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A Friendly Environment Approach for determination of paracetamol

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Abstract

This paper involves a determination of paracetamol using less environment harmful reagent; the hydroxy analog of the pharmaceutical naproxen replaces the chemical reagent in which it is used as a coupling agent for the diazotized p-aminophenol (the hydrolysis product of paracetamol).The paper offers a determination of an analgesic paracetamol in the presence of high content of another analgesic.

Paracetamol azo-dye formed shows the higher absorption peak at 500 nm. Absorbance-concentration relation is liner over the range from 10 to 650 µg/20ml, (i.e. 0.5-32.5 ppm) with a good sensitivity (molar absorptivity $1.2x10^4$ $l.mol^{-1}.cm^{-1}$) ; good precision (RSD better than ±0.275%) and high accuracy (relative error less than + 0.77%), Sandell's sensitivity index is $0.0124\mu g.cm^{-2}$, the calculated limit of detection (LOD) is 0.0030 µg/ml and the evaluated limit of quantitation (LOQ) is 0.0101 µg/ml. The application of the method exhibits a successful results for determination of paracetamol in dosage forms and it's already applied for the determination of paracetamol in presence of naproxen.

Key words: paracetamol , naproxene , spectrophotomety , friendly environment.

طريقه طيفيه صديقه للبيئه لتقدير الباراسيتامول

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الخلاصه

يتضمن هذا البحث تقدير الباراسيتامول باستخدام كاشف أكثر امنا للبيئة اذ تم احلال النابروكسين المحور الى مناظره هيدروكسي نابروكسين (مركب دوائي) محل الكواشف الكيميائيه من خلال استخدامه كعامل اقتران للأمينوفينول (ناتج التحلل المائي للباراسيتامول) المؤزوت ، يقدم البحث تقديرا للباراسيتامول الدواء المسكن في وجود محتوى عالي من مسكن آخر (النابروكسين).

تظهر صبغة الباراسيتامول الازويه المتكونه اقصى امتصاص لها عند طول موجي 500 نانومتر. وتظهر قيم الامتصاص ارتباط خطي مع التركيز ضمن المدى الممتد من 10 إلى 650 ميكروغرام / 20 مل ، (أي مايعادل 0.5−32.5 جزء في المليون) مع حساسية جيدة (معامل الامتصاص المولاري $1.2x10^4$ ، لتر مول$^{-1}$ سم$^{-1}$) ومضبوطيه جيدة (RSD أفضل من 0.275%±) ودقة عالية (خطأ نسبي اقل من 0.77%+) ، كذلك قيمه جيده لدلالة ساندل للحساسية 0.0124 ميكروغرام سم$^{-2}$ ، والحد الأدنى للكشف (LOD) هو 0.0030 ميكروغرام / مل والحد الأدنى للتقدير الكمي (LOQ) هو 0.0101ميكروغرام / مل. تم تطبيق الطريقة بنجاح لتقدير الباراسيتامول في أشكاله الدوائيه وامكانية تطبيقه لتقدير الباراسيتامول.

الكلمات المفتاحية : باراسيتامول , نابروكسين , طريقة طيفية , صديقة للبيئه .

Introduction

Nowadays, the most important development concept in analytical chemistry is the modified version of an environmentally friendly approach [1], some of these concepts are the selection of the safer compounds [2].

A green, and economic method for determination of paracetamol in pharmaceutical preparations established, the method uv spectrophotomtry, which based on dissolving of sample in water, estimating the quantity of paracetamol at two wavelengths , then replacing the concentration in the equation of multi component system[3].

There were other procedures that can be classified under friendly environment these are phenylephrine via oxidative coupling [4], sulphacetamide as a diazotized agent coupled to paracetamol [5] and anthranilic acid as a coupling agent for diazotized paracetamol which is form a colored azo dye measured at 421 nm.[6]

The same principle for determination of paracetamol but with more harmful reagents has been reported .The hemolysis compound [7] nitroaniline used for determination of paracetamol [8] , the irritant [9] thymol was used as a coupling agent for determination of paracetamol in alkaline medium to produce a colored product measured at 600nm.[10] and irritant [11] hexacyanoferrate was used for determination of paracetamol as an oxidant in the presence of ammonia followed by coupling reaction with phenol to form a colored product measured at 630nm.[12] ,in addition to that the skin inflammatory compound [13] phloroacetophenone was used as a coupling compound to determine the diazotized p-aminophenol (hydrolyzed paracetamol) in basic medium [14]. Dichlorodicyano benzoquinone which produces the toxic CN in water [15] was used for determination of paracetamol via charge transfer reaction [16].

The aim of this work is the determination of a diazotized p-aminophenol (hydrolyzed paracetamol) using modified naproxen (mNap) as a safer compound than chemical reagents.

Experimental

Apparatus

All spectral and absorbance measurement were carried out on double-beam Jasco V-630 spectrophotometer with 1.0 cm matched quartz cells. pH measurements were performed using HANNA 301 pH meter, BEL balance was used for weight measurements, reflux was utilized by electrothermal heater and stirring was utilized by Wisd stirrer.

The chemicals

All chemical reagents used were of an analytical grade

- Hydrolyzed paracetamol solution (HPAR) (100 µg/ml) : A10 ml ethanol was used to dissolve accurately weighed quantity of powder 0.025 g PAR (SDI) , then 100-150 ml distilled water was added, (shaking was used to increase the solubility) ,filtered in to 250.0 ml in volumetric flask , and the procedure for hydrolysis of paracetamol had been followed [17].

-Paracetamol solution (1000 µg/ml): 0.25 g of paracetamol was dissolved in 10 ml ethanol then the solution was completed to 250.0 ml in a volumetric flask with distilled water.

-Modified Naproxen (hydroxy naproxen) synthesized and identified in previous research[18] **was used in this article , Modified Naproxen (mNap) (8 x 10^{-4}M):** 0.0184 g of mNap (SDI) was dissolved in 2 ml ethanol and the volume was completed to 100 ml with distilled water in a volumetric flask. The solution was kept in dark bottle and is stay stable for at least one month.

-Sodium Nitrite ($NaNO_2$) 1%:, to prepare the solution, 1.0 g of pure sodium nitrite was dissolved in distilled water and the volume was completed to 100 ml in a volumetric flask.

- Sodium hydroxide solution (1M): to prepare this solution an appropriate dilution of the concentrated solution (Fluka) was diluted with distilled water to 1000 ml in a volumetric flask and then transferred to a plastic bottle.

- Paracetamol Tablet solution (1000 µg.ml^{-1}): 10 tablets (each one contains 500 mg PAR) was weighted and finely powdered. Quantity of powder exactly equivalent to 0.25 g PAR was dissolved in 10.0 ml ethanol, a dilution by 100-150 ml distilled water was done then it was filtered and completed to 250.0 ml in volumetric flask, similar procedure for hydrolysis of paracetamol had been followed.

- Paracetamol injection solution(1000 µg.ml^{-1})*:* The contain of 3 injections were mixed , a 2.5 ml equivalent to 250 mg paracetamol was diluted to 250.0 ml with distilled water in a volumetric flask , 150.0 ml of the last solution was prepared by following the preparation of HPAR in Tablet.

- Paracetamol syrup solution(1000 µg/ml):A 10.41ml of antipyrol syrup (each 5 ml contain 120 mg PAR) was diluted to 250 ml with distilled water in a volumetric flask ; 150 ml of the last solution was prepared by following the preparation of HPAR in Tablet.

Procedure and calibration graph:

To increasing volume (0.1-6.5) ml of 100µg.ml^{-1} standard paracetamol solution, the following reagents has been added in the following orders : 1.0 ml of H_3PO_4 (1M), 1.0 ml of 1% $NaNO_2$, 0.5 ml of 3% sulphamic acid, 3 ml of (8 x 10^{-4}M) mNap and 2 ml of NaOH(1M) has been finally added , then they were diluted to 20 mL, The absorbance has been measured at 500 nm against blank.

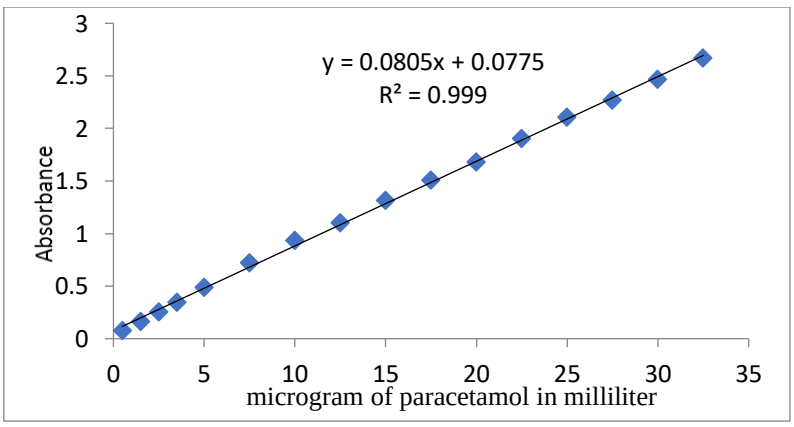

Figure 1 - Calibration Graph for Estimation of Paracetamol

The relation between absorbance and concentration shows a good linearity over the range of the concentration between 10 to 650 µg of Paracetamol in 20 ml (0.5-32.5 ppm) with good sensitivity in which that the molar absorptivity is 1.2 x 10^4l.mol^{-1}.cm^{-1} and sensitivity index of Sandell is 0.0124 µg/cm^2.

The study of the optimum reaction conditions

The selection of acid and its quantity

The effect of different quantities (0.5-2.5 ml) of many acids (hydrochloric, sulphuric, nitric, phosphoric, and acetic acid) (1M) on absorption intensity has been studied Table (1) shows the results.

Table (1): Selection of Acid and its Quantity

Acid used (1M)	Absorbance/ ml of acid				
	0.5	**1.0**	**1.5**	**2.0**	**2.5**
HCl	0.175	0.200	0.244	0.380	0.115
H_2SO_4	0.148	0.178	0.235	0.093	0.055
HNO_3	0.151	0.162	0.176	0.193	0.206
H_3PO_4	0.254	**0.455**	0.447	0.097	0.064
CH_3COOH	0.213	0.234	0.257	0.453	0.121

Table (1) makes it clear that , the maximum absorptions intensity of the colored product results when 1.0 ml of H_3PO_4 was used to justify the reaction medium.

Effect of nitrite quantity with time

Between 0.1 ml to 1.2 ml of $NaNO_2$ (1%) has been checked with a standing time from 0 to 5 min, Table (2).

Table (2): The Effect of Nitrite Quantity With Time

ml of (1%) $NaNO_2$ solution	Absorbance / minute standing time				
	1	**2**	**3**	**4**	**5**
0.1	0.448	0.443	0.448	0.447	0.431
0.3	0.445	0.448	0.446	0.445	0.447
0.5	0.452	0.454	0.456	0.458	0.459
0.7	0.476	0.484	0.489	0.488	0.474
1.0	0.472	**0.493**	0.488	0.489	0.473
1.2	0.478	0.487	0.491	0.489	0.481

Table (2) exhibits that the reaction needs two minutes to reach optimum and 1.0 ml of 1% $NaNO_2$ is the best quantity required for the completion.

Effect of sulphamic acid quantity with time

Between 0.3-1.5 ml of 3% of sulphamic acid was used, and absorbance of the solutions was measured at different standing time.

Table (3):Effect of Sulphamic Acid Quantity With Time

ml of sulphamic acid (3%) solution	Absorbance/minute standing time with shaking				
	1	2	3	5	7
0.3	0.044	0.040	0.068	0.053	0.051
0.5	0.443	0.452	0.456	**0.489**	0.480
0.7	0.445	0.452	0.452	0.485	0.483
1.0	0.441	0.447	0.458	0.486	0.483
1.2	0.444	0.438	0.456	0.480	0.477
1.5	0.446	0.438	0.459	0.472	0.478

Table (3) indicate that five minutes as a standing time was preferred and 0.5 ml of 3% of sulphamic acid was selected .

The Effect of coupling agent quantity

The effect of (1-5) ml of (8×10^{-4} M) coupling agent has been studied against 10-150 µg of Paracetamol/20 ml ; the determination coefficient of a measured absorbance has been evaluated. Table (4) shows that 3 ml and 4 ml of coupling agent solution gives the higher determination coefficient but 3 ml exhibits the best sensitivity.

Table (4): The Effect of Coupling Agent Quantity

ml of mNap (8×10^{-4}M)	Absorbance, µg/20 ml of Para								R^2
	10	30	50	70	100	150	200	250	
1	0.044	0.129	0.213	0.299	0.444	0.685	0.866	1.116	0.9990
2	0.075	0.148	0.234	0.339	0.460	0.701	0.900	1.128	0.9994
3	**0.076**	**0.162**	**0.254**	**0.348**	**0.488**	**0.721**	**0.944**	**1.169**	**0.9999**
4	0.075	0.157	0.243	0.338	0.467	0.687	0.907	1.115	0.9999
5	0.075	0.148	0.240	0.325	0.462	0.687	0.897	1.102	0.9997

Selection of base and its quantity

A higher conjugation and a bigger chromophor area are the results of removing the acidic hydrogen from conjugated product; for this reason, four types of bases or basic salts at different volumes (1-5) ml of each have been tested. See Table (5).

Table (5):The Selection of Base and its Quantity

Base used (1M)	ml of base used				
	1	2	3	4	5
NaOH	0.049	**0.489**	0.446	0.432	0.211
KOH	0.415	0.451	0.460	0.461	0.458
Na_2CO_3	0.042	0.434	0.443	0.457	0.450
$NaHCO_3$	0.070	0.455	0.301	0.213	0.179

Table (5) shows that 2 ml of sodium hydroxide (1M) is the best one and it was used from the beginning.

The Effect of surfactant

In order to study the effect of surfactants on absorption intensity, 2ml of SDS, CPC, and CTAB surfactants with different orders of additions were followed as its shown in Table (6).

Table (6): Effect of Surfactants

Surfactant solution (1×10^{-3}M)	Absorbance/order* of addition					
	I	II	III	IV	V	VI
SDS	0.486	0.487	0.487	0.488	0.480	0.477
CTAB	0.342	0.349	0.354	0.354	0.351	0.348
CPC	0.347	0.354	0.350	0.343	0.342	0.339

* I. paracetamol (Para) + surfactant (S) + H_3PO_4 (H) + $NaNO_2$ (N) + Sulphamic acid (F) + mNaproxen (D) + NaOH (B)

II. Para +H+S+N+F+D+B
III. Para +H+N+S+F+D+B
IV. Para +H+N+F+S+D+B
V. Para +H+N+F+D+S+B
VI. Para +H+N+F+D+B+S

The Stability of reaction

The stability of the colored product against time has been followed using three different concentrations of Paracetamol, Table (7) indicates that the colored product keeps stable for at least 60 minutes.

Table (7): The Stability of the Colored Product

Time, minute	Absorbance/µg of Para present in 20ml		
	50	100	200
2	0.252	0.486	0.944
5	0.252	0.486	0.944
10	0.252	0.484	0.944
15	0.254	0.484	0.944
20	0.254	0.484	0.944
25	0.254	0.484	0.944
30	0.254	0.484	0.944
35	0.254	0.484	0.944
40	0.254	0.484	0.944
45	0.254	0.484	0.944
50	0.254	0.484	0.944
55	0.254	0.484	0.944
60	0.254	0.484	0.944
90	0.254	0.484	0.944
120	0.254	0.484	0.944
180	0.254	0.484	0.944
1 day	0.254	0.484	0.944

Absorption Spectra

Under the optimum reaction conditions, the absorption spectrum of the colored product against blank (Fig.2) shows that wavelength of maximum absorption intensity is 500 nm.this wavelength has been used in subsequent investigations.

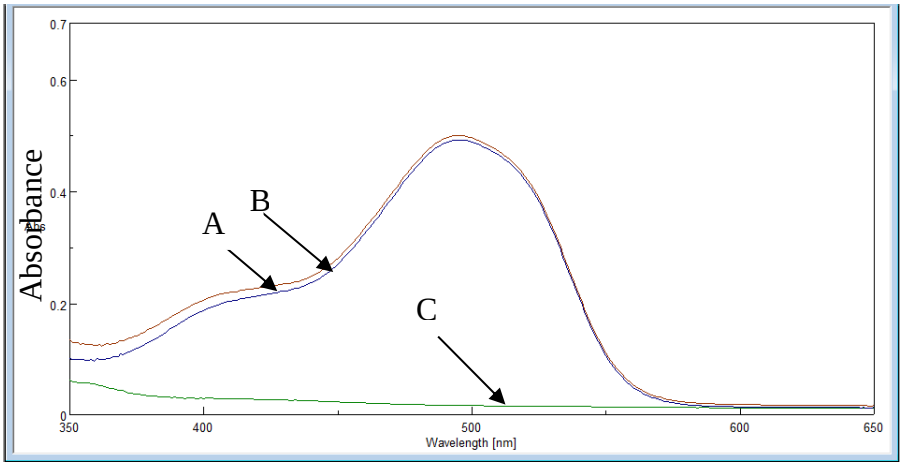

Figure (2): Absorption Spectrum

A: Sample Against Blank
B: Sample Against Distilled Water
C: Blank Against Distilled Water

Accuracy and Precision

Paracetamol is determined at three different concentrations for checking the accuracy and precision, Table (8) indicates that the reaction is accurate (the relative error from -2.11 to 0.77) and precise (the relative standard deviation is from ±0.068 to ±0.275) .

Table (8): Accuracy and Precision

Quantity Para taken µg/20 ml	Relative Error %*	Relative Standard Deviation %*
50	0.77	±0.275
100	-0.62	±0.146
150	-2.11	±0.068

*Average of five determination

Effect of organic solvents

The characteristic of the colored product is more detectable using acetic acid and water than that using other solvents which they were turbid or completely separated into two layers. Water is still being a choice.

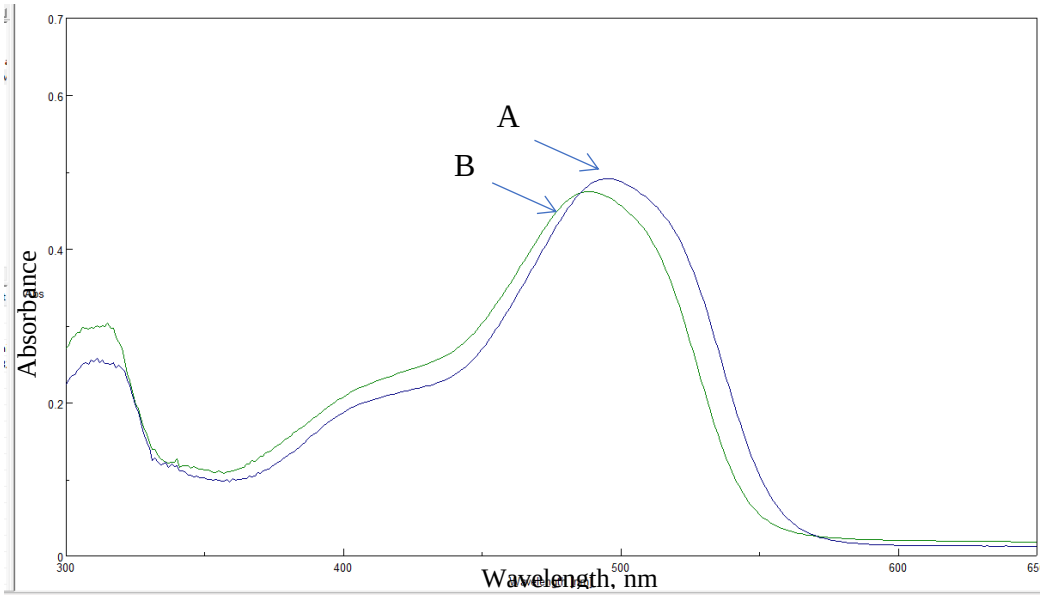

Figure (3): Effect of Organic Solvents
A: Acetic acid B: Water

Effect of foreign compounds

to realize the application of this method, the interferences of foreign compounds have been studied by following the recommended procedure of 100 µg of paracetamol in the presence of 100, 300, 500, 1000 µg of expected foreign compounds using the recommended procedure. Table (9).

Table (9): Effect of Interferences

Interferences	Recovery /µg of Interferences			
	100	300	500	1000
Starch	100.0	101.6	102.7	103.2
Glucose	99.2	102.2	101.2	100.3
Gum Arabic	97.1	100.2	101.0	100.4
Lactose	98.9	97.2	99.45	102.1

Table (10) indicates that there was no interfering effect caused by the studied foreign compounds at different fold excess of these compounds.

Application of the method

The method has been applied to the determination of paracetamol in the dosage forms. The results are listed in Table (10) indicating a good applicability of the method.

Table (10): Application of the Method

Quantity of HPAR /20 ml	Recovery(%) of NAP*			
	Paracetamol Tablet (500 mg) –SDI	Panda Tablet (1000 mg)- Paracetamol- Joswe	Paracetamol Syrup 120 mg in 5 ml- S.D.I	Paracetamol injection (500 mg/ 5 ml)- Pharmaceutical /India
50	98.3	100.1	100.0	99.9
100	98.7	99.8	97.9	99.8
150	99.2	100.0	98.2	99.9

*Average of three determinations

Evaluation of analytical data

T- test has been used for evaluation of the method statistically ; The present method and British Pharmacopeia one [19] have been applied at the same time for t-test calculation [20] ; the value compared with statistical Tables for four degrees of freedom at 95% validation level; Table (11) shows that there is an identical ability to application.

Table (11): Application of Method on Drug Formulation and Evaluation of T-Test

Drug	Recovery * %		t-exp
	Present method	British Pharmacopeia method	
Paracetamol Tablet (500 mg) –S.D.I	101.0	99.6	0.35+
Panda Tablet (1000 mg)-Paracetamol-Joswe	99.5	100	-0.21
Paracetamol Syrup 120 mg in 5 ml- S.D.I	99.7	99.8	+1.45
Paracetamol injection (500 mg/ 5 ml)-Pharmaceutical /India	99.3	99.9	+1.67

* Average of three determinations

Conclusion

A Friendly environment precise with good sensitivity method has been used for the determination of paracetamol in their pharmaceutical preparations (tablet, syrup, and injection) excluding the toxic reagents, don't need organic solvent; and don't need separation steps or adjustment of pH.

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