Spectrophotometric determination of Phenylephrine hydrochloride and Salbutamol sulphate drugs in pharmaceutical preparations using diazotized Metoclopramide hydrochloride

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Abstract:

A spectrophotometric method has been proposed for the determination of two drugs containing phenol group [phenylephrine hydrochloride (PHP) and salbutamol sulphate (SLB)] in pharmaceutical dosage forms. The method is based on the diazotization reaction of metoclopramide hydrochloride (MCP) and coupling of the diazotized reagent with drugs in alkaline medium to give intense orange colored product (λ_{max} at 470 nm for each of PHP and SLB). Variable parameters such as temperature, reaction time and concentration of the reactants have been analyzed and optimized. Under the proposed optimum condition, Beer's law was obeyed in the concentration range of 1-32 and 1-14 μg mL^{-1} for PHP and SLB, respectively. The limit of detection (LOD) and limit of quantification (LOQ) for each of PHP and SLB were 0.60, 0.52 μg mL^{-1} and 2.02, 1.72 μg mL^{-1}, respectively. No interference was observed from common excipients present in pharmaceutical preparations. The good correlation coefficients and low relative standard deviation assert the applicability of this method. The suggested method was further applied for the determinations of drugs in commercial pharmaceutical preparations, which was compared statistically with reference methods by means of *t*- test and *F*- test and were found not to differ significantly at 95% confidence level. The procedure was characterized by its simplicity with accuracy and precision.

Key words: Phenylephrine HCl, Salbutamol sulfate, Spectrophotometry, Diazotization and coupling reaction, diazotized metoclopramide hydrochloride.

Introduction:

Phenylephrine hydrochloride(PHP),[(R)-1-(3-hydroxyphenyl).2-(methylamino) ethanol hydrochloride], is a white crystalline powder, and it belongs to the group of medicines called sympathomimetics[1]. It acts stimulating the alpha receptors in certain areas of the body. It is used locally, as decongestant, for non-specific and allergic conjunctivitis, sinusitis and nasopharyngitis [2]. PHP nasal drops are used for treating symptoms such as runny nose, sneezing, itching of the nose and throat [3]. Various methods have been reported in the literature for the analysis of PHP including spectrophotometry [4–8], spectrophotometry with chromogenic reagent [9,10], and chromatography [11,12].High-performance liquid chromatography [13–16], micellar liquid chromatography [17], micellar electrokinetic chromatography [18], capillary zone electrophoresis [19- 20], spectro-fluorimetric and derivative spectrophotometric methods [21], have also been reported for the determination of PHP.

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Salbutamol sulfate, 4-[2-(*tert*-butylamino)-1-hydroxyethyl]-2 (hydroxymethyl) phenol (SLB) is a selective β2-agonist antiasthmatic. Its primary action is to stimulate adenyl cyclase which catalyzes the formation of cyclic adenosin monophosphate[22]. The drug is official in *European Pharmacopoeia*[23], and *British Pharmacoeia*[2]. According to literature, several analytical methods have been developed for SLB determination in the dosage forms and biofluids, including HPLC [24 –26] and spectrophotometric methods[27-32], but most of them require extensive sample preparation prior to the measurement step, some are less sensitive and some other are relatively complicated in terms of assay procedure or equipment requirement for analysis. UV-Vis spectrophotometry is the technique of choice for pharmaceutical applications, as it offers the advantages of simple and low cost instruments that are available at all laboratories.

In the current work, a very simple and sensitive spectrophotometric method has been described for the determination of two of phenolic drugs: PHP and SLB, which were react immediately with diazotized metochlopramide in alkaline medium to form an orange color product which has an absorbance peak at 470nm. The method had been applied successfully for the determination of PHP and SLB in pharmaceutical preparations, respectively.

Materials and methods:

1. Apparatus

All spectral and absorbance measurements were carried out on a Shimadzu UV–Vis 260 digital double beam recording spectrophotometer using 1-cm path length quartz cells and the measurements were performed at 25ºC.

2. Reagent and materials

All chemicals used were of analytical reagent grade and distilled water was used throughout. Pure PHP, SLB and metochlopramide(MP)drugs sample were kindly provided from state company for Drug Industries and Medical Appliance, SDI, Samara. Iraq. Dosage forms were obtained from commercial sources. Diazotized metochlopramide (DMP), 5 mM was prepared daily by dissolving 0.1772 gm of MP in a minimum volume of distilled water , add 3 ml of 1M hydrochloric acid in a 100 ml volumetric flask. Add 0.0345 gm amount of sodium nitrite (Merck) and stir the mixture. After 5 min the volume is made up to the mark with distilled water. More dilute solutions were prepared by suitable dilution with distilled water. Sodium hydroxide, (BDH), 0.5M solution and hydrochloric acid, (Fluka) 1M solution were prepared by dilution of concentrated solutions .PHP and SLB stock solutions, 500 μg ml^{-1}. A 0.0500 gm amount of the each drug was dissolved in distilled water in a 100 ml calibrated flask and the solution was made up to the volume with the same solvent. Serial dilutions with distilled water were made to cover the working range.

Procedure

1. General procedure for the determination of PHP and SLB

An aliquot of sample containing 1-32 μg $mL^{-1}$of PHP and 1-14 μg $mL^{-1}$of SLB was transferred into a series of 25 ml standard flasks. A volume of 3 mL and 4mL of 5mM DMP solution were added for the determination of PHP and SLB, respectively. Then, 1mL of sodium hydroxide (0.5M) was added for the determination of PHP, SLB. The contents of the flasks were diluted to the mark with distilled water, mixed well and left for 15 min. The

absorbance was measured at 470 nm at room temperature 25°C against reagent blank containing all materials except PHP or SLB. A calibration graph was drawn and the regression equation calculated. For the optimization of conditions and in all subsequent experiments, a solution of 250 µg was used and the final volume was 25 ml.

***2. Procedure for* pharmaceutical preparations**

- ***Nasal drops solutions of PHP:*** The contents of three bottles of nasal drops (0.25% Phenylephrine hydrochloride/10mL) were mixed. An aliquot corresponding to 50 mg of drug (10mL) was diluted to 50 mL with distilled water in a volumetric flask to obtain 500µgmL^{-1} of PHP.
- ***Tablets solutions (2mg of SLB / tablet)***: Thirty tablets were accurately weighed and finely powdered. An amount of the powder equivalent to 50 mg of the drug, was dissolved in distilled water, transferred into 100 mL volumetric flask and diluted to 50 mL with same solvent. The solution was filtered by using whattmann filter paper, and transferred into a 100mL volumetric flask. The residue was washed and diluted to volume with the same solvent to obtain 500µg mL^{-1} of the drug.
- ***Syrup solutions of SLB(2mg / 5 mL):*** An aliquot corresponding to 25 mg of SLB drug (31.2 mL) was diluted to 50 mL with distilled water in a volumetric flask to obtain 250 µg mL^{-1} of SLB. Further appropriate solutions of pharmaceutical preparations were made by simple dilution with distilled water.

Results and discussion:

The parameters affecting mainly on the sensitivity and stability of the coloured product resulting from the diazotization coupling reaction of PHP and SLB with DMP in alkaline medium were carefully studied and optimized**.**

1. Absorption spectra

PHP and SLB are reacted with diazotized metoclopramide in the presence of sodium hydroxide solution giving orange colored products, their absorption spectra under optimum condition gave λmax at 470 nm for PHP and SLB respectively **(Fig. 1)**, whereas the reagent blank gave negligible absorbance at λmax 470 nm.

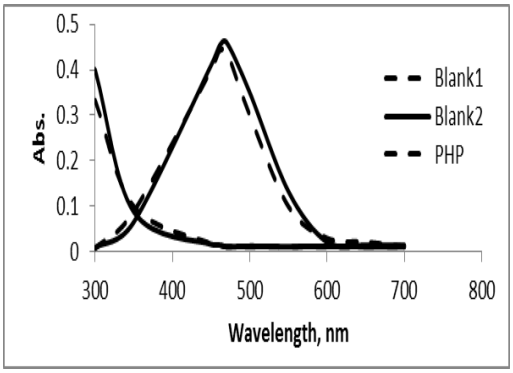


Fig.1: Absorption spectra of the product obtained by the reaction of diazotized Metoclopramide with 16 µg mL^{-1} of phenolic drugs in the presence of sodium hydroxide, all versus reagent blank, and reagent blank versus distilled water

2. The effect of different acids on Diazotization

The effect of different acids on the diazotization reaction was studied. As an evident from the maximum absorbance and stability of the product formed, hydrochloric acid gave satisfactory results; other mineral acids such as HNO_3, H_2SO_4, H_3PO_4, and CH_3COOH were tested and found unsatisfactory**.** The effect of different volumes (0.5 to 6 mL) of 1M HCl solution on the absorbance of the azo dyes was studied. Hydrochloric acid volume of 3mL was found necessary for complete diazotization, further increase in volume resulted a decrease in the absorbance of the reaction product. Thus 3mL of 1M HCl was

adequate for the maximum absorbance **(Fig. 2)**.

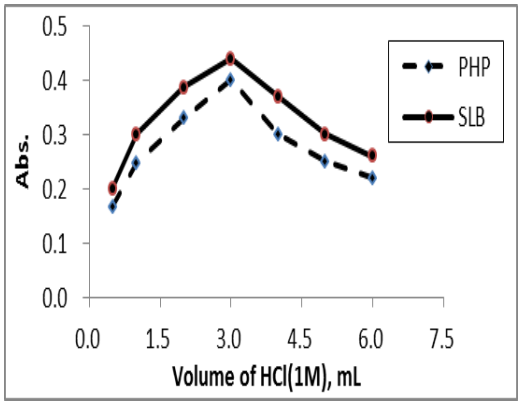


Fig.2: Effect of hydrochloric acid

3. The effect of Diazotized MCP Concentration

A 1:1 mole ratio of MP to sodium nitrite of (5mM) was used in order to prevent the effect of excess of sodium nitrite. The effect of DMP (5mM) on the intensity of the developed color at the selected wavelengths was ascertained by adding different amounts of the reagent. It was found that the optimum volumes of DMP (5mM) were 3mL for the determination of PHP , and 4mL for the determination of SLB **(Fig.3)**; and they were sufficient for the production of maximum and reproducible color intensity. DMP is easily diazotized, and gives water soluble azo dyes, under the conditions of the determination of phenolic drugs(PHP and SLB) thus eliminating the need for an extraction and a time consuming procedure. Diazotization reaction was carried out at room temperature and the minimum time required for diazotization process was 1 min.

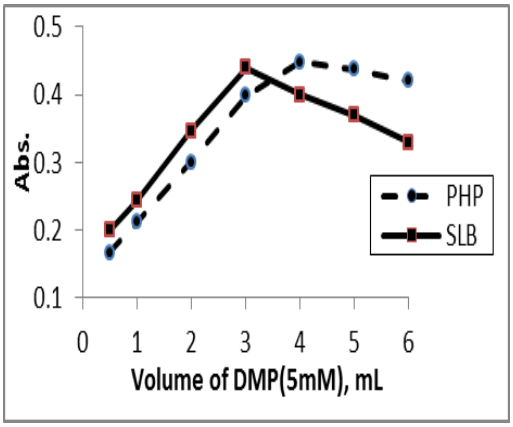


Fig.3: Effect of DMP (5mM)

4. The effect Reaction Medium

To find a suitable medium for the reaction, different aqueous bases were used, such as sodium hydroxide, ammonium hydroxide, sodium carbonate and sodium acetate. The best results were obtained when sodium hydroxide was used. In order to determine the optimum concentration of sodium hydroxide, different volumes of 0.5M sodium hydroxide solution (0.5-5 mL) were used. It was found that a maximum absorbance and stable color was formed with 1mL of sodium hydroxide for the determination of PHP and SLB **(Fig.4)**, larger volumes had no effect on the absorbance of the colored species. The optimized volumes were employed for further determination of phenolic drugs.

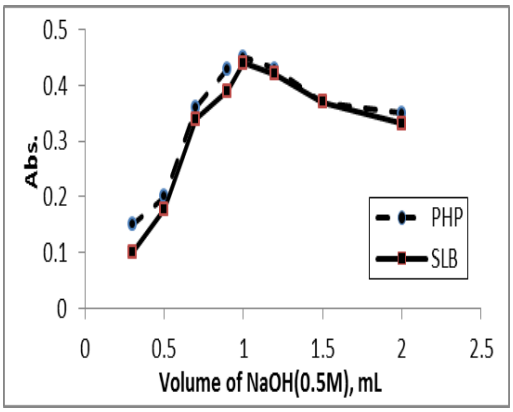


Fig.4: Effect of NaOH (0.5M) on the absorbance

5. The effect of temperature and reaction time

The reaction time was determined by following the color development at room temperature and in a water-bath at different temperatures ranging from 0 to 45°C. The absorbance was measured against reagent blank treated similarly. It was observed that the absorbance reached its maximum value after 15min at room temperature for PHP and SLB, and the color was stable for a period of more than 120 min for PHP and SLB. Fading was observed thereafter. These optimum conditions were used for color development in the subsequent experiments.

6. The effect of order of addition

The effect of order of addition on the absorbance of the complexes was studied under the optimum experimental conditions, and the results indicated that these complexes are formed with high sensitivity by the following order: Drug+ DMP + NaOH.

Quantification and analytical data

The absorbance of the formed product conform with Beer's law in the concentration range 1-32 and 1-14 µg mL^{-1} for PHP and SLB respectively. Negative deviation from Beers law was observed at high concentration. The molar absorptivity of 9.51×10^{3} $L.mol^{-1}$ cm^{-1} for PHP and 6.47×10^{4} $L.mol^{-1}cm^{-1}$ for SLB indicating that the method is sensitive. The linearity was represented by the regression equation and the corresponding correlation coefficients which were found to be more than 0.99 for the two drugs were determined for the proposed method as shown in (Table 1) representation excellent linearity.

Table 1: The analytical values of statistical treatments for the calibration graphs

Parameters	Value	
	PHP	**SLB**
r^2	0.9987	0.9996
Regression equation	*y=0.0477x+0.1119*	*y=0.1152x+0.0334*
Standard deviation of the residuals, Sy/x	0.019	0.011
Standard deviation of the slope, Sb	6.19×10^{-4}	8.03×10^{-4}
Standard deviation of the intercept, Sa	0.011	0.007
Linear range, µg mL^{-1}	1-32	1-14
Molar absorptivity ε ($L.mol^{-1}.cm^{-1}$)	9.51×10^{3}	6.47×10^{4}
LOD µg mL^{-1}	0.601	0.515
LOQ µg mL^{-1}	2.020	1.718
Sandell´s sensitivity, µg cm^{-2}	2.14×10^{-2}	0.89×10^{-2}

Precision and accuracy:

The accuracy of the proposed method was tested by measuring the content of PHP and SLB in pure form at three different concentration levels (low, medium and high) by measuring five replicate at 4, 12 and 16µg mL^{-1} for PHP and 4, 6, and 8µg mL^{-1} for SLB concentration levels (Table 2). The relative standard deviation (representing precision) and mean percent recovery (representing accuracy) obtained by the proposed method can be considered to be very satisfactory.

Table 2: The accuracy and precision of the proposed method

Phenolic drug	Conc. µgml^{-1}		E%	Rec.%	RSD%
	Present*	Found			
PHP	4	4.09	+2.35	102.35	1.52
	12	12.15	+1.25	101.25	1.14
	16	15.88	-1.79	98.21	0.78
SLB	4	4.09	+2.25	102.25	1.62
	6	5.88	-2.00	98.00	1.09
	8	8.05	+0.68	100.68	0.88

*Average of five determinations.

Interferences

The extent of interference by some excipients which often accompany pharmaceutical preparations were studied by measuring the absorbance of solutions containing 10µg/ml of SLB and various amounts of diverse species in final volume of 25 ml. It was found that the studied excipients do not interfere in the present method, even when present in large excess. Typical results are given in (Table 3).

Table 3: The effect of excipients (100µg mL^{-1}) on the recovery of SLB (10µg mL^{-1})

excipient	SLB		
	Found * µgmL^{-1}	E%	Rec.%
Lactose	10.11	+1.11	101.11
Talc	9.96	-0.43	99.57
Starch	9.89	-1.02	98.98
Mg stearate	9.98	-0.16	99.84
PVP	10.11	+1.07	101.07

*Average of five determinations.

Applications

The application of the proposed method to the assay of various pharmaceutical samples of PHP (nasal drops) and SLB (tablets and syrup)) gave reproducible and accurate results as shown in (Table 4). Further, the proposed method is very economical when compared to chromatographic British pharmacopoeia methods [2]. However, the results obtained from the method can be considered to be very satisfactory.

No interference from commonly encountered tablet excipients was observed in the determination, (Table 4). To evaluate the validity and reproducibility of the proposed method, the results obtained were compared with those obtained by standard BP method[33]. The same pharmaceutical preparations for the phenolic drugs were analyzed by standard BP method. The results obtained by the two different methods (Table 5) were statistically compared using the Student t-test and variance ratio F-test at 95% confidence level [34]. In all cases, the calculated t- and F-values did not exceed the theoretical values, indicating that there is no significant difference between either methods in accuracy and precision in the determination of the phenolic drugs in pharmaceutical preparations.

Table 4: The application of the proposed method for the determination of phenolic drugs in pharmaceutical preparations

Phenolic drug	Pharmaceutical preparation	Conc.,µg.mL^{-1}		E %	Rec.%	RSD%
		Present	Found*			
PHP	Nasophrine NasalDrops (0.25%)	4 12 16	3.91 12.10 15.89	-2.25 +0.83 -0.69	97.75 100.83 99.31	1.67 1.11 0.93
SLB	Butadin Tablets	4 6 8	3.99 5.89 8.09	-1.95 -1.87 +1.24	98.05 98.13 101.24	1.81 0.98 0.68
	Butadin Syrup (SDI)	4 6 8	4.05 8.09 7.91	+1.13 -1.10 -1.13	101.13 101.10 98.88	1.56 1.22 0.88
	Butalin Syrup (Julphar)	4 6 8	3.89 6.08 7.89	-2.53 +1.32 -1.38	97.50 101.32 98.63	1.62 0.99 0.67

Table 5: The comparison of the proposed method with standard BP method[2] using t- and F-statistical tests

Pharmaceutical preparations	Rec.% Proposed method	Rec.% Standard method	Value	
			t (theor.)	F (theor.)
PHP pure	100.00	100.00	1.276 (4.303)	10.582 (161.4)
Nasophrine Nasal drops	99.29	100.27		
SLB pure	100.00	100.00	0.593 (2.447)	1.165 (9.227)
Butadin tablet	99.14	99.30		
Butadin Syrup	100.37	98.50		
Butalin syrup	99.15	99.80		

Stoichiometric relationship

The mole ratio of the azo dyes formed between the drug and the reagent used was investigated applying the continuous variation (Jobs) method [34] using equimolar solutions (8×10^{-4}M) of the drug and reagent. The results showed in **Fig. 5** indicated that the azo dye products were formed in the ratio of 1:1(DMP: Drug). This may be attributed to the fact that the phenol group present in the drug is responsible for the coupling with DMP in sodium hydroxide medium.

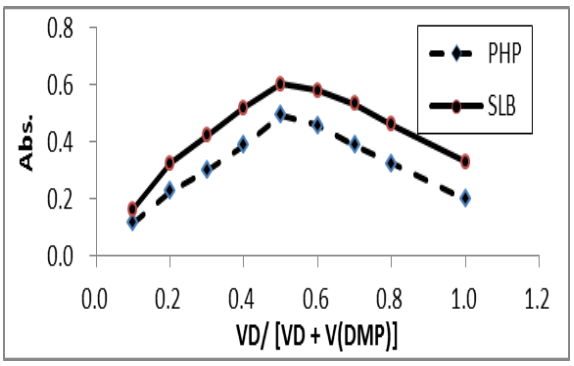
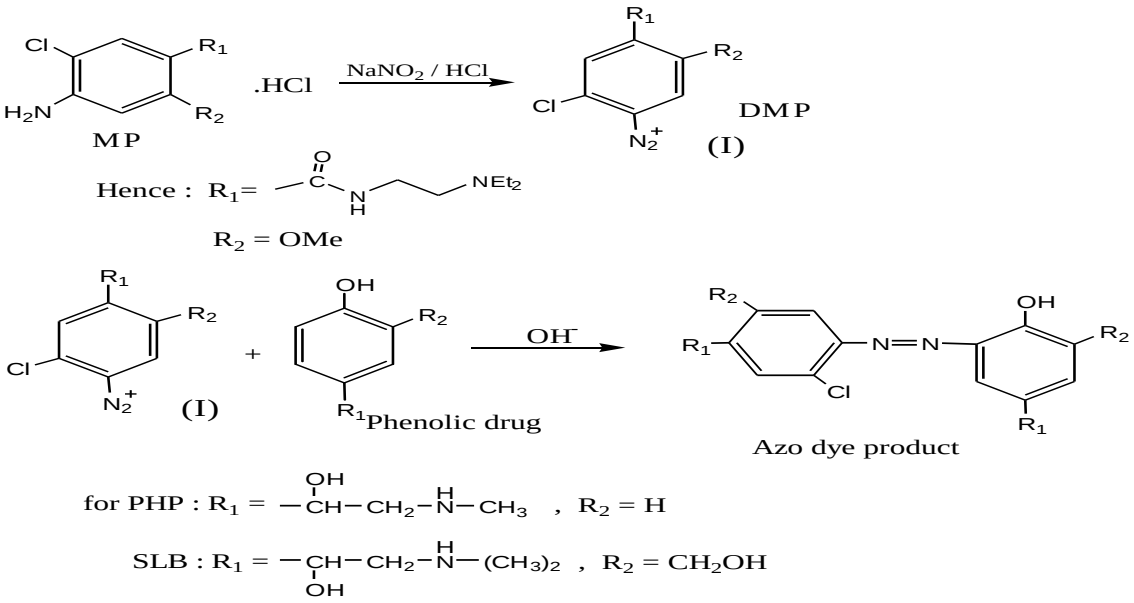


Fig. 5: Continuous variation plots of DMP with PHP and SLB

The formation of the colored azo dyes may occur as follows:



The apparent stability constant was estimated by comparing the absorbance of a solution containing stoichiometric amounts of the drug and DMP to one containing an excessive amount of DMP reagent. The average conditional stability constants or formation constant (k) of the complexes are 2.94×10^5 and 2.09×10^5 $l.mol^{-1}$ for PHP and SLB respectively. This indicates that these complexes are relatively stable.

Conclusion:

The proposed method is simple, sensitive and economical when compared with already reported methods especially those based on nonaqueous medium and to chromatographic British Pharmacopoeia methods and do not require any pretreatment of the drugs or extraction procedure and has good accuracy and precision. The method is important to the assay of various pharmaceutical samples of PHP (nasal drops) and SLB (tablet and syrup), and the results suggested that there is no interference, which is presented in commercial dosage forms.

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التقدير الطيفي لادوية الفنيل فرين هيدروكلورايد والسالبيوتامول سلفات في المستحضرات الصيدلانية باستخدام الميتوكلوبرامايد هيدروكلورايد المؤزوت

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الخلاصة:

يتضمن البحث تطويرطريقة طيفية لتقدير دوائين يحتويان على مجموعة فينول(الفنيل فرين هيدروكلورايد والسالبيوتامول سلفات) في المستحضرات الصيدلانية. وتعتمد الطريقة على تفاعل الازوتة للميتوكلوبرامايد هيدروكلورايد ومن ثم ازدواج الكاشف المؤزوت مع الادوية اعلاه في وسط قاعدي معطيا نواتج ملونة ذات لون برتقالي(عند الطول الموجي الاعظم470 نانومتر لكل من الفنيل فرين هيدروكلورايد والسالبيوتامول سلفات ،وتم دراسة مختلف المتغيرات مثل درجة الحرارة، زمن التفاعل وتراكيز المواد المتفاعلة. عند الظروف المثلى،كان قانون بير ينطبق عند مدى التركيز من 1-32 ومن 1- 14 مايكروغرام لكل مللتر لكل من الفنيل فرين هيدروكلورايد والسالبيوتامول سلفات على التوالي.وقيم حد الكشف وحد الكمية لكل من الفنيل فرين هيدروكلورايد والسالبيوتامول سلفات كانت 0.60 و 0.52 مايكروغرام لكل مللتر و2.02 و1.72 مايكروغرام لكل مللتر، على التوالي. لم يتم تسجيل اي تداخل من قبل المضافات الموجودة في المستحضرات الصيدلانية. طبقت الطريقة وبنجاح لتقدير الادوية في المستحضرات الصيدلانية المحلية وقورنت النتائج احصائيا مع الطرق القياسية باستخدام *t*- test و*F*- test وقد وجد انه لا يوجد فرق معنوي عند مستوى ثقة 95%. تميزت الطريقة المقترحة ببساطتها وذات دقة وتوافقية جيدة