National Ribat University

Faculty Of Graduate Studies & Scientific Research

Simultaneous Determination of Pseudoephedrine Hydrochloride and Triprolidine Hydrochloride in Tablets by Multi-Linear regression Spectrophotometry

A Thesis Submitted in Partial Fulfillment of the Requirements for Master Degree in Drug Quality Control

By :Tagwa Rabie Ali Mansoor

Supervisor :Dr. Imad Osman Abu Reid

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Dedication

This work is dedicated to my

Loving parents, brothers and sisters.

Chapter 1

Introduction and Literature review

1.1 Introduction

Presently various combinations in dosage forms are present in enormous amount and are increasing rapidly. These multicomponent formulations provide the increased therapeutic index, multiple actions, less side effects and quicker relief. The analytical process deal with two parts of chemical characterization either it is quantitative or qualitative. The quantitative analytical analysis provides the amount of chemical identities present in the formulation. The main objective behind the analytical estimation is to provide the assurance that particular formulation contains the equal amount of active pharmaceutical ingredient as mentioned in the label [1].

For the estimation of multicomponent in formulation the various instrumental techniques like spectrophotometric and chromatographic techniques are used due to their advantages of being less time consuming, cheap, specific and accurate [2].

Multicomponent UV Spectrophotometric methods are based on recording and mathematically processing absorption spectra .They offer the following advantages [3]:Avoiding prior separation techniques e.g. extraction, concentration of constituents and cleanup steps that may required ,spectral data are readily acquired with ease, the process is fast, accurate and simple, wide applicability to both organic and inorganic systems, typical detection limits of 10^{-4} to 10^{-5} M and moderate to high selectivity.

Such methods include [4]:

- Simultaneous equation method: applied when a sample contains two absorbing drugs (x and y) each of which absorbs at the λ_{max} of the other.
- Difference spectrophotometry: the essential feature of difference spectrophotometry is that the measure the absorbance difference (ΔA) between two equimolar solutions

of the analyte in different chemical forms which exhibit different spectral characteristics. The selectivity and accuracy of spectrophotometric analysis of samples containing absorbing interferences may be markedly improved by this technique [4].

- Derivative spectrophotometry (DS): the theory behind DS is the conversion of a normal spectrum (zero-order spectrum) to its first, second or higher derivative spectra by differentiating absorbance of the sample with respect to wavelength [5] .The differentiation of zero-order spectrum can lead to separate of overlapped signals, elimination of background caused by presence of other compounds in a sample [6], improvement of resolution of mixtures, and enhancement of sensitivity and specificity [7].
- Derivative ratio spectral method: based on the derivation of the ratio spectral for resolving binary mixtures. It permit use of the wavelength of highest value of analytical signals with several maxima and minima, which give an opportunity for the determination of active compounds in the presence of other compounds and excipients which could possibly interfere in the assay; by conversion of zero-order spectra to its first, second and higher derivatives spectra [8,9].
- Double divisor ratio spectra derivative method: this method is based on the use of the derivative of the ratio spectrum obtained by dividing the absorption spectrum of the ternary mixture by a standard spectrum of a mixture of two of the three compounds in the mixture, and the measuring at either the maximum or minimum wavelengths. It can only be used for the mixtures that the ratio of the concentrations of two interfering compounds (used as double divisor) is known [10].
- Successive ratio - derivative spectra method: this method is used for simultaneous determination of the three compounds in ternary mixtures without need to know the ratio of concentration of species. It is based on the successive derivative of ratio spectra in two successive steps [11].
- Q-absorbance ratio method: is a modification of the simultaneous equations method. According to this method, the ratio of absorbance at any two wavelengths for substance, which obeys Beer's law, is constant value independent to concentration and path length. This constant is term "Hufner's Quotient" or Q-value. The method

involves the measurement of absorbance at two wavelengths, one being the λ_{max} of one of the components (λ 2) and the other being a wavelength of equal absorptivity of the two components (λ 1) called iso-absorptive point [5,12].

- Isosbestic “isoabsorptive" point method: this technique can be used only if the spectra of the same concentration of the two studied drugs cross at a point called isosbestic or iso-absorptive point. At the isosbestic point both drugs have equal absorptivities and their mixture acts as a single component and gives the same absorbance as pure drug.
- Absorpitivity factor method: the absorptivity factor is applied for the analysis of binary mixture if only there is a large difference in the absorptivity between both drugs, so there is no occurrence of an isoabsorptive point [13].
- Dual wavelength method: dual wavelength method facilitates analyzing a component in presence of an interfering component by measuring the absorbance difference (ΔA) between two points in the mixture, one of the drugs consider as a component of the interest and other drug as an interfering component. The method based on selection of two wavelengths where the interfering component shows the same absorbance (ΔA = 0) where as the component of interest shows significant difference in absorbance with concentration. Δ A between two points on the mixture spectra is directly proportional to the concentration of the component of interest independent of interfering component [14].
- Ratio subtraction method (RSM): this method apply when we have two drugs with overlapping spectrum (x and **y**), and the spectrum of **x** extended more than **y**. The determination of **x** can be done by dividing the spectrum of the mixture by a certain concentration of **y** as a divisor (y0) [15].
- Absorption factor method (AFM): this method describes the analysis of a binary mixture where the two components **x** and y have overlapped spectra.y shows interference at λ_{max} of **x**, while **x** shows no interference with **y** at another wavelength (λ 2).
- Multivariate Chemometric methods: Chemometrics recognizes that it is often better to measure many nonselective signals and then combine them in multivariate model (multivariate analysis), whereby multiple variables are considered simultaneously. A multivariate measurement is defined as one in which multiple measurements are

made on a sample of interest. So, more than one variable or response are measured for each sample [16, 17].

1.2 Objectives

Rationale:

The individual spectra of TRI and PSH show extensive overlapping over the wavelengths of 220 – 270 nm, hence their determination when present in combination is not possible with classical spectrophotometric techniques.

The objectives of this research were:

- To develop a new spectrophotometric method based on multi-wavelength linear regression to overcome the problem of spectral overlap.
- To apply this developed method for the estimation of PSH and TRI combined in tablets.

1.3 literature review

Triprolidine, 2-[(1E)-1-(4-methylphenyl)-3-(pyrrolidin-1-yl)prop-1-en- 1-yl] pyridine (Figure 1),act as anti allergic , histamine H1 Antagonist that blocks the action of endogenous histamine, which subsequently leads to temporary relief of the negative symptoms brought on by histamine[18].

Pseudoephedrine Hydrochloride, (1S, 2S)-2-(methylamino)-1-phenylpropan-1-ol (Figure 2), it acts as vasoconstrictor, adrenergic agents, sympathomimetic and bronchodilator agents [18].

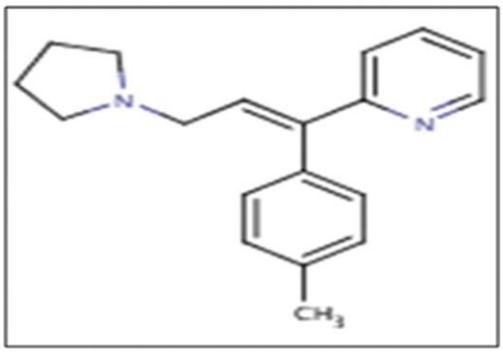


Figure 1: chemical structure of Triprolidine.

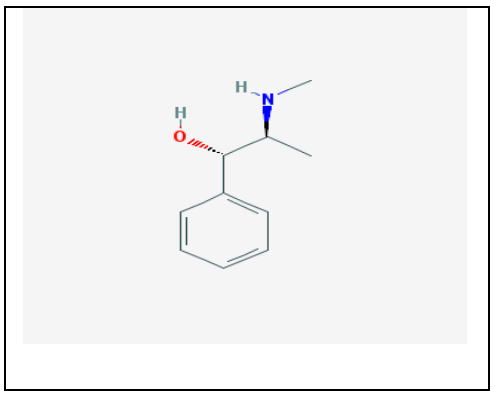


Figure 2: chemical structure of pseudoephedrine.

The combination of triprolidine and pseudoephedrine is used for treatment of allergic rhinitis, symptoms of the common cold nasal decongestion.

The combination of triprolidine (TRI) and pseudoephedrine hydrochloride (PSH) in tablets and syrup dosage form is official in United State Pharmacopeia (USP), normal phase HPLC method on silica column using mixture of alcohol and 0.4 % ammonium acetate solution (17:3 V/V) as mobile phase , with ultraviolet detection at 254 nm was employed for the determination of the two analytes [19].

Literature review revealed that only few methods have been developed for the determination of PSH and TRI in combination.

First derivative spectrophotometric chromatography and high performance liquid chromatography were developed for the determination of PSH and TRI in tablets. In the UV-spectrophotometric method the determination was carried out at the wavelengths 240.2 and 263.5 nm; selected for the first order derivative method. The chromatographic method was performed on a C18 column using methanol: water mixture (80:20 v\v) adjusted to pH 3.0 with phosphoric acid. The flow rate was 1ml/min and the analytes were monitored at 246.2 nm. [18]

Partial least-squares multivariate calibration over the range of 235 – 315 nm was used for the determination of the two analytes. [20]

Second order derivative spectrophotometric method was developed and used for the determination of the two analytes from dissolution study at 271 nm and 321 nm [21].

Proportional isoabsorptive point spectrophotometric method using 290 nm and 266 nm (the iso absorptive point) was employed for the determination of two actives [22].

Comparison of the ratio spectra derivative spectrophotometry, derivative spectrophotometry and vierordt's method was used for quantitative analysis of two analytes over the range of 264nm and -291.8nm. [23]

1.4 Theoretical back ground

A number of methods have been developed to determine the composition of binary mixture spectrophotometrically. Most of these are directed at mixtures where one component can be isolated from the other or they require a Beer's law experiment to measure the molar absorptivity of each of the substance in the mixture. However, multi-wavelength linear regression analysis (MLRA) was described [24] and proved to be capable of resolving mixture with overlapping spectra without determining molar absorptivities or complicated mathematics. Using this method, the composition of a binary mixture with overlapping spectra can be resolved with only three measurements, the absorbance of a standard solution for each component, and the unknown mixture itself.

Assuming additivity, the absorbance of a mixture is the sum of the absorbencies of its components. If we have a mixture consisting of two components, 1 and 2 with an unknown concentration of C1 and C2, then absorbance of the unknown mixture,

A mixture = A1 + A2 but applying Beer's law: $A_1 = €_1bC1$ and $A_2 = €_2bC_2$

Substituting: $A_{mixture} = €_1bC_1 + €_2bC_2$

However, the absorbencies of standard solutions of the same substances will follow the same Beer's law relationship and have the same molar absorbance, €, and one centimeter path length, b, as the unknown solutions under the same conditions.

Therefore, we can write:

$$A_{standard1} = €_1bC_{standard1} \quad \text{and} \quad A_{standard2} = €_2bC_{standard2}$$

Rearranging these relation: $€_1b = \frac{A\ standard1}{C\ standard1}$ and $€_2b = \frac{A\ standard2}{C\ standard2}$

Substituting:

$$A_{MIXTURE} = \frac{\text{A standard1}}{\text{C standard1}}\ C1 + \frac{\text{A standard2}}{\text{C standard2}}\ C2$$

$$A_{MIXTURE} = \frac{C1}{\text{C standard1}}\ \text{A standard1} + \frac{C2}{\text{C standadr2}}\ \text{A standard2}$$

Divided by A standard 1 and simplifying we obtain:

$$\frac{\text{A mixture}}{\text{C standard1}} = \frac{C1}{\text{C standard1}} + \frac{C2}{\text{C standard2}}\ X\ \frac{\text{A standard2}}{\text{A standard1}}$$

Therefore, a plot of:

$$\frac{\text{A mixture}}{\text{C standard}_1}\ \text{against}\ \frac{\text{A standard2}}{\text{A standard1}}$$

Will give:

$$\text{Slope} = \frac{C2}{\text{C standard2}} \qquad \text{and} \qquad \text{intercept} = \frac{C1}{\text{C standard1}}$$

That is, the concentration of unknown component 2 (C_2) in the mixture, equals the slope time the concentration of the standard solution for component 2. Likewise, the concentration of the unknown component 1 (C_1) in the mixture equals the product of the intercept times the concentration of the standard solution for component 1.

Or simply

C_1 = intercept x $C_{standard\ 1}$ and

C_2 = slope x $C_{standard2}$

Chapter 2

Materials and Methods

2.1 Materials

- Triprolidine hydrochloride and pseudoephedrine hydrochloride working standards were obtained from (Blue Nile Pharmaceutical Company, Khartoum North- Sudan).
- Trifed tablets (AL-Hikma Pharmaceutical Industry- Jordon): labeled to contain 60 mg of pseudoephedrine hydrochloride and 2.5 mg of triprolidine hydrochlorides were purchased from local market.
- Hydrochloric acid analytical grade reagent (HCl).
- Laboratory produced distilled water was used throughout the analysis.

2.2 Instruments

- UV-VIS spectrophotometer single beam (model UV min1240 Shimadzu - Japan).
- Ultrasonic bath – Germany.

2.3 Reagents

- Hydrochloric acid (0.1 N) diluent:

The reagent was prepared by transferring 8.1 ml of concentrated HCl into 1000 ml volumetric flask, and diluted to volume with distilled water.

2.4 Samples and standard solutions preparation

2.4 .1 Stock standard solutions

Standard stock solutions of TRI (160 μg/ml) and PSH (3800 μg/mL) were prepared by accurately weighing and diluting about 8 mg TRI and 190 mg PSH into two separate 50ml volumetric flask with 0.1N HCl.

2.4.2 Linearity standards

Separate linearity standards of two analytes were prepared by proper dilution of suitable aliquots from their corresponding stock standard solutions with 0.1 HCl to give concentration in the range of (6.4-32 μg/ml) for TRI and (152-760 μg/ml) for PSH.

2.4.3 Preparation of working standards

Working standards were prepared by quantitative dilution with 0.1 N HCl of suitable volumes from the stock standard solutions and used in different parts of analytical work.

2.4.4 Laboratory synthetic mixtures :

Five synthetic mixture containing different amounts of TRI and PSH were prepared by accurate dilution of aliquots from their corresponding stock standard solutions.

2.4.5 Preparation of the experimental sample:

A total of ten tablets were accurately weighed, powdered and mixed well. A quantity of the resulted powder equivalent to one tablet was weighed and transferred into a 100 ml volumetric flask , the final volume was adjusted with 0.1 N HCl. This process was

replicated for six different weights equivalent to one tablet to produce six experimental sample. The solutions were sonicated for 15 min then filtered using 0.45 μ filter.

2.5 General procedure:

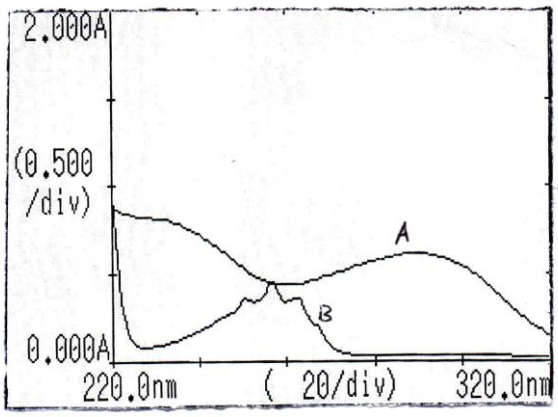
The absorbances of the working standards, mixtures and sample were read at 5 nm intervals within the wavelength range of 240-265 nm.

The concentration of TRI and PSH in synthetic mixtures and the samples were calculated according to the MLRA principle from the slope and intercept of the straight line, using Microsoft Excel Spreadsheet.

Chapter 3

Results and Discussion

The individual spectra of TRI and PSH (Fig. 3), showed considerable overlapping over the wavelength range of 220-320 nm, accordingly application of the classical spectrophotometric techniques for their determination in combined dosage form is not possible.



A= Triprolidine

B= Pseudoephedrine

Figure 3: UV spectra of TRI (160 µg/ml) and PSH (3800 µg/mL) in 0.1 N HCl.

Multi-wavelength linear regression analysis is one of the approaches that can be used when the overlapping between the spectra of the two analytes is very extensive .The application of the technique requires existence of a linear relation between the concentration of the analytes and their absorbances over the wavelength range selected and additivity of their absorbances at each wavelength.

3.1 Linearity

Both TRI and PSH showed good correlation between the concentration absorbance at each of the selected wavelength over the range of 220-320 nm ($r > 0.99$) and small intercept, the regression data of the two analytes is presented in Table 1 and 2. The

presented data suggests possible application of the proposed method for determination of TRI and PSH in combined dosage forms using MLRA.

Table 1: Triprolidine linearity data at selected wavelengths

µg/ ml	Absorbances					
	240nm	**245nm**	**250nm**	**255nm**	**260nm**	**265nm**
6.4	0.329	0.29	0.244	0.208	0.198	0.206
12.8	0.657	0.576	0.482	0.407	0.384	0.4
19.2	1.027	0.903	0.755	0.637	0.601	0.626
25.6	1.131	0.993	0.831	0.701	0.661	0.689
32	1.427	1.254	1.048	0.883	0.833	0.868
Slope	37500	32935.39	27485.955	23089.89	21727.53	22654.49
Intercept	0.1132	0.0997	0.0849	0.074	0.0713	0.0739
$\mathbf{r^2}$	0.9873	0.9872	0.9873	0.9874	0.9875	0.9875

Table 2: pseudoephedrine hydrochloride linearity data at selected wavelengths

µg/ ml	Absorbances					
	240nm	**245nm**	**250nm**	**255nm**	**260nm**	**265nm**
152	0.063	0.107	0.155	0.178	0.156	0.109
304	0.128	0.197	0.285	0.326	0.283	0.194
456	0.193	0.292	0.422	0.482	0.419	0.287
608	0.217	0.338	0.497	0.572	0.497	0.337
760	0.285	0.434	0.627	0.716	0.624	0.426
Slope	0.0003	0.0005	0.0007	0.0008	0.0007	0.0005
Intercept	0.0173	0.0351	0.0504	0.0582	0.0508	0.0375
$\mathbf{r^2}$	0.9911	0.9950	0.9962	0.9967	0.9968	0.9964

$\mathbf{r^2}$= correlation coefficient

3.2 Determination of synthetic mixture (Accuracy)

The method accuracy was tested by analyzing five laboratory prepared synthetic mixtures containing different amount from TRI and PSH ,the results obtained showed good agreement between actual and theoretical amounts of the two analytes. For TRI the recovery from the synthetic mixtures was (99.66 - 107.18 %), and the recovery of PSH was (98.04 - 99.87 %).

The absorbance data at selected wavelengths, the absorbances ratio and the accuracy calculation are shown in tables 3, 4 and 5.

Table3: The absorbance data at selected wavelengths

$\tilde{\lambda}$(nm)	TRI	PSH	m 1	m 2	m 3	m 4	m 5
240	1.108	0.237	0.766	1.026	0.858	0.585	1.341
245	0.967	0.365	0.763	0.992	0.88	0.61	1.332
250	0.812	0.516	0.767	0.958	0.903	0.633	1.322
255	0.694	0.619	0.769	0.932	0.915	0.648	1.309
260	0.654	0.584	0.724	0.872	0.86	0.608	1.231
265	0.679	0.402	0.629	0.785	0.734	0.516	1.086

m= synthetic mixture

Table4: The absorbance ratio data at selected wavelengths

λ(nm)	TRI/PSH	m1/PSH	m2/PSH	m3/PSH	m4/PSH	m5/PSH
240	4.6751	3.2320	4.3291	3.6202	2.5107	5.7553
245	2.6493	2.0904	2.7178	2.4109	1.6897	3.6897
250	1.5736	1.4864	1.8565	1.750	1.2363	2.5820
255	1.1211	1.2423	1.5056	1.4781	1.0536	2.1284
260	1.1198	1.2397	1.4931	1.4726	1.0482	2.1224
265	1.6890	1.5646	1.9527	1.8258	1.2709	2.6748
	Slope	0.5600	0.7963	0.6036	0.4039	1.0033
	Intercept	0.6119	0.6066	0.8022	0.5994	1.0009
Correlation coefficient		0.9999	0.9999	0.9999	0.9999	0.9999

Table 5: The accuracy results of the synthetic mixtures

sample	Triprolidine (µg/mL)		Content %	Pseudoephedrine (µg/mL)		Content %
	Theoretical	actual		Theoretical	actual	
1	0.0181	0.0194	107.18	0.4699	0.4608	98.06
2	0.0258	0.0259	100.38	0.4658	0.4608	98.92
3	0.0195	0.0194	99.48	0.6161	0.6144	99.72
4	0.0132	0.0131	99.24	0.4580	0.4584	100.08
5	0.0329	0.0328	99.69	0.7649	0.764	99.88
mean			101.19	mean		99.33
Standard deviation			3.37	Standard deviation		0.836
RSD%			3.33	RSD%		0.0084

3.3 Analysis of commercial Sample

The proposed method was applied to analysis of five samples taken from commercial tablets dosage.

The results obtained were in good agreement with the labeled amounts 104.20% and 92.55% with relative standard deviations of 0.77 % and 1.07% for TRI and PSH respectively. This support the suitability of the proposed method for determination of TRI and PSH in tablets dosage formulation .The tablets analysis data is presented in tables 6-9.

Table 6: Samples weight taken:

Sample no.	Weigh taken	µg Active	
		Triprolidine	Pseudoephedrine
S1	0.1339	24.96	598.92
S2	0.1341	24.99	599.82
S3	0.1340	24.97	599.37
S4	0.1339	24.96	598.92
S5	0.1341	24.99	599.82
S6	0.1340	24.97	599.37

S= sample

Table 7: The absorbance data at selected wavelengths (samples)

λ̃(nm)	TRI	PSH	S 1	S 2	S 3	S 4	S5	S 6
240	1.105	0.233	1.081	1.096	1.101	1.088	1.093	1.104
245	0.964	0.361	1.047	1.063	1.074	1.047	1.06	1.079
250	0.809	0.512	1.024	1.047	1.045	1.036	1.03	1.05
255	0.691	0.615	1.015	1.033	1.036	1.013	1.025	1.04
260	0.651	0.58	0.963	0.972	0.98	0.96	0.978	0.986
265	0.676	0.406	0.854	0.854	0.867	0.866	0.859	0.866

Table8: The absorbance ratio data at selected wavelengths (Samples)

λ̃(nm)	TRI/PSH	S1/PSH	S2/PSH	S3/PSH	S4/PSH	S5/PSH	S6/PSH
240	4.7424	4.6394	4.7038	4.7253	4.6695	4.6909	4.7381
245	2.6703	2.9002	2.9445	2.9750	2.9002	2.9362	2.9889
250	1.5800	2	2.0449	2.0410	2.0234	2.0117	2.0507
255	1.1235	1.6504	1.6796	1.6845	1.6471	1.6666	1.6910
260	1.1224	1.6603	1.6758	1.6896	1.6551	1.6862	1.7
265	1.6650	2.1034	2.1034	2.1354	2.1330	2.1157	2.1330
	Slope	0.8246	0.8368	0.84090	0.8307	0.8345	0.8428
	Intercept	0.7188	0.7255	0.7333	0.7181	0.7230	0.7376
Correlation confident		0.99978	0.99986	0.999901	0.99961	0.99970	0.99989

Table 9: The assay results of samples

sample	Triprolidine (µg/mL)		Content %	Pseudoephedrine (µg/mL)		Content %
	Theoretical	found		Theoretical	found	
S1	24.96	25.70	102.97	598.92	549.17	91.69
S2	24.99	26.08	104.34	599.82	554.33	92.42
S3	24.97	26.20	104.92	599.37	560.27	93.48
S4	24.96	25.89	103.73	598.92	548.67	91.61
S5	24.99	26.01	104.06	599.82	552.37	92.09
S6	24.97	26.26	105.16	599.37	563.54	94.02
	Average		104.20	Average		92.55
	Standard deviation		0.80	Standard deviation		0.99
	RSD%		0.77	RSD%		1.07

Chapter 4

Conclusion and References

4.1 Conclusion

- The MLRA is straight forward procedure allowing the accurate resolution of binary mixtures of compounds with overlapped spectra.
- The cost effectiveness and simplicity of method render it as suitable alternative to other expensive methods e.g. chromatographic methods for the analysis of binary mixtures of compounds with overlapped spectra in laboratories and countries where such sophisticated equipments are not affordable.
- The accuracy and simplicity of the method suggested it suitability in case where quick results are demanded e.g. as in-process analysis procedure during blend analysis in industrial setups.

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Table of Contents

Chapter 3 : Results and Discussion

Chapter 4 :

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Abbreviations

AFM	Absorption Factor Method
C_{18}	Octadecylsilane
DS	Derivative Spectrophotometry
HCl	Hydrochloric acid
HPLC	High Performance Liquid Chromatography
min	Minute
mL	Milliliter
MLRA	Multi-Wavelength Linear Regression Analysis
nm	Nanometer
PSH	Pseudoephedrine Hydrochloride
RSM	Ratio Subtraction Method
TRI	Triprolidine hydrochloride
USP	United State Pharmacopeia
UV	Ultraviolet
µg	Microgram

Abstract

A simple, accurate and inexpensive method has been developed for the determination of triprolidine hydrochloride and pseudoephedrine hydrochloride in tablets,Multi-wavelength Linear Regression Analysis.The method utilized the slope and intercept of the straight line obtained by plotting the ratio of the sample absorbances divided by the pseudoephedrine standard of known concentration against the absorbances ratio of triprolidine standard and pseudoephedrine standard.

The recovery the synthetic mixture was 99.33% and 101.19% withthe relative standard deviations of 0.0084% and 3.33% for triprolidine and pseudoephedrine respectively

The results obtained by applying the method to the analysis of two analytes in tablets were in good agreement with label claim, 104.20% and 92.55% with relative standard deviations of 0.77% and 1.07% for triprolidine and pseudoephedrine respectively.

List of figures

List of tables

Chapter one

Introduction and Literature Review

Chapter Two

Materials and methods

Chapter Three

Results and Discussion

Chapter Four

Conclusion