Archives of Pharmaceutical Sciences Ain Shams University 2021; Vol. 5(1): 52-62

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Analytical Chemistry

Original Article

Simultaneous Determination of Xipamide and Triamterene by First Derivative, Ratio Difference, and Derivative Ratio Spectrophotometric Methods

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ABSTRACT

Validated, rapid, and sensitive spectrophotometric techniques were established for the simultaneous determination of Xipamide and Triamterene. The first technique is based on the determination of Triamterene with zero-crossing of Xipamide using the zero-order method at 367.0 nm. The second technique is based on the determination of both Xipamide and Triamterene by the first derivative method with zero-crossing of Triamterene and Xipamide respectively, at 265.6 and 388.6 nm. The third technique is the ratio difference spectrophotometric method depending on obtaining peak amplitude difference at 256.0 and 273.0 nm for Xipamide and 288.0, 302.0 nm for Triamterene. The fourth method is the derivative ratio spectrophotometric method depending on obtaining the first derivative of the ratio spectrum with zero-crossing of Xipamide and Triamterene at 365.2 and 308.6 nm; respectively. Linear relationship was obtained upon using concentration range (1.0-10.0 µg/mL) for Xipamide and (1.0-16.0 µg/mL) for Triamterene with LOD less than 0.3 µg/mL for both drugs. The suggested spectrophotometric techniques showed Lower LOD and more sensitivity other than any reported spectrophotometric methods and were applied in pure and dosage form (Epitens®).

Keywords: *Xipamide; Triamterene; Zero-order; First derivative; Ratio difference; Derivative ratio.*

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Citation | Fares NV, El Fiky HA, Badawey AM, Abd El Ghany MF, 2021. Simultaneous determination of Xipamide and Triamterene by first derivative, ratio difference, and derivative ratio spectrophotometric methods. Arch Pharm Sci ASU 5(1): 52-62

DOI: 10.21608/aps.2021.58496.1053

Print ISSN: 2356-8380. **Online ISSN**: 2356-8399.

Received 25 March 2021. **Accepted** 26 May 2021.

Published by: Ain Shams University, Faculty of Pharmacy

1. INTRODUCTION

Xipamide shown in **(Fig. 1a) [1]** is a (4-chloro-N-(2, 6-dimethyl phenyl)-2-hydroxy-5-sulfamoylbenzamide) ($C_{15}H_{15}Cl\ N_2O_4S$) used for the treatment of high blood pressure. Xipamide has an effective action rather than thiazides and decreases the loss of potassium. Triamterene showed in **(Fig. 1b) [2, 3]** (6-phenylpteridine-2, 4, 7-triamine) ($C_{12}H_{11}N_7$) is a potassium-sparing diuretic preventing hypokalemia in the body and also used for the treatment of edema. Triamterene showed hyperkalemia as its main side effect. So, to counter this effect it is used in combination with Xipamide to overcome this side effect **[4]**.

The literature review revealed that many methods were reported for determination of Xipamide including Spectrophotometric **[5]**, Spectroflurometric **[6]**, Voltammetric **[7]** and HPLC methods **[8-10]**, and for determination of Triamterene including spectrophotometric **[11-15]**, Spectroflurometric **[16-18]**, Electrochemical

[19, 20], and HPLC methods **[21, 22]**. Few methods were stated for obtaining both Xipamide and Triamterene in a mixture including Spectrophotometric **[23, 24]** and HPLC methods **[25-27]**.

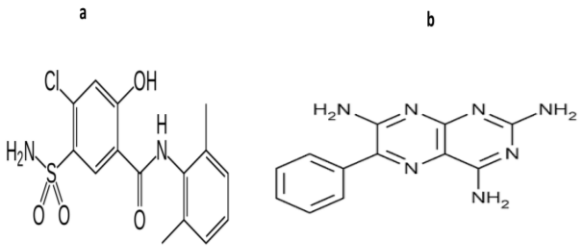

Fig. 1. Chemical structures of (a) Xipamide and (b) Triamterene

UV-visible spectroscopic methods are quantitative techniques depending on the functional group of the drug. **[28].** The functional group of Xipamide (sulfamoyl group) and amino groups of triamterene allow them to absorb Visible UV light within range (200-400 nm). The ratio Difference Spectrophotometric Method **[29]** depends on the direct proportionality of the amplitude difference and the concentration. The derivative Ratio spectrophotometric method **[30]** depends on the first derivatization of the ratio spectra and recording at no interference wavelengths.

The proposed methods aim to establish new, selective, rapid, and precise Spectrophotometric techniques to determine Xipamide and Triamterene in pure and dosage forms with lower LOD and higher sensitivity. These methods would ease actual and financial regulation of resources for quality control (QC) aspects.

2. Experimental

2.1. Apparatus

Double beam Shimadzue UV-Vis spectrophotometer (UV-1800, Japan), Double beam (Libra, biochrom, England), and 1 cm quartz cells

Sonicator (Branson Model 3510 Ultrasonic Cleaner, UK)

Analytical Balance Sartorius CPA225D, Italy.

2.2. Materials and reagents

2.2.1. Pure samples

Pure standards of Xipamide and Triamterene were kindly obtained from Epico, Egypt. The purity of Xipamide was tested and found to be 99.61±1.206 according to the reported method **[24]**, while Triamterene was found to be 100.05±0.844 according to the reported method **[3]**.

2.2.2. Market sample

Epitens®' tablet was purchased from the market, manufactured by Epico, Egypt. Epitens® was labeled to contain 10.0 mg of Xipamide and 30.0 mg of Triamterene, batch number (11824).

2.2.3. Reagents

Methanol (HPLC grade, Sigma, Germany), Methanol (HPLC grade, Merck, Germany), Methanol (HPLC grade, Honeywell, America),

2.3. Standard and Working Solutions

2.3.1. Xipamide and Triamterene Stock Standard Solution (1000.0 µg/mL)

To prepare stock solutions, 0.1 g of Xipamide and Triamterene were individually dissolved in methanol, transferred to 100-mL volumetric flasks, and diluted with methanol.

2.3.2. Xipamide and Triamterene Working Standard Solution (100.0 µg/mL)

10 mL from Xipamide and Triamterene Stock Standard Solution (1000.0 µg/mL) were transferred separately to a 100-mL volumetric flask and diluted with methanol.

2.4. Procedures

2.4.1. Spectral characteristics of Xipamide and Triamterene

Aliquots of 0.5 mL of Xipamide and Triamterene were individually transferred from their working stock solutions to different 10-mL volumetric flasks and diluted with methanol. The zero-order spectrum of Xipamide and Triamterene (5 µg/mL) was recorded. Triamterene could be determined at 367.0 nm without any interference of Xipamide, while Xipamide could not be determined due to interference of Triamterene.

2.4.2. First derivative method

To different 10-mL volumetric flasks, accurate volumes of Xipamide (0.1-1.0 mL) and Triamterene (0.1-1.6 mL) were transferred from their corresponding working standard solutions and diluted with methanol. Obtained concentration ranges were (1.0-10.0 µg/mL) and (1.0-16.0 µg/mL) for Xipamide and Triamterene; respectively. First derivative peak amplitude was recorded at 265.6 nm (zero interference of Triamterene) and 388.6 nm (zero interference of Xipamide), using $\Delta\lambda = 4$ and scaling factor = 10.

2.4.3. Ratio difference method

Different concentrations of Xipamide and Triamterene were prepared within linearity (1.0-10.0 µg/mL) and (1.0-16.0 µg/mL) for Xipamide and Triamterene; respectively. The peak amplitude of Xipamide was recorded without any interference of Triamterene at 256.0 and 273.0 nm after the division of Zero-order spectra of Xipamide by zero-order spectrum of Triamterene (6.0 µg/mL) as Triamterene will be constant so the difference in peak amplitude will equal zero. Repeating these steps for the determination of Triamterene by dividing its spectra by Xipamide (4.0 µg/mL), Triamterene could be determined at peak amplitude 288.0 and 302.0 nm.

2.4.4. Derivative ratio method

Different concentrations of Xipamide and Triamterene were prepared within range (1.0-10.0 µg/mL) and (1.0-16.0 µg/mL) for Xipamide and Triamterene; respectively. Spectra of the first derivative were obtained after the division of the Zero-order spectrum of xipamide over Zero-order spectrum of Triamterene (6.0 µg/mL) and Xipamide could be determined at peak amplitude 308.6 nm, while Triamterene could be determined by the same procedures using Xipamide (4.0 µg/mL) as a divisor and recording peak amplitude at 365.2 nm.

2.4.5. Laboratory prepared mixtures

Lab mixtures of both drugs were prepared by transferring different volumes within linearity (1.0-10.0 µg/mL) and (1.0-16.0 µg/mL) for Xipamide and Triamterene; respectively from their working standard solutions.

2.4.6. Application to a pharmaceutical formulation

Two tablets of Epitens® were ground and mixed. Amounts equal to 10.0 mg of Xipamide and 30.0 mg of Triamterene were accurately transferred to a 100-mL volumetric flask and diluted with methanol. The solution was filtered into the 100-mL volumetric flask to prepare a working standard solution of concentration 100.0 µg/mL of Xipamide and 300 µg/mL of Triamterene. Further dilution was performed to obtain a concentration of 1.0 µg/mL of Xipamide and 3.0 µg/mL of Triamterene.

3. Results and Discussion

3.1. Spectrophotometric measurement

Studying different solvents and some of the instrumental parameters such as the wavelength increment ($\Delta\lambda$) and the scaling factor were important to review their impact on the shape and resolution of the obtained spectra. DMSO, 0.1 N NaOH, and 0.1 N HCl were tried as solvents for

both drugs, different Δλ (4, 8, and 16) and scaling factors (10 and 100) were tried, all previously mentioned solvents showed bad resolution and high level of noise. The best spectra for both drugs were obtained upon using methanol as solvent, Δλ= 4 and scaling factor= 10. After recording the zero-order spectrum of Xipamide and Triamterene, Triamterene can be determined at 367.0 nm without any interference of Xipamide, while Xipamide cannot be determined due to overlapping of Triamterene as revealed in **(Fig. 2)**.

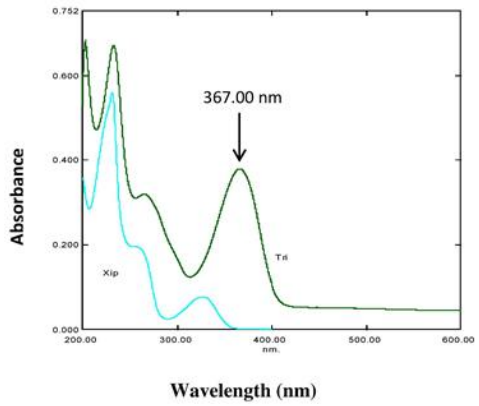

Fig. 2. Zero order spectra of both Xipamide and Triamterene (5.0 µg/mL each)

Concerning the first derivative method, the peak amplitude of Xipamide was recorded at 265 .6 nm (zero interference of Triamterene) and 388.6 nm for Triamterene (zero interference of Xipamide) as displayed in **(Fig. 3)**. Regarding Ratio difference method, different concentrations of Xipamide (2.0, 4.0, 6.0, 8.0 µg/mL) and Triamterene (4.0, 6.0, 8.0, 10.0 µg/mL) were attempted as a divisor, the concentrations showing best resolution and reproducibility were (4.0 and 6.0 µg/mL) for Xipamide and Triamterene; respectively as presented in **(Fig. 4) and (Fig. 5).** While for derivative ratio method, peak amplitude for Xipamide and Triamterene was recorded at different wavelengths (234.60. 247.00, 273.40, 308.6 nm) for Xipamide and (279.60, 365.20, 368.00, 384.00 nm) for Triamterene with mean recoveries of 104.61±2.258 (234.60 nm), 102.99±2.346 (247.00 nm) and 103.01±2.181 (273.40 nm) for Xipamide, while for triamterene 103.72±2.192 (279.60 nm), 102.89±1.913 (368.00 nm) and finally 103.60±2.268 (384.00 nm), the most sensitive wavelengths with better recovery and least standard deviation were 308.60 (100.19±1.089) and 365.20 (100.49±0.707) for Xipamide and Triamterene; respectively as displayed in **(Fig. 6) and (Fig. 7)**. **Fig. 8** and **Fig. 9** showed that both Xipamide and Triamterene were superimposed with their synthetic laboratory-prepared mixtures at the selected wavelengths.

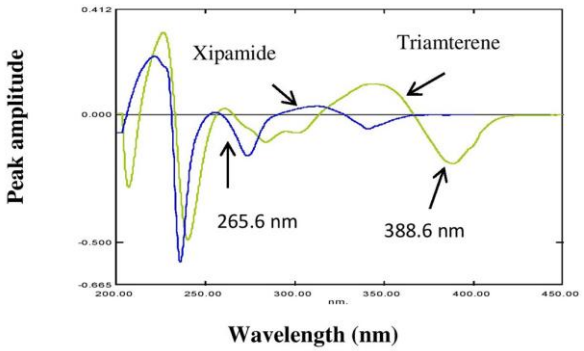

Fig. 3. First derivative spectra of different concentrations of both Xipamide and Triamterene at 265.6 & 388.6 nm

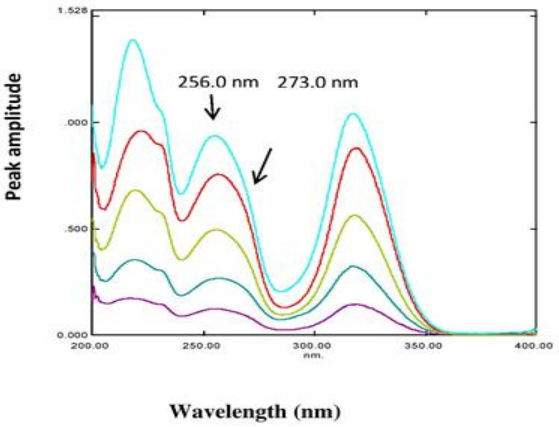

Fig. 4. Ratio absorption spectra of intact Xipamide (1.0-10.0 µg/mL) after resolution from Triamterene (6.0 µg/mL) using ratio difference method at specified wavelength 256.0 & 273.0 nm

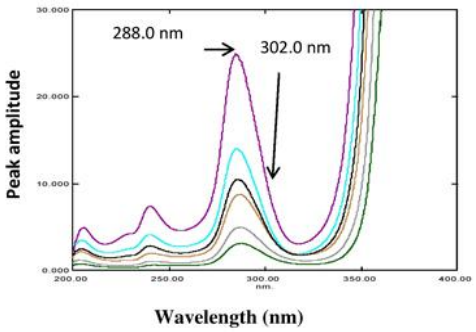

Fig. 5. Ratio absorption spectra of intact Triamterene (1.0-16.0 µg/mL) after resolution from Xipamide (4.0 µg/mL) using ratio difference method at specified wavelength 288.0 & 302.0 nm

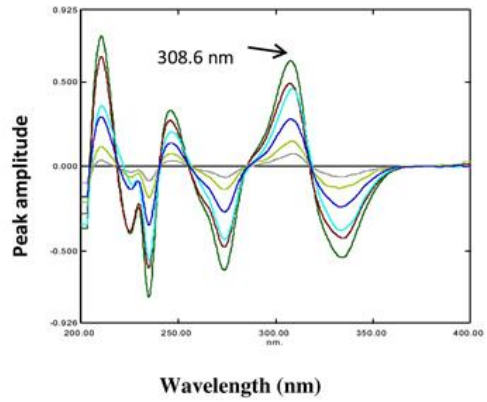

Fig. 6. First derivative of ratio spectra for Xipamide (1.0-10.0 µg/mL) with Triamterene as a divisor (6.0 µg/mL) at 308.6 nm

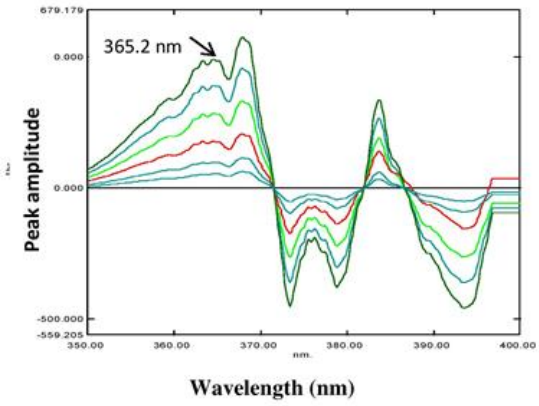

Fig. 7. First derivative of ratio spectra for Triamterene (1.0-16.0 µg/mL) with Xipamide as a divisor (4.0 µg/mL) at 365.2 nm

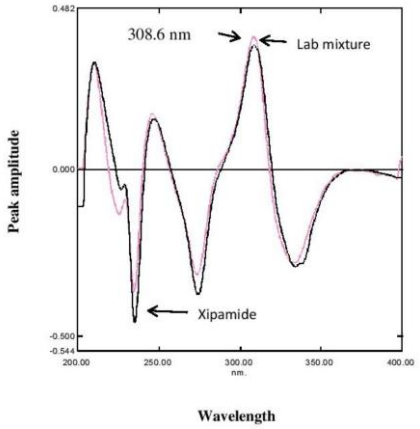

Fig. 8. First derivative of ratio spectra for Xipamide (6.0 µg/mL) with Laboratory prepared mixture (6.0 µg/mL of Xipamide and 2.0 µg/mL of Triamterene)

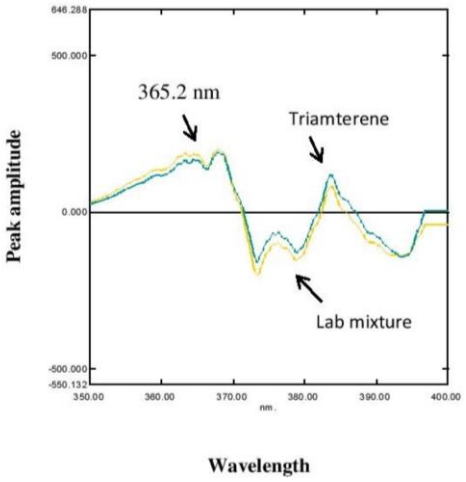

Fig. 9. First derivative of ratio spectra for Triamterene (4.0 µg/mL) with Laboratory prepared mixture (8.0 µg/mL of Xipamide and 4.0 µg/mL of Triamterene)

3.2. Method Validation

3.2.1. Linearity

Xipamide and Triamterene showed direct relation between concentrations and peak amplitude within range (1.0-10.0 µg/mL) and (1.0-16.0 µg/mL); respectively.

3.2.2. Accuracy

Xipamide and Triamterene concentrations were determined using the corresponding regression equation. The obtained results showed

good accuracy with mean recovery less than 100.90 and standard deviation less than 1.53 for both drugs as displayed in **Table 1**.

Table 1. Validation parameters for Spectrophotometric determination of Xipamide and Triamterene

Parameter	Xipamide				Triamterene		
	First derivative	Ratio difference	Derivative ratio	Zero order	First derivative	Ratio difference	Derivative ratio
Linearity :							
Range (µg/mL)		1.0-10.0 µg/mL				1.0-16.0 µg/mL	
Intercept	0.0005	0.0037	0.0135	0.0597	0.0011	0.882	19.687
Slope	0.0128	0.0521	0.0654	0.0758	0.0305	0.7861	36.077
Correlation coefficient(r)	0.9996	0.9999	0.9997	0.9999	0.9997	0.9999	0.9998
SD of the residuals	0.000935	0.00191	0.003623	0.003679	0.002829	0.049757	3.094408
SE of intercept	0.000813	0.001663	0.003152	0.002702	0.002078	0.036545	2.27275
Slope (X coefficient)	0.012774	0.052096	0.065361	0.075808	0.030532	0.786072	36.07661
SE of slope (X coefficient)	0.000134	0.000274	0.000519	0.000326	0.000250	0.004405	0.273938
Accuracy (mean±SD)	99.55± 0.907	99.0± 0.820	100.19± 1.089	99.43± 0.939	100.82± 0.473	99.90± 1.529	100.49± 0.707
Precision:							
Repeatability*	0.813	1.373	1.179	0.884	1.034	0.900	1.045
Intermediate precision**	1.272	1.506	1.263	1.028	1.136	1.274	1.194
LOD (µg/mL)***	0.241	0.121	0.183	0.160	0.306	0.209	0.283
LOQ (µg/mL)****	0.730	0.367	0.554	0.485	0.928	0.633	0.858

*The intra-day precision (n= 3), average of three different concentrations (2.0, 4.0 and 6.0 µg/mL) and (4.0, 6.0 and 10.0 µg/mL) for both Xipamide and Triamterene; respectively repeated three times within day

**The inter-day precision (= 3), average of three different concentrations (2.0, 4.0 and 6.0 µg/mL) and (4.0, 6.0 and 10.0 µg/mL) for both Xipamide and Triamterene; respectively repeated three times in three successive days

Limit of detection and* limit of quantitation are determined via calculations

LOD= (SD of the response/slope) × 3.3.

LOQ= (SD of the response/slope) × 10

3.2.3. Precision

On three successive days and within a day, different concentrations of Xipamide (2.0, 4.0, and 6.0 µg/mL) and Triamterene (4.0, 6.0, and 10.0 µg/mL) were analyzed to check Precision as illustrated in **Table 1.**

3.2.4. Specificity

Specificity was done by using different concentration ratios of Xipamide and Triamterene within linearity. The mean recovery results of Xipamide and Triamterene by the suggested spectrophotometric techniques were presented in **Table 2** showing excellent selectivity.

Table 2. Determination of Xipamide and Triamterene in the laboratory prepared mixtures by Spectrophotometric methods

Binary mixture Xipamide: Triamterene ratios	First derivative %Recovery*		Ratio difference %Recovery*		Derivative ratio %Recovery*		Zero order %Recovery*
	Xipamide	Triamterene	Xipamide	Triamterene	Xipamide	Triamterene	Triamterene
3: 1	98.75	99.75	101.75	99.92	98.75	99.42	98.42
2: 1	99.67	101.42	99.67	98.25	100.00	100.33	100.42
1: 1	98.56	100.56	99.00	98.89	101.89	101.33	99.11
1: 2	98.13	98.50	101.75	98.75	100.50	98.50	101.00
1: 3	100.83	100.00	99.67	99.50	98.17	100.00	98.50
Mean ± SD	99.19±1.076	100.05±1.076	100.37±1.291	99.06±0.655	99.86±1.470	99.92±1.052	99.49±1.163

*Average of three determinations

Table 3. Statistical comparison of the results of the proposed Spectrophotometric methods, the Reported and the Official methods for determination of Xipamide and Triamterene

Value	First derivative	Ratio difference	Derivative ratio	Reported method*	Zero order	First derivative	Ratio difference	Derivative ratio	Official method**
	Xipamide	Xipamide	Xipamide	Xipamide	Triamterene	Triamterene	Triamterene	Triamterene	Triamterene
Mean	99.55	99.00	100.19	99.61	99.43	100.82	99.90	100.49	100.05
SD	0.907	0.820	1.089	1.206	0.939	0.473	1.529	0.707	0.844
N	5	5	5	4	5	5	5	5	4
V (variance)	0.823	0.672	1.186	1.454	0.882	0.224	2.338	0.500	0.712
Student's-t test*** (2.365)	0.083	0.864	0.748		1.041	1.631	0.187	0.834	
F-test***	1.768 (6.590)	2.163 (6.590)	1.226 (6.590)		1.239 (9.120)	3.184 (6.590)	3.282 (9.120)	1.425 (6.590)	

*Ratio subtraction spectrophotometric method **[24]** for determination of Xipamide

BP determination of Triamterene by Potentiometric method **[3]

***The values in the parenthesis are the corresponding theoretical values of t and F at (p=0.05). No significant difference by using one way ANOVA with F equals 1.176 (F_{crit}=3.287), F equals 1.518 (F_{crit}=2.895) and p equals (0.352, 0.237) for Xipamide and Triamterene; respectively

3.2.5. Statistical analysis

The proposed spectrophotometric methods were statistically compared to the Ratio subtraction spectrophotometric technique for Xipamide **[24]** and the Official Potentiometric method for Triamterene **[3]** according to ICH guidelines **[31, 32]** as illustrated in **Tables 3** with insignificant changes in the produced results.

3.2.6. Robustness

The robustness of the proposed methods was evaluated by studying different parameters including different devices (Libra, biochrom, England), different lots of solvent (Merck, sigma, and Honeywell), and different wavelengths. The obtained results were acceptable and displayed in **Table 4**

Table 4. Robustness results of the proposed methods

Parameters	First derivative		Ratio difference		Derivative ratio	
	Xipamide	Triamterene	Xipamide	Triamterene	Xipamide	Triamterene
	Recovery ± RSD		Recovery ± RSD		Recovery ± RSD	
Different device	101.35±0.541	100.60±0.384	99.05±0.620	100.57±0.321	98.92±0.672	99.93±0.462
Lots of solvent	101.13±0.372	100.97±0.282	100.12±0.623	100.74±0.698	98.92±0.736	100.08±0.377
Wavelength*	100.91±1.165	100.51±0.411	99.58±1.099	100.81±0.238	99.35±0.922	100.39±0.773

*peak amplitude was recorded at the selected wavelengths ± 1.0 for the proposed methods except for first derivative method for determination of Xipamide at ±0.2

Table 5. Analysis of pharmaceutical dosage form (Epitens®) and application of standard addition technique by the proposed Spectrophotometric methods for determination of Xipamide

First derivative				Ratio difference				Derivative ratio			
Epitens® Recovery* % ± SD	Standard addition			Epitens® Recovery* % ± SD	Standard addition			Epitens® Recovery* % ± SD	Standard addition		
	Pure taken µg/mL	Pure found µg/mL	Recovery %*		Pure taken µg/mL	Pure found µg/mL	Recovery %*		Pure taken µg/mL	Pure found µg/mL	Recovery %*
98.33±0.577	**0.50**	0.49	98.00	99.33± 1.155	0.50	0.50	100.00	99.33± 0.577	0.50	0.50	**100.00**
	1.00	1.01	101.00		1.00	0.99	99.00		1.00	1.01	**101.00**
	2.00	2.03	101.50		2.00	1.98	99.00		2.00	2.00	**100.00**
	Mean ± SD		100.17± 1.893		**Mean±SD**		99.33± 0.577		**Mean±SD**		100.33± 0.577

*Average of three determinations

3.3. Application to a pharmaceutical formulation

Xipamide and Triamterene were successfully determined in pharmaceutical form (Epitens®) using the suggested spectrophotometric techniques without any interference from the excipients in tablets. There was no need for pretreatment or any extraction of the sample. The obtained mean recoveries were acceptable for Xipamide and Triamterene. Standard addition technique was applied to validate the developed methods as displayed in **Tables 5 and Table 6**. Also, a comparison between the proposed and the reported methods were shown in **Table 7**.

Conclusion

UV spectrophotometric methods play an important role in the determination and analysis of many components in analytical fields due to

many advantages such as accuracy of the device, is simple, ease of operation, and low solvent consumption. Determination of Xipamide and Triamterene by the proposed spectrophotometric methods showed high selectivity in pure forms and pharmaceutical form.

Table 6. Analysis of pharmaceutical dosage form (Epitens®) and application of standard addition technique by the proposed Spectrophotometric methods for determination of Triamterene

Zero order				First derivative				Ratio difference				Derivative ratio			
Epitens® Recovery * % ±SD	Standard addition			Epitens® Recovery * % ±SD	Standard addition			Epitens® Recovery * % ±SD	Standard addition			Epitens® Recovery * % ± SD	Standard addition		
	Pure taken µg/mL	Pure found µg/mL	Recovery %*		Pure taken µg/mL	Pure found µg/mL	Recovery %*		Pure taken µg/mL	Pure found µg/mL	Recovery %*		Pure taken µg/mL	Pure found µg/mL	Recovery %*
	1.50	1.51	100.67		**1.50**	1.51	100.67		**1.50**	1.53	102.00		**1.50**	1.52	101.33
96.67± 1.858	**3.00**	2.98	99.33	100.67 ± 1.000	**3.00**	2.98	99..33	96.22±1. 169	**3.00**	3.05	101.67	99.33±1. 732	**3.00**	2.95	98.33
	6.00	6.02	100.33		**6.00**	5.97	99.50		**6.00**	6.12	102.00		**6.00**	5.91	98.50
	Mean±SD		100.11± 0.697		**Mean±SD**		99.83 ±0.730		**Mean±SD**		101.89± 0.191		**Mean±SD**		99.39± 1.685

*Average of three determinations

Table 7. A comparison between the proposed and the reported methods

Parameters	Xipamide					Triamterene				
	First derivative	Ratio difference	Derivative ratio	Reported spectro	Reported HPLC	First derivative	Ratio difference	Derivative ratio	Reported spectro	Reported HPLC
LOD	0.241	0.121	0.183	0.76	0.09	0.306	0.209	0.283	0.81	0.06
selectivity	99.19± 1.076	100.37± 1.291	99.86± 1.470	100.3± 1.29	100.75± 0.69	100.05± 1.076	99.06± 0.655	99.92± 1.052	100.3± 0.75	100.92± 0.44
Linearity range µg/mL^{-1}		1-10		2-10	0.1–20		1-16		2-12	0.2–50
Cost and greeness	Low cost and green as methanol is more green than acetonitrile				High cost	Low cost and green as methanol is more green than acetonitrile				High cost

Declarations

Ethics approval and consent to participate

Not applicable

Consent to publish

Not applicable

Availability of data and materials

The data generated or analyzed during this study all are included in the main manuscript.

Competing interests

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding statement

No funding source was received

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