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Article

Comparative study of analytical methods by direct and first-derivative UV spectrophotometry for evaluation of losartan potassium in capsules

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Losartan potassium is an antihypertensive non-peptide agent, which exerts its action by specific blockade of angiotensin II receptors. The aim of the present study was the validation and application of analytical methods for the quality control of losartan potassium 50 mg in pharmaceutical capsules, using direct and first-derivative UV spectrophotometry. Based on losartan potassium spectrophotometric characteristics, a signal at 205 nm of the zero-order spectrum and a signal at 234 nm of the first-derivative spectrum, were found adequate for quantification. The results were used to compare these instrumental techniques. The linearity between the signals and concentrations of losartan potassium in the ranges of 3.0-7.0 mg L^{-1} and 6.0-14.0 mg L^{-1} for direct and first-derivative spectrophotometry in aqueous solutions, respectively, presented a correlation coefficient (r) of 0.9999 in both cases. The methods were applied for losartan potassium in capsule dosage obtained from local pharmacies, and were shown to be efficient, easy to apply and low cost. These methods do not use polluting reagents and require relatively inexpensive equipment.

Uniterms: Losartan potassium. Direct UV spectrophotometry. First-derivative UV spectrophotometry.

O losartano potássico é um agente anti-hipertensivo não peptídico, que exerce sua ação por bloqueio específico dos receptores da angiotensina II. Este trabalho propôs a validação e aplicação de métodos analíticos orientados ao controle de qualidade de losartano potássico 50 mg na forma farmacêutica cápsula, utilizando a espectrofotometria direta e derivada de primeira ordem na região do UV. Baseado nas características espectrofotométricas de losartano potássico, um sinal a 205 nm do espectro de ordem zero e um sinal a 234 nm do espectro de primeira derivada foram adequados para a quantificação. Os resultados foram usados para comparar essas duas técnicas instrumentais. O coeficiente de correlação entre as respostas e as concentrações de losartano potássico na faixa de 3,0-7,0 mg L^{-1} e 6,0-14,0 mg L^{-1} para espectrofotometria direta e derivada de primeira ordem em solução aquosa, respectivamente, foi de (r) of 0,9999 para ambos os casos. Os métodos foram aplicados para quantificação de losartano potássico em cápsulas obtidas de farmácias de manipulação locais e demonstraram ser eficientes, fáceis de aplicar e de baixo custo. Além disso, não necessitam de reagentes poluentes e requerem equipamentos economicamente viáveis.

Unitermos: Losartano potássico. Espectrofotometria direta. Espectrofotometria derivada de primeira ordem.

INTRODUCTION

Losartan potassium (Figure 1) is an imidazole derivative, chemically described as 2-butyl-4-chloro-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt. Losartan was developed by DuPont-Merck laboratories as a potent non-peptide angiotensin II receptor (type AT_1) antagonist for hypertension treatment (Barreiro, Fraga, 2001; Korolkovas, 2007). Losartan is administered in its active form and

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is partially converted into an active metabolite which is responsible for the drug's prolonged pharmacological effect. The therapeutic efficacy of losartan, as well as its renal and antihypertensive effects, seems to be similar to those of angiotensin converting enzyme (ACE) inhibitors. However, its adverse effects are different, mainly regarding coughing, whose incidence is significantly lower compared with ACE inhibitors (Oigman, 1996). Losartan potassium is a light yellow solid with a molecular weight of 461; melting point of 183.5-184.5 ºC; aqueous solubility of 3.3 mg mL^{-1} at pH 7.8 and pKa value of 4.9 (Lastra *et al*., 2003; Williams *et al*., 1996).

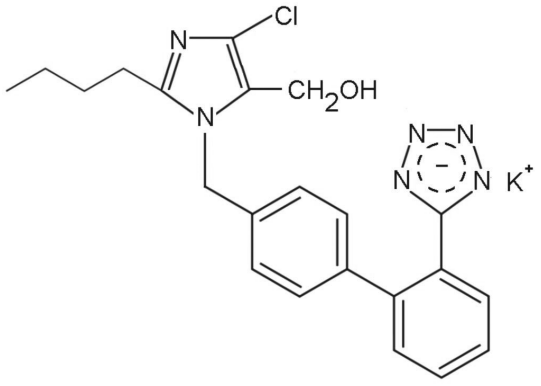

FIGURE 1 - Losartan potassium chemical structure.

The literature has described several analytical methods for losartan potassium determination in tablets, when used as a single active principle or in combination with hydrochlorothiazide, using high performance liquid chromatography (HPLC), capillary electrophoresis, supercritical fluid chromatography, high performance thin layer chromatography and derivative ultraviolet spectrophotometry (Ansari *et al*., 2004; Erk, 2001; Lastra *et al*., 2003; Mccarthy *et al*., 1998; Williams *et al*., 1996). For losartan potassium determination in pharmaceutical capsules, two HPLC methods have been reported (Bonfilio *et al*., 2009; Maio, Dias, Bergold, 2005).

However, to date, no analytical method has been described in the literature that uses direct or first-derivative spectrophotometry for quantitative analysis of losartan potassium in pharmaceutical capsules, which is frequently formulated in magistral pharmacies. Moreover, no pharmacopoeia have yet described a monograph for the finished product.

The aim of the present study was to investigate the validation and application of analytical methods for quality control of 50 mg losartan potassium pharmaceutical capsules, using both direct and first-derivative UV spectrophotometry.

MATERIALS AND METHODS

Pharmaceutical products, chemical reference substance and solvent

Pharmaceutical capsules containing 50 mg of losartan potassium were kindly provided by three magistral pharmacies localized in the region of Alfenas, Minas Gerais state, Brazil, and were coded as products A, B and C. The capsules had a four-month validity period (January 26th, 2008; December 6th, 2007 and June 12th, 2007, respectively). The capsules were described as containing the following pharmaceutical grade excipients: magnesium stearate (All-Chemistry and YOD, Brazil); aerosol (All-Chemistry and Ely Martins, Brazil); sodium dodecyl sulphate (All-Chemistry e Gerbrás, Brazil); talc (DEG, Labsynth and Pharma Nostra, Brazil); starch (DEG, Brazil) and microcel MC-102 1 (DEG, Brazil).

Losartan potassium salt of 98.90% purity supplied by IPCA Laboratories Limited (Athal, India), lot 5069LB2RI and expiration date of 2009/09 was used as the chemical reference substance. Distilled water was used as the solvent.

Equipment

The following equipment was used: Shimadzu UV-1601 (Kyoto, Japan) recording double beam UV–visible spectrophotometer connected to a computer running Shimadzu UVPC version 3.9 software; ultrasonic bath model USC2800A (Unique, São Paulo, Brazil); analytical balance model 410 (Kern, Kern, Germany); pHmeter PA 200 (Marconi S.A., Piracicaba, Brazil); water distiller system model 425 (Nova Técnica, Piracicaba, Brazil) and quantitative filter paper (Vetec, Rio de Janeiro, Brazil).

Losartan potassium stock standard solution

Stock standard solution of losartan potassium was prepared by accurately weighing 25.0 mg of losartan potassium reference substance into a 50 mL volumetric flask and adding 40 mL of distilled water. The flask was sonicated for 10 min, filled to volume with distilled water, and the solution was then filtered through quantitative filter paper.

Capsule solution

From the average weight obtained of 20 capsules of each product (by subtracting the weight of the shell from the weight of the full 20 capsules), a weight equivalent to 25.0 mg of losartan potassium was accurately transferred

into a 50 mL volumetric flask to which 40 mL of distilled water was added. The flasks were coded as A, B and C, sonicated for 10 min and filled to volume with distilled water. Subsequently, the solutions were filtered through quantitative filter paper.

Spectrophotometric measurements

Zero-order spectra were obtained in the UV range 300-200 nm with a fixed slit width of 2 nm, scan speed of about 3200 nm min^{-1} and 0.2 nm data interval. The first-derivative spectra were obtained through instrumental electronic differentiation (UVPC version 3.9 software) using a delta lambda of 8 nm. The amplitude values, obtained in the first-derivative spectra, were arbitrary units of the distance from the central zero base line to the signal obtained at 234 nm. The spectrophotometric measurements were recorded using distilled water as a blank solution.

Method validation (Barros, Hirata, 2002; Brasil, 2003; F. Bras., 1988; ICH, 1995; INMETRO, 2000; Ribani, 2004; USP, 2007).

Selectivity

Selectivity was evaluated by zero-order and the first-derivative absorption spectra analyses at 5.0 mg L^{-1} and 10 mg L^{-1}, respectively, in the range 300-200 nm using losartan potassium and pharmaceutical capsule products A, B and C solutions. This procedure was also carried out using three excipient mixtures containing the same quantitative composition as the pharmaceutical products A, B and C.

Linearity

For the linearity study, the losartan potassium stock solution was diluted as appropriate with distilled water to obtain final losartan potassium concentrations of 3.0, 4.0, 5.0, 6.0 and 7.0 mg L^{-1} in five replicates. The analytical curve was produced by plotting drug concentration versus the absorbance values at 205 nm. A second analytical curve for the final concentrations of 6.0, 8.0, 10.0, 12.0 and 14.0 mg L^{-1} was constructed by plotting drug concentration versus amplitude values of the first-derivative spectra at 234 nm.

Precision

Precision was evaluated with respect to both repeatability and intermediate precision. Repeatability was evaluated by analyzing six losartan potassium work standard solution replicates using distilled water as the solvent. The solutions were analyzed using both direct and first-derivative UV spectrophotometry at 5.0 mg L^{-1} and 10.0 mg L^{-1}, respectively. This procedure was repeated over a short period of time on the same day.

Intermediate precision was also evaluated by analyzing six independent losartan potassium solutions, where this procedure was repeated on different days by different analysts. The R.S.D values for determinations were also calculated.

Accuracy

Accuracy was determined by recovery of known amounts of losartan potassium work standard added to the pharmaceutical capsule products A, B and C. In the direct spectrophotometric method, products A, B and C sample solutions were prepared in triplicate at a losartan potassium concentration of 2.5 mg L^{-1}. Adequate standard solution volumes were added to the sample solutions to obtain final concentrations of 4.0, 5.0 and 6.0 mg L^{-1}. In the first-derivative spectrophotometric method, products A, B and C sample solutions were prepared in triplicate at a concentration of 5.0 mg L^{-1}. Adequate standard solution volumes were added to the sample solutions to obtain final concentrations of 8.0, 10.0, and 12.0 mg L^{-1}. The resulting mixtures were analyzed by the proposed methods and the percentage recoveries were calculated.

Robustness

In order to verify the method's resilience to slight and deliberate variations in the analytical parameters, losartan potassium solutions at 5.0 and 10.0 mg L^{-1} were analyzed by direct and first-derivative UV spectrophotometric methods, respectively. The robustness was assessed by comparison of the results obtained under standard conditions against those obtained using different cuvettes and at different room temperatures (Turning off the air conditioner).

Detection and quantitation limits

The detection (DL) and quantitation (QL) limits of the spectrophotometric methods were calculated using Equations (1) and (2):

$$DL = 3(S.D/a) \quad (1)$$

$$QL = 10(S.D/a) \quad (2)$$

where S.D. is the 20 spectrophotometric blank reading (distilled water) standard deviation and a is the calibration curve slope obtained in the linearity study.

Aqueous stability

The losartan potassium stock solution was diluted to concentrations of 5.0 and 10.0 mg L^{-1} using distilled water and analyzed by direct and first-derivative UV spectrophotometry, respectively. The analyses were carried out in the periods of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 12 and 24 hours after solution preparation.

Average weight determination

In order to determine the mean weight of pharmaceutical capsule products A, B and C, 20 capsules were weighed and then capsule content removed. The empty shells were weighed, and the content average weight obtained by subtracting the weight of the shell from the weight of the full 20 capsules, as recommended by the Brazilian Pharmacopoeia (F. Bras., 1988). The R.S.D values for determinations were then calculated.

Pharmaceutical capsule assay

The validated analytical methods were applied to determine losartan potassium content for the pharmaceutical capsule products A, B and C using both direct and first-derivative UV spectrophotometric methods at 5.0 mg L^{-1} and 10.0 mg L^{-1}, respectively. The results were obtained by comparing the sample spectrophotometric measurements (n=5) with those obtained from losartan potassium standard solutions (n=3) at the same concentration levels.

Content uniformity determination

The content of ten capsules of each product was individually transferred to 100 mL volumetric flasks and 40 mL of distilled water was added. The flasks were sonicated for 10 min and filled to volume with distilled water. The solution was filtered with quantitative filter paper, diluted to concentrations of 5.0 and 10.0 mg L^{-1} and analyzed by direct and first-derivative UV spectrophotometric methods, respectively, by comparing the sample spectrophotometric measurements with those obtained from losartan potassium standard solutions (n=3) at the same concentration levels.

RESULTS AND DISCUSSION

Lastra and coworkers studied losartan potassium solution spectrophotometric behavior at various pH values and concluded that a pH variation from 5 to 9 did not alter losartan potassium spectral characteristics (Lastra *et al*., 2003). Distillation is the most common process used in magistral pharmacies for preparing the purified water to be used in the drug-manipulation and quality control activities, and the recommended pH of distilled water is between 5.0 and 7.0 (USP, 2007). The use of water as a solvent in chemical analysis laboratories has many advantages in terms of environmental aspects, cost and safety compared with the use of an organic solvent. Therefore, considering the losartan potassium aqueous solubility of 3.3 mg mL^{-1} (Lastra *et al*., 2003; Williams *et al*., 1996) and the factors mentioned above, the use of distilled water as solvent was deemed adequate for our validation purposes, making the methods simple and convenient.

The zero-order spectrum of losartan potassium solution at 5.0 mg L^{-1} in distilled water showed maximum drug absorption wavelength at 205 nm with absorbance values of 0.5 (Figure 2). Therefore, the absorbance values at 205 nm were used in the direct spectrophotometric method while 5.0 mg L^{-1} was fixed as the 100 percent level on the analytical curve.

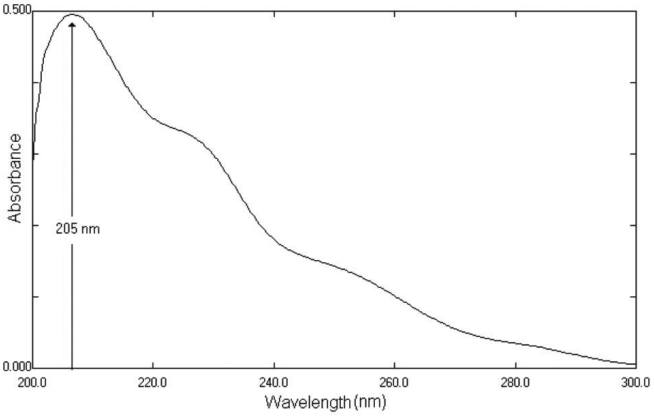

FIGURE 2 – Losartan potassium zero-order absorption spectrum at 5 mg L^{-1} using distilled water as solvent.

Previously published studies justified the use of first-derivative spectrophotometry for losartan potassium determination in tablets by stating that the maximum drug absorption wavelength is close to 205 nm and that no absorption peak is observed at other wavelengths (Lastra *et al*., 2003). Moreover, the interference from the tablet excipients verified at close to 205 nm, precludes the analytical use of zero-order spectrophotometry for losartan potassium determination in tablets (Ansari *et al*., 2004).

The absorption spectrum differentiation through derivative spectrophotometry does not increase the original spectrum information, but derivative operation reduces the broad band intensity, yielding overlapping peak resolution enhancements, obeying Beer's law (Paschoal et al., 2003).

The first-derivative spectrum, obtained through instrumental electronic differentiation of the losartan potassium zero-order absorption spectrum, shows an intense negative peak at 234 nm (Figure 3). At this wavelength, a losartan potassium solution of 5.0 mg L^{-1} shows absorbance values of 0.25. For the subsequent analyses, 10.0 mg L^{-1} was fixed at the 100 percent level of the analytical curve in the first-derivative spectrophotometric method in order to produce a analytical signal that corresponded to those observed under the direct spectrophotometric method.

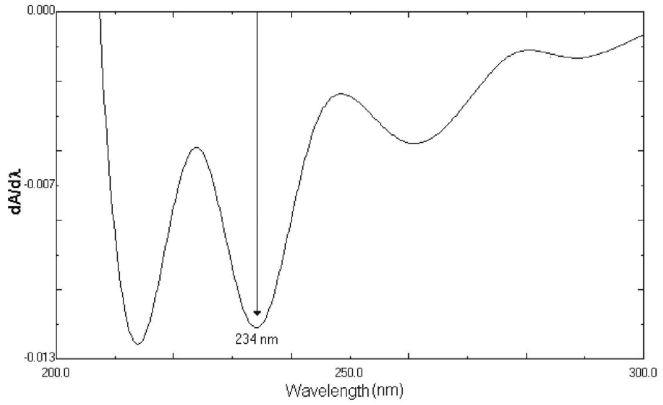

FIGURE 3 – Losartan potassium first-order absorption spectrum at 5 mg L^{-1} using distilled water as solvent.

In these experiments, formulation excipients of capsules A, B and C did not present absorbance at 205 nm, demonstrating the direct spectrophotometric method selectivity for losartan potassium analysis in pharmaceutical capsules (Figure 4). Use of direct spectrophotometry is advantageous because it can be used by analytical laboratories that do not have access to a **spectrophotometer** with derivative mode. However, direct spectrophotometric

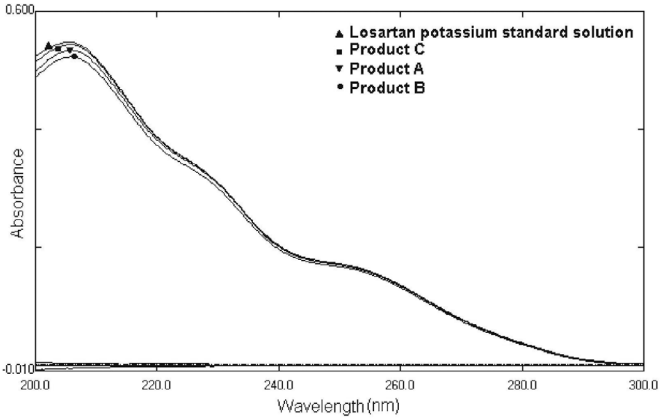

FIGURE 4 – Zero-order absorption spectra of standard losartan potassium aqueous solution at 5 mg L^{-1}, capsule products A, B and C at 5 mg L^{-1} and A, B and C product excipients.

method selectivity was confirmed using only the following excipients: magnesium stearate, aerosil, sodium dodecyl sulfate, talc, starch and microcel MC-102 1. Because there is a considerable variety in the excipients used in the drug-manipulation process, the direct spectrophotometric method selectivity should be further verified for pharmaceutical capsules containing different excipients than those tested in this study, which could be considered a drawback of this method.

The first-derivative spectra analyses showed that capsule A, B and C formulation excipients did not interfere in the first-derivative spectrophotometric method (Figure 5).

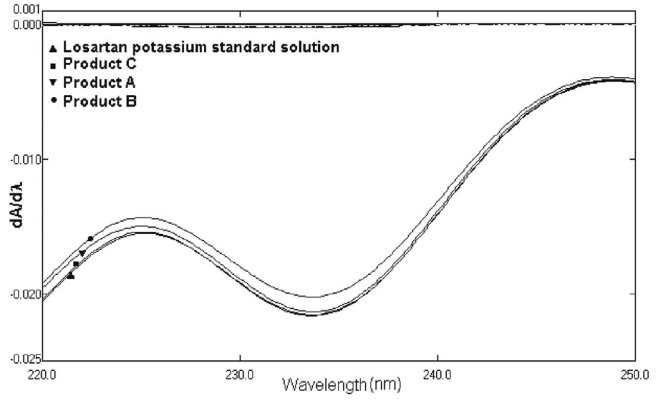

FIGURE 5 – First-derivative absorption spectra of standard losartan potassium aqueous solution at 10 mg L^{-1}, capsule products A, B and C at 10 mg L^{-1} and A, B and C product excipients.

Although the spectrophotometric methods are not effective for identifying or quantifying impurities and degradation products, the drug substance used in the losartan potassium capsule manipulation should have been adequately analyzed and an analysis certificate should issued by the supplier guaranteeing compliance with the acceptance criteria in accordance with the drug substance monograph on losartan potassium provided by the United States Pharmacopoeia, which establishes a 0.2% limit for any individual impurity and no more than 0.5% of total impurities (USP, 2007).

The linearity results were evaluated by linear regression analysis based on the minimum-square method. The correlation coefficient value obtained from direct spectrophotometric method over the range 3.0 to 7.0 mg L^{-1} was r=0.9999 and the calibration equation was: $A = 0.095C - 0.0048$. From the first-derivative spectrophotometry, the correlation coefficient value obtained over the range 6.0 to 14.0 mg L^{-1} was r=0.9999 and the calibration equation was $dA/d\lambda = -0.0022C - 0.0004$. In both cases, the

relative standard deviation of each point (n=5) was lower than 2%. The results show linear correlation between analytical responses and drug concentration.

Overall relative standard deviations for repeatability and intermediate precision were 0.95 % and 0.75 % using direct spectrophotometry. In the case of first-derivative spectrophotometry, the overall relative standard deviations for repeatability and intermediate precision were 0.95 % and 0.75 %. These experimental results confirmed good precision of the methods when performed on the same or different days by different analysts. Relative standard deviations lower than 5% are considered acceptable (Brasil, 2003).

The spectrophotometric analytical methods showed good accuracy, evaluated by the recovery test (Tables I and II). The mean recovery percentages of 99.00, 101.74 and 98.91 for products A, B and C, respectively, using direct spectrophotometry, and 101.19, 99.86 and 101.56 % for products A, B and C using first-derivative spectrophotometry, corroborated satisfactory recovery. Recovery values from 98.0 to 102.0 % are deemed acceptable.

The robustness test examines the experimental conditions for the method, and the potentially responsible factors such as experimental and environmental conditions, to be taken into account during method development given that changes in the optimal conditions can result in significant errors. For both analytical methods, the low RSD values demonstrated that the analysis factors (cuvette and room temperature) did not have a significant effect on analytical responses (Tables I and II).

The direct spectrophotometry detection and quantitation limits were found to be 0.01 and 0.04 mg L^{-1}, respectively, whereas detection and quantitation limits for first-derivative spectrophotometry were found to be 0.07 and 0.23 mg. L^{-1}, respectively. These results demonstrated that the analyses were being performed in a region above the quantitation limit value.

Aqueous stability of losartan potassium was checked by evaluation of direct and first-derivative spectra at regular time intervals up to 24 hours, and yielded no significant alteration in spectral characteristics (Figures 6 and 7).

The average weights of pharmaceutical capsule products A, B and C were 132.33 mg, 155.12 mg and 158.02 mg, respectively. All products showed acceptable weight values as stipulated by the Brazilian Pharmacopoeia, which establishes that capsules of ≤ 300 mg may not deviate by more than 10.0 % w/w from the average weight (F. Bras., 1988).

TABLE I – Direct spectrophotometry validation values for losartan potassium evaluation in capsules

Parameter	Condition	Concentration level (mg L^{-1})	Absorbance mean Values	R. S. D. (%)	Mean recovery (%)
Precision					
Repeatability	Series 1	5.0	0.482	0.79 (n=6)	
	Series 2	5.0	0.482	1.11 (n=6)	
Intermediate	Day 1	5.0	0.490	0.70 (n=6)	
	Day 2	5.0	0.487	0.79 (n=6)	
Accuracy	Sample A	4.0	0.377	0.55 (n=3)	
		5.0	0.477	0.36 (n=3)	99.00
		6.0	0.570	0.62 (n=3)	
	Sample B	4.0	0.372	0.82 (n=3)	
		5.0	0.466	0.33 (n=3)	101.74
		6.0	0.563	0.00 (n=3)	
	Sample C	4.0	0.396	0.39 (n=3)	
		5.0	0.498	0.83 (n=3)	98.91
		6.0	0.596	0.86 (n=3)	
Robustness	Cuvette 1	5.0	0.599		
	Cuvette 2	5.0	0.599	0.12 (n=3)	
	Air conditioner turned off	5.0	0.600		

TABLE II – First-derivative spectrophotometry validation values for losartan potassium evaluation in capsules

Parameter	Condition	Concentration level (mg L^{-1})	Response Mean Values (dA/dλ)	R. S. D. (%)	Mean recovery (%)
Precision					
Repeatability	Series 1	10.0	-0.0204	0.92 (n=6)	
	Series 2	10.0	-0.0208	0.86 (n=6)	
Intermediate	Day 1	10.0	-0.0219	0.53 (n=6)	
	Day 2	10.0	-0.0203	0.99 (n=6)	
Accuracy	Sample A	8.0	-0.0148	0.39 (n=3)	
		10.0	-0.0188	0.31 (n=3)	101.19
		12.0	-0.0225	0.26 (n=3)	
	Sample B	8.0	-0.0159	0.00 (n=3)	
		10.0	-0.0200	0.50 (n=3)	99.86
		12.0	-0.0237	0.24 (n=3)	
	Sample C	8.0	-0.0163	0.71 (n=3)	
		10.0	-0.0202	0.00 (n=3)	101.56
		12.0	-0.0241	0.24 (n=3)	
Robustness	Cuvette 1	10.0	-0.0221		
	Cuvette 2	10.0	-0.0222	0.21 (n=3)	
	Air conditioner turned off	10.0	-0.0221		

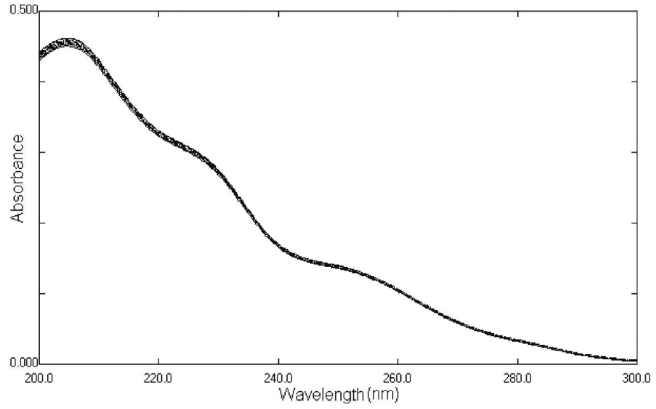

FIGURE 6 – Aqueous stability evaluation of 5.0 mg L^{-1} losartan potassium aqueous solutions using zero-order spectra at regular time intervals up to 24 hours.

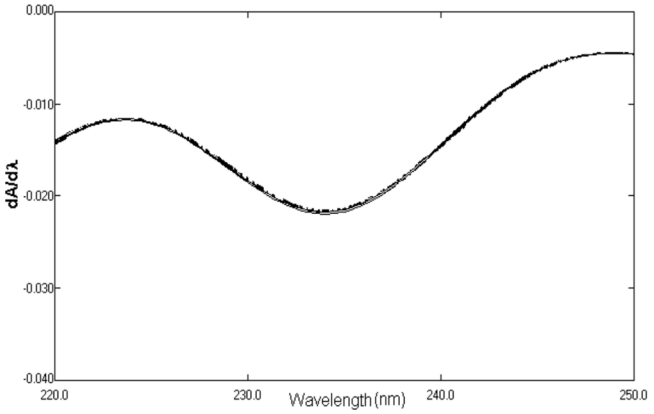

FIGURE 7 – Aqueous stability evaluation of 10.0 mg L^{-1} losartan potassium aqueous solutions using first-derivative absorption spectra at regular time intervals up to 24 hours.

The methods were applied to losartan potassium pharmaceutical capsule products A, B and C , and the drug percentage values related to label claim are shown in Table III. The results show that the drugs assayed were in accordance with Brazilian Pharmacopoeia, which establishes limits between 90 and 110 % of the labeled amount for finished products (F. Bras., 1988).

The content uniformity test showed that individual active content values and relative standard deviations of pharmaceutical capsule products A and C (n=10) were acceptable and met the requirements. Individual values of active content for sample B were found to lie in the range of 85–115%; however the relative standard deviation observed was higher than 6 % (Table III). The individual

TABLE III – Losartan potassium assay and content uniformity test in pharmaceutical capsule products A, B and C

	Product A		Product B		Product C	
Spectrophotometry	Direct	First-Derivative	Direct	First-Derivative	Direct	First-Derivative
Capsules assay						
Losartan (%)	98.06	99.18	96.08	94.54	99.25	99.61
R. S. D. (%)	1.10 (n=5)	0.78 (n=5)	1.93 (n=5)	1.16 (n=5)	1.00 (n=5)	0.61 (n=5)
Losartan (mg)	49.03	49.59	48.04	47.27	49.63	49.81
Content uniformity						
Losartan (%)	98.85	100.13	96.04	99.70	100.51	101.02
R. S. D. (%)	3.40 (n=10)	3.00 (n=10)	6.08 (n=10)	6.95 (n=10)	3.37 (n=10)	4.47 (n=10)
Losartan (mg)	49.40	50.10	48.00	49.90	50.30	50.50

results should lie between 85 and 115 % of label claim, with a R. S. D. < 6.0 % (F. Bras., 1988).

The proposed analytical methods were compared using individual active content values obtained from the content uniformity test. The statistical analysis was carried out using a 10×3×2 factorial design (ten active content values, three products and two methods). Data were submitted to analysis of variance followed by Tukey's test at a 0.05 significance level. The parameters of pharmaceutical capsule products (A, B and C) and analytical methods (direct and first-derivative spectrophotometry) were compared. The results showed no significant active content values differences among products A, B and C, or between direct and first-derivative spectrophotometric methods ($p>0.05$).

CONCLUSIONS

Both direct and first-derivative spectrophotometric methods were shown to be efficient, low cost and easy to apply for losartan potassium determination in pharmaceutical capsules. They do not use polluting reagents and require relatively inexpensive equipment.

All validation parameters were found to be highly satisfactory, indicating linearity, selectivity, precision, accuracy, robustness and adequate detection and quantification limits of both direct and first-derivative spectrophotometric methods. The methods were therefore shown to be suitable for losartan potassium evaluation of pharmaceutical capsules and for routine use in quality control laboratories.

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