 nm, tramadol exhibits no absorbance at this wavelength.

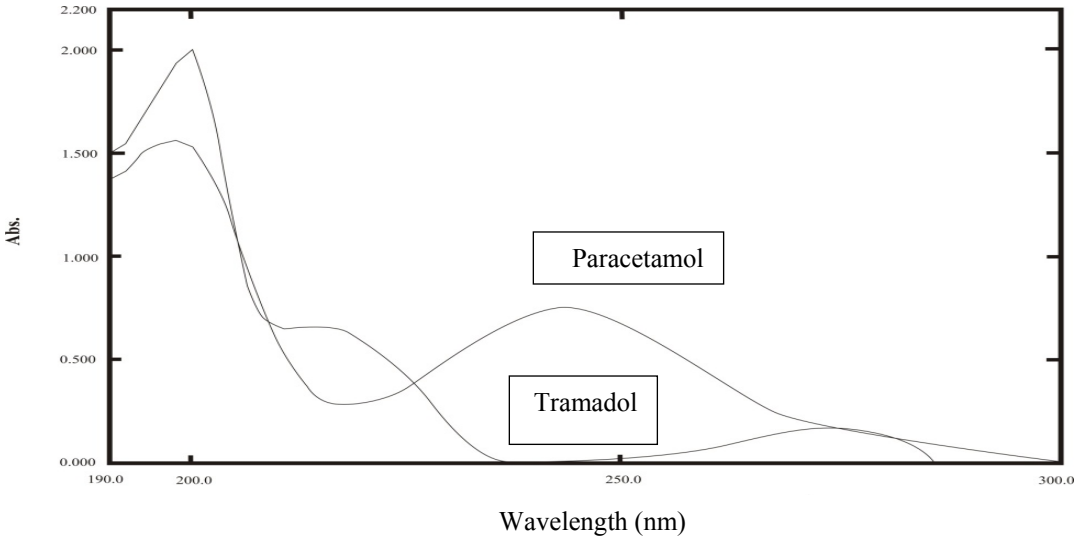

Fig. 1: Absorption spectra of 25 µg/ml of each of tramadol hydrochloride and paracetamol

Recommended procedure and calibration curves

Volumes between (0.2-1.8) ml of stock solutions of the two drugs were transferred to volumetric flasks and diluted to10 ml with distilled water, and between (0.2-2.5) ml of stock solutions of paracetamol were transferred to volumetric flasks and diluted to10 ml with distilled water. The absorbances of paracetamol were measured at the two wavelengths 242 nm and 227 nm, tramadol absorbances were measured at 227 nm. Fig. (2) shows the calibration graphs of paracetamol at 242 nm (A), paracetamol at 227 nm (B left) and tramadol at 227 nm (B right).

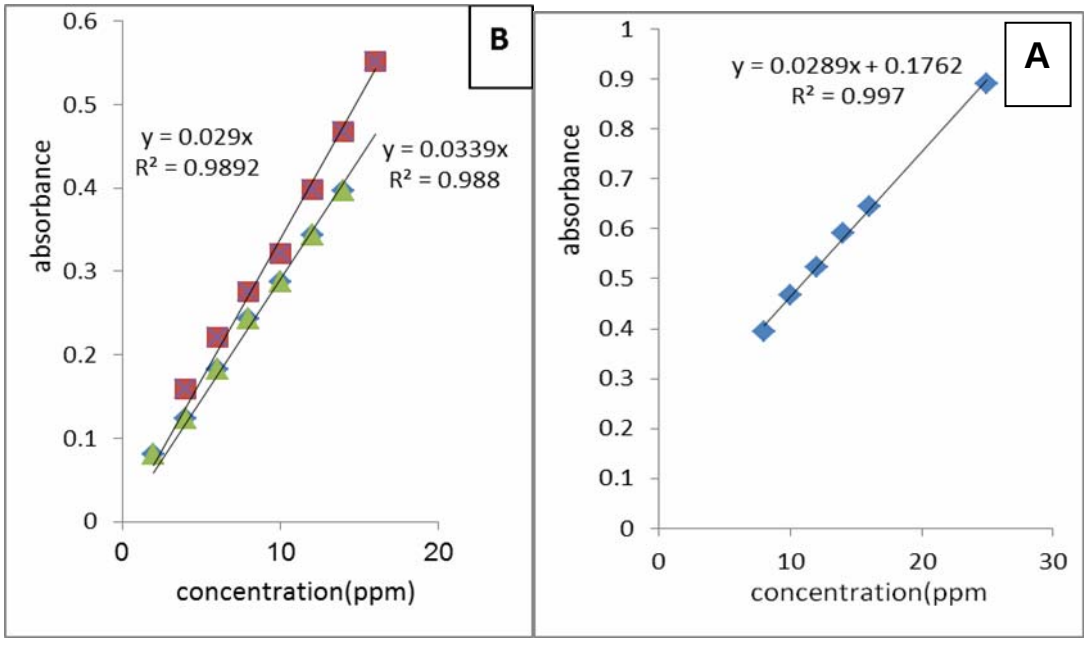

Fig. 2: Calibration graphs; A: paracetamol at 242 nm (λ_{max}), B: (left; paracetamol at 227 nm and B: (right; tramadol hydrochloride at 227 nm).

Fig. (2) shows that Beer's law for paracetamol is obeyed over the concentration range 8-25 ppm at 242 nm and 4-16 ppm at 227 nm, for tramadol it is obeyed over the range 2-14 ppm at 227 nm. Table (1) shows the linear regression data for the calibration graphs.

Table 1: Linear regression data for calibration graphs

Parameters	Paracetamol At λ_{max} 242 nm	Paracetamol At λ 227 nm	Tramadol At λ_{max} 227 nm
Linearity range (μg ml^{-1})	8-25	4–16	2-14
Slope	0.028	0.029	0.0339
Determination coefficient (R^2)	0.997	0.989	0.988
Molar absorptivity ($l.mol^{-1}.cm.^{-1}$)	$7.201x10^3$	$6.115x10^3$	$5.391x10^3$

Accuracy and precision

Accuracy and precision values depicted in (Tables 2, 3, and 4) show that the proposed method provides an acceptable accuracy and a good precision. The repeatability of sample and measurements of concentration were expressed in terms of recovery %, R.S.D.% and R.E%. These values were found (Paracetamol at 242 nm) to be 99.32 , ± 0.646, and 0.75% respectively, 100.5, ± 0.505, and 0.5% (paracetamol at 227 nm), respectively, and 101.7, ± 0.011, and 1.17% for tramadol at 227 nm, respectively.

Table 2: Accuracy and precision of the calibration curve (Paracetamol at λ_{max} 242 nm)

Amount present (μg/ml)	Amount found* (μg/ml)	Recovery,* %	R.S.D,%*	R.E,%*
10	10.27	102.75	±0.1538	+2.75
15	14.38	95.9	±1.14	-4.1
Average		99.32	± 0.646	0.75

*Average of five determinations

Table 3: Accuracy and precision of the calibration curve (paracetamol at λ 227 nm)

Amount present (μg/ml)	Amount found* (μg/ml)	Recovery,* %	R.S.D,%*	R.E,%*
4	4.01	100.25	±1.002	+0.25
12	12.09	100.75	±0.001	+0.75
Average		100.5	±0.505	0.5

*Average of five determinations.

Table 4: Accuracy and precision of the calibration curve (Tramadol at λ_{max} 227 nm)

Amount present (μg/ml)	Amount found* (μg/ml)	Recovery,* %	R.S.D,%*	R.E,%*
4	4.07	101.75	±0.007	+1.75
12	12.07	100.6	±0.016	+0.6
Average		101.7	± 0.011	1.17

*Average of five determinations

APPLICATION OF THE METHOD

Paracetamol tablet

To test the applicability of the present method, it has been applied to the determination of paracetamol tablets (500 mg, SDI, IRAQ), three tablets were pulverized and mixed well, then weight equivalent to 0.0250 g of paracetamol has been dissolved in a sufficient amount of distilled

water with stirring, the volume was then completed to 250 ml in a volumetric flask, and different concentrations equivalent to (8, 12, 16 and 25 ppm) were measured at 242 nm. The results as average recoveries are listed in (Table 5).

Tramadol tablet

Tramadol tablets (Trabar-50 mg, Mepha, Germany) were powdered and mixed, an accurate weight of the powder equivalent to 0.010 g of tramadol was weighed, diluted to 100 ml with distilled water, and different concentrations (4, 6, 8, 10, 12 and 14 ppm) were prepared and measured at 227 nm. The results are listed in (Table 5).

Everfescent tablet

To test the applicability of the present method for a simultaneous determination of paracetamol and tramadol, a weight equivalent to 0.0250 g of paracetamol of effervescent (paracetamol 325 mg and 37.5 mg tramadol per tablet from Laprophan Myantalgic, Casablanca-Maroc Pharmaceuticals, Ltd.), is dissolved in 250 ml distilled water to produce 100 ppm of paracetamol and 11.5 ppm of tramadol, the recovered concentrations were calculated as follows:

A (paracetamol) at 242 nm = εbc at 242 nm

Where A is the absorbance, εis the molar absorptivity, b is the cell thickness (1 cm) , and c is the molar concentration

A at 227 nm = εbc of paracetamol at 227 nm + εbc of tramadol at 227 nm

C (tramadol) at 227 nm=[A- (εc)of paracetamol at 227 nm]/[ε of tramadol at 227 nm.]

The results of application are listed in (Table 5.)

Table 5: Application of the method

Pharmacutical preparation		Present(mg)	Found(mg)	Recovery (%)*
Effervescent Tablet	325 mg paracetamol per tablet**, Laprophan My antalgic, Casablanca-Maroc	325	317.68	94.20
	37.5 mg tramadol per tablet***, Laprophan Myantalgic, Casablanca-Maroc	37.5	32.4	86.40
Tablet	Tramadol (at 227 nm) Trabar-50 mg mepha, Germany	50	49.94	99.94
	Paracetamol (at 242 nm) (500 mg) SDI, IRAQ	500	500.7	100.14

*Average of three determinations.

** In the presence of 37.5 mg of tramadol

*** In the presence of 325 mg of paracetamol

Table (5) shows that the method can be applied to the determination of paracetamol in its pharmaceutical preparation (500 mg tablet) and to the determination of tramadol in its pharmaceutical preparation (50 mg tablet), also the method exhibits a good application to determination of paracetamol in the presence of tramadol but it cannot be applied to the determination of tramadol in the presence of paracetamol.

Effect of interferences:

The low recovery of tramadol may be due to the presence of additives. In order to study the effect of additives, the effect of four common expected additives as interfering compounds on the absorbance of tramadol has been studied at the maximum wavelength of tramadol, 227 nm. (Table 6) shows the results.

Table 6: Effect of interferences

Interfering compound	Recovery% of 25 µg tramadol / µg interfering compund			
	100	250	500	5000*
Glucose	98.48	95.45	93.93	83.33
Lactose	100	100	96.96	
Arabic Gum	98.48	98.48	95.45	
Starch	98.48	96.96	93.93	

* Mixture of the four interfering compounds (contain 5000 µg of each).

Table (6) shows a gradual decrease in tramadol recoveries with a linear increase in the concentration range of additives.

Comparison of the methods

A comparison between the present method with the literature methods (Shukla *et al*., 2011; Charg and Dhabale, 2010), exhibits that the two literature methods depend on measurements at 270 nm as a wavelength for the determination of tramadol, the two methods were applied for tablet dosage form of paracetamol and tramadol. The present method was applied successfully to the determination of paracetamol (PARA) in the presence of 37.5 mg of tramadol (TRMA) and 2.77 g additives. Table (7) shows the results.

Table 7: Comparison of the method

Analytical Parameteres	Present method	Literature method (Shukla *et al.*, 2011)	Literature method (Charg and Dhabale, 2010)
Wavelength(nm)	PARA 242, TRMA 227	PARA 248, TRMA 271	PARA 243.5, TRMA 270.5
Linearity range(µg.ml^{-1})	PARA 4-16, TRMA 2-14	PARA 3-15, TRMA 2.5-15	PARA 3-15, TRMA 20-100
solvent	Water	Methanol	Water
Method of calculation	Law of multicomponent system	Calibration curve equation	Standard addition method
R.S.D%	Better than ±0.646	Better than ± 2%	Better than ±0.07
Molar absorbtivity l.mol^{-1}.cm^{-1}	PARA 7.218x10^3, TRMA 5.391x10^3	------	PARA 9.135 x10^3, TRMA 1.796 x10^3
Dosage form	Tablet, everfescent (PARA, TRMA, and PARA in the presence of TRMA)	Tablet PARA and TRMA in the presence of each other	Tablet PARA and TRMA in the presence of each other

CONCLUSION

The present method is simple, precise, protects human health, environmentally safe, and economic. At the same time, the method is applicable to the determination of paracetamol, and tramadol in their pharmaceutical preparations without prior separation steps from excipients as well as for the determination of paracetamol in the presence of tramadol but it is inapplicable for the determination of tramadol in the presence of paracetamol.

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