STABILITY INDICATING DERIVATIVE SPECTROPHOTOMETRIC METHOD FOR DETERMINATION OF TRANDOLAPRIL IN BULK AND IN FORMULATION[**]

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Trandolapril is an oral angiotensin-converting enzyme (ACE) inhibitor approved by the USFDA for the therapy of hypertension and congestive heart failure. This paper describes the validation of zero- and first-order derivative UV spectrophotometric methods for the estimation of trandolapril in bulk and in its marketed tablet formulation. Preliminary spectrophotometric determination of the drug was carried out in phosphate buffer pH 2.0 or 0.1 N HCl. A total of 17 parametric method variants were investigated out of which three variants employing peak–zero (P–0) and peak–peak (P–P) techniques were validated with respect to linearity, accuracy, precision, and robustness. The developed methods were also assessed for stability indicating potential in force degraded solutions. Linearity was observed in the concentration range of 1.0–70.0 μg/mL with an excellent correlation coefficient (r^2) ranging from 0.9981–0.9998. The limits of assay detection values were found for the range of 0.88–1.23 μg/mL, and quantitation limits ranged from 2.66–6.09 μg/mL for the proposed methods. The proposed methods were extended to the quantification of the drug in its marketed tablet formulation with good recoveries (90–98%).

Keywords: *angiotensin-converting enzyme, UV spectrophotometric method, trandolapril.*

УФ-СПЕКТРОФОТОМЕТРИЧЕСКИЕ МЕТОДЫ ПРОИЗВОДНЫХ ДЛЯ ОПРЕДЕЛЕНИЯ ТРАНДОЛАПРИЛА В НЕРАСФАСОВАННОМ ВИДЕ И В ТАБЛЕТИРОВАННОМ СОСТАВЕ

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Трандолаприл — пероральный ингибитор ангиотензинпревращающего фермента (АПФ), одобренный USFDA для лечения гипертонии и застойной сердечной недостаточности. Описана валидация УФ-спектрофотометрических методов производных нулевого и первого порядка для оценки трандолаприла в нерасфасованном виде и таблетированной форме. Предварительное спектрофотометрическое определение препарата проведено в фосфатном буфере pH 2.0 или 0.1 н HCl. Исследовано 17 вариантов параметрического метода, из которых три варианта с использованием методов пик-ноль (P-0) и пик-пик (P-P) проверены с точки зрения линейности, точности, прецизионности и устойчивости. Разработанные методы также оценены на стабильность, указывающую на возможность деградации растворов. Линейность наблюдалась в диапазоне концентраций 1.0–70.0 мкг/мл с хорошим коэффициентом корреляции r^2 = 0.9981–0.9998. Для предложенных методов LOD = 0.88–1.23 мкг/мл, LOQ = 2.66–6.09 мкг/мл. Предложенные методы использованы для количественного определения препарата в его таблетированной форме с выходом 90–98%.

Ключевые слова: *ангиотензинпревращающий фермент, УФ-спектрофотометрический метод, трандолаприл.*

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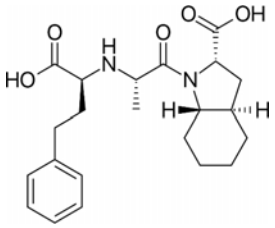
Introduction. Trandolapril, chemically, [(2*S*,3a*R*,7a*S*)-l-[(*S*)-N-[(*S*)-l-ethoxycarbonyl-3-phenylpropyl] alanyl] hexahydro-2-indolinecarboxylic acid], is an oral angiotensin-converting enzyme (ACE) inhibitor approved by the USFDA for the therapy of hypertension and congestive heart failure [1–3].



A survey of the available literature on trandolapril revealed very few reports on the analytical method development for this drug. Most of the available literature reports involve the application of chromatographic techniques for the estimation of the drug in bulk, in pharmaceutical dosage forms and in body fluids. These include the determination of the pure drug in bulk or in its pharmaceutical dosage forms by HPLC [4–8] and HPTLC [9]. The drug has also been estimated in drug combinations with other cardiovascular agents like verapamil, perindopril, indapamide, ramipril by HPLC [10–13], HPTLC [14]. Some chromatography-based stability-indicating methods have been reported for the drug by HPLC [15–17] and HPTLC [18] for drug analysis in bulk and in its pharmaceutical dosage form. A study on the stereochemical purity of trandolapril has been carried out by HPLC [19]. M. Dendeni [20] has reported impurity profiling and stress degradation study on the drug and elucidation of degradation pathway for by-products of the drug. A few reports on bioanalytical determination are also available which include the determination of trandolapril in human plasma by LC-MS [21–23]. A comparative pharmacokinetic study of trandolapril, its active metabolite, and verapamil in human plasma using HPLC–MS/MS has also been reported [24]. Derivatization of the drug with bromocresol green [25, 26] and bromothymol blue [26] has been used to develop colorimetric assays for trandolapril.

Derivative spectrophotometry is a versatile technique with enhanced sensitivity and selectivity compared to zero-order methods. Presently, there is only one report on UV spectrophotometric estimation of trandolapril [27] in combination with verapamil. However, there is no report on the complete exploration of zero-order and first-order derivative UV spectrophotometric spectra of trandolapril for the development and validation of zero-order or higher-order UV/visible spectrophotometric methods for this drug. Hence, the present work reports the development of simple, rapid, and reproducible zero-order and first-order derivative spectrophotometric methods for the quantification of trandolapril in bulk and in its marketed tablet formulation. The developed methods were validated with respect to various parameters outlined in the ICH guideline Q2 (R1) [28].

Experiment. Trandolapril was kindly gifted by Lupin Pharmaceuticals Pvt. Ltd., Goa (Batch number-G102965). All chemicals and reagents employed in the study were of analytical reagent (AR) grade and were purchased from Merck Laboratory India Pvt. Ltd., (Mumbai, India). All solutions for analysis were freshly prepared using triple distilled water obtained from Milli-Q plus purification system Millipore (Bradford, USA). A blister pack of tablets of trandolapril (Mavik® by Lupin Pharmaceuticals) (label claim 2 mg) was purchased from the local market for analysis in the formulation.

All the glassware, including pipettes, measuring cylinders, volumetric flasks, beakers, test tubes and round bottom flask were of Class A grade and purchased from Borosil. The instrument employed for recording the absorption spectra was Perkin Elmer lambda 3200 UV-visible spectrophotometer (serial no:1906001) with a scanning speed of 60 nm/min, spectral slit width of 2.0 nm, and resolution of 2.0 nm, equipped with 10-mm matched quartz cells. Melting point apparatus (model T0603160; EIE Instruments Pvt. Ltd., Ahmedabad, India) was used for the determination of the melting point of trandolapril.

A standard stock solution A of trandolapril (1 mg/mL) was prepared daily by dissolving 10 mg of trandolapril in 10 mL of the reagent (phosphate buffer pH 2, 0.1 N HCl or methanol; methods A, B or C, respectively). This solution was diluted 1 in 10, to obtain the stock solution (100.0 ug/mL). Further, working standard solutions ranging from 1.0 to 100.0 ug/mL of trandolapril were prepared by serial dilutions of the stock solution with the appropriate reagent phosphate buffer pH 2, 0.1 N HCl and methanol). The test tubes were kept stoppered to avoid the loss of solvent due to evaporation. Zero- and first-order derivative spectra of these solutions were recorded over the wavelength range 210–400 nm against the reagent blank and the absorbance values (zero order spectra) or amplitudes of the maximum and minimum (first order spectra) were measured.

All stress studies were conducted with the drug at a drug concentration of 1.0 mg/mL. Hydrolytic studies were carried out under acidic and basic conditions by refluxing the drug in 0.1 N HCl and 0.1 N NaOH, respectively, at 80°C for 8 h.

Oxidative studies were carried out at room temperature in 3% hydrogen peroxide (H_2O_2) for half an hour. Thermal degradation was carried out by exposing the drug (200 mg) in a petri-dish, sealed with aluminum foil (to avoid photo-degradation), to a temperature of 60°C for 21 days. Subsequently, the petri-dish was removed, cooled to room temperature and their contents dissolved in acetonitrile (diluent).

Two spectrophotometric methods A and B (in phosphate buffer pH 2.0 and 0.1 N HCl, respectively) were performed with a total of 17 parametric variations. Amongst these, two optimized variants of method A, and one optimized variant of method B were validated with respect to various parameters outlined in the ICH guideline Q2(R1).

The stock solution (100.0 μg/mL) was serially diluted with an appropriate reagent phosphate buffer pH 2.0 or 0.1 N HCl and methanol) to prepare working standard solutions with concentrations ranging from 1.0–70.0 μg/mL of the drug. All these dilutions, prepared in triplicate, were analyzed by various zero-order and first-order spectrophotometric method variants.

The intraday precision of the methods (selected based on linearity studies) was determined by the analysis of three varying concentrations of the drug (10.0, 20.0, and 30.0 μg/mL) on a single day. Determination of inter-day precision was carried out by analyzing three samples of varying concentrations on three successive days. The precision was expressed as RSD% corresponding to each calculated concentration of the analyte.

A preneutralized, equal volume mixture of stress-degraded solutions of trandolapril (prepared under conditions of acidic and alkaline hydrolysis), was suitably diluted to obtain the unspiked solution of the drug (original drug concentration: 10.0 μg/mL) for accuracy analysis. This solution was then spiked by 50, 100, and 150% to provide corresponding concentration increases of 5.0, 10.0, and 15.0 μg/mL, by mixing the unfortified solution separately with equal volumes of the standard drug solutions of strengths of 20.0, 30.0, and 40.0 μg/mL, respectively. The drug concentration in the fortified solutions (final analyzed concentrations of 15.0, 20.0, and 25.0 μg/mL) and the unfortified solution were then determined ($n = 3$). Method accuracy was expressed as percent recovery of the fortified drug concentration with reference to the unfortified one. Robustness was assessed by carrying out deliberate variations in the method parameters, including temperature and pH, and performing analysis with the selected method variant to study the impact on the drug recovery from the test solutions.

Twenty tablets of trandolapril (Mavik® by Lupin Pharmaceuticals) with a label claim of 2 mg were crushed and powdered. The powder weight equivalent to 10 mg of trandolapril was dissolved in ethanol to prepare 100 mL of solution A (100.0 μg/mL). The solution was suitably diluted and analyzed for the drug content by three variants of the developed method. Three replicate determinations were carried out for the assay procedure.

Results and discussion. Derivative spectrophotometry significantly advances the scope of spectrophotometric method development when compared with zero-order spectrophotometry, as it offers the possibility of enhancing the specificity/selectivity of the analytical procedure. This is because additional variations are available in terms of peak amplitudes in the derivative curves, which can be exploited to develop analytical procedures for drug analysis in the presence of excipients, degradation products and other impurities. In the present work, a comprehensive study is being reported in which all possible zero- and first-order derivative spectrophotometric curves of trandolapril have been thoroughly explored to develop sensitive and reproducible stability-indicating methods for the drug.

A preliminary analysis of UV absorption and solubility characteristics of the drug was carried out to select an appropriate solvent system for the development of the method. The experimental log$P$ of trandolapril is 3.5 and the two pK_a values of the drug are 3.8 and 5.10 [29]. The drug has low solubility in water (2.5 mg/mL) at 25°C [29]. Solubility characteristics of trandolapril were studied in various solvents and buffers at varying pH and based on its solubility profile, phosphate buffer pH 2.0, 0.1 N HCl, absolute ethanol and methanol were selected for the UV spectrophotometric method development and validation. Based on the solubility profile of the drug, absolute ethanol and methanol were first selected as solvents for the UV spectrophotometric method development and validation. However, the absorbance curves obtained in both ethanol and methanol were found to be highly inconsistent and peaks were not clearly discernible in both zero-order and first-order spectra. Hence, solubility and absorbance characteristics were explored in various buffers. The study on absorbance profile in phosphate buffer at varying pH values ranging from 2.0–7.0 revealed the most satisfactory results at pH 2.0. Considering the solubility characteristics in an acidic medium,

UV absorbance studies were conducted in 0.1 N HCl and in acetate buffer pH 3.0 and 4.5; however, a satisfactory absorbance profile was noted only with 0.1 N HCl. Finally, two media were selected for method development, i.e., phosphate buffer pH 2.0 and 0.1 N HCl. The zero- and first-order derivative spectra for the standard solutions of trandolapril, ranging from 1.0 to 70.0 μg/mL, were recorded over the wavelength range of 210–400 nm, taking phosphate buffer pH 2.0 or 0.1 N HCl as the corresponding reagent blank. The amplitudes of the maxima and minima were measured for all derivative spectra. Figure 1 shows the zero-order and first-order derivative UV overlay spectra of trandolapril in phosphate buffer pH 2.0 and 0.1 N HCl.

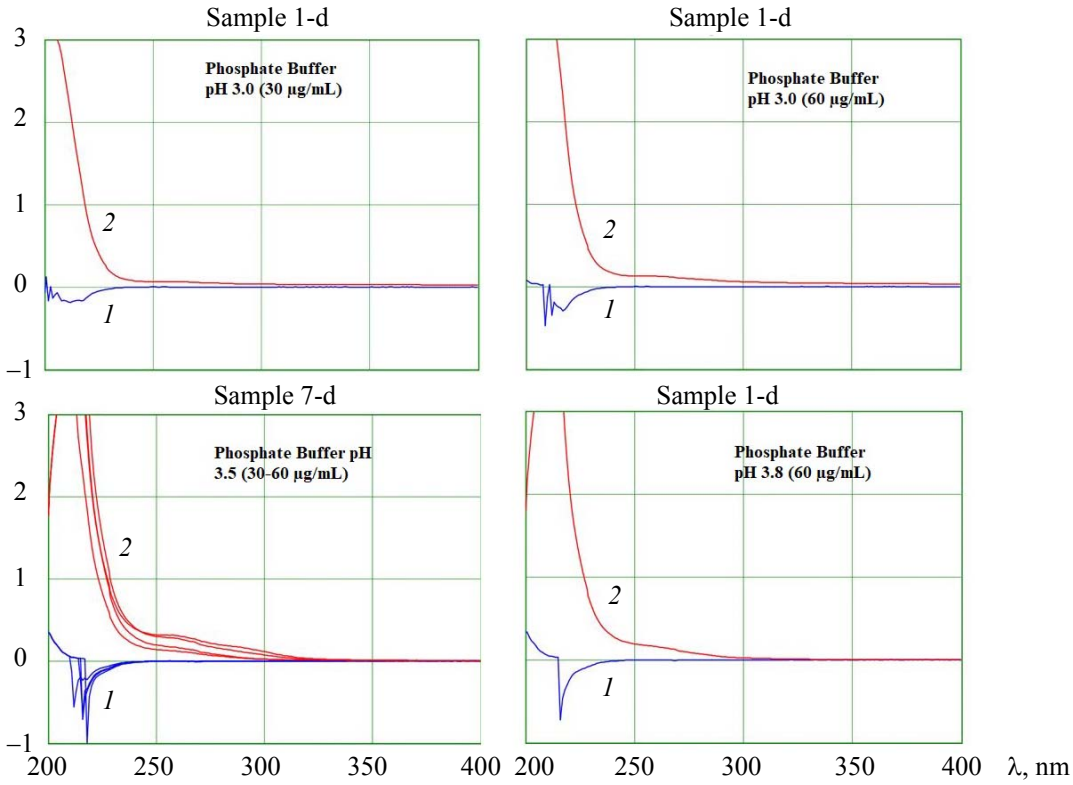


Fig. 1. Zero-order (1) and first-order (2) derivative UV overlay spectra of trandolapril in phosphate buffers of varying pH 3.0 (30 μg/mL)

The absorbance measurements (in case of zero-order spectra) and the peak-to-zero (P–0) or peak-to-peak (P–P) amplitude measurements (in case of first-order derivative spectra) were done at varying wavelengths in the concentration range of 1.0–70.0 μg/mL of the drug. The regression parameters, Beer's law limits, and wavelength range for the working standard solutions of trandolapril employing 17 variants (zero-order and first-order) of methods A (in phosphate buffer pH 2.0) and B (in 0.1 N HCl) are summarized in Table 1. Four zero-order and three first-order derivative UV spectrophotometric variants were studied for method A, whereas, three zero-order and seven first-order derivative UV spectrophotometric variants were studied for method B. Values of the correlation coefficient r^2 were found to be above 0.9 in many cases, indicating good linearity over the working concentration ranges. Amongst these, two variants of method A (**3** and **7**), and one variant of method B (**8**) were selected for further analytical validation, as absorbance values/peak amplitudes afforded the best linear correlation in these methods, as assessed from their correlation coefficients (r^2 values), which were close to 1.0. Figure 2 shows the standard plots of trandolapril with the selected method variants. The method was validated with respect to linearity and range, accuracy and precision, and limit of detection (LOD) and limit of quantification (LOQ). The various method validation parameters are summarized in Tables 1 and 2.

TABLE 1. Linearity and Range for the Explored Methods for Analysis of Trandolapril by Zero-Order and First-Order Derivative Spectrophotometry

Method		Beer's law limit, µg/mL	Wavelength, nm	Technique	Regression equation	Corr. coeff. (r^2)
1	Zero order	(1-70)	220[a]	Abs	$y = 0.0056x + 0.0599$	0.9333
2	Zero order	(1-70)	208[a]	Abs	$y = 0.0032x + 0.0186$	0.9538
3	Zero order	(1-70)	214[a]	Abs	$y = 0.0025x + 0.0064$	0.9992
4	Zero order	(1-70)	230[a]	Abs	$y = 0.0074x + 0.0286$	0.9902
5	First order	(1-70)	209-225[a]	P-P	$y = 0.0074x + 0.0268$	0.9946
6	First order	(1-70)	235[a]	P-0	$y = 0.0074x + 0.0297$	0.9932
7	First order	(1-70)	230-235[a]	P-P	$y = 0.0076x + 0.0201$	0.9981
8	First order	(1-70)	232-236[b]	P-P	$y = 0.0075x + 0.0251$	0.9984
9	First order	(1-70)	227-230[b]	P-P	$y = 0.0173x + 0.1189$	0.9106
10	First order	(1-70)	220[b]	P-0	$y = 0.0005x + 0.0012$	0.9566
11	First order	(1-70)	230[b]	P-0	$y = 0.0012x + 0.0004$	0.9938
12	First order	(10-70)	227-232[b]	P-P	$y = 0.0011x + 0.0013$	0.9903
13	First order	(10-70)	220[b]	P-0	$y = 0.0003x + 0.0004$	0.9754
14	First order	(5-70)	209[b]	P-0	$y = 0.0012x + 0.0004$	0.9904
15	Zero order	(1-70)	220[b]	Abs	$y = 0.0007x + 0.0013$	0.9871
16	Zero order	(1-70)	233[b]	Abs	$y = 0.0002x + 0.0006$	0.9714
17	Zero order	(1-70)	210[b]	Abs	$y = 0.0006x + 0.0002$	0.9892

[a] Calibration data in phosphate buffer pH 2.0 (method A).
[b] Calibration data in 0.1N HCl (method B).

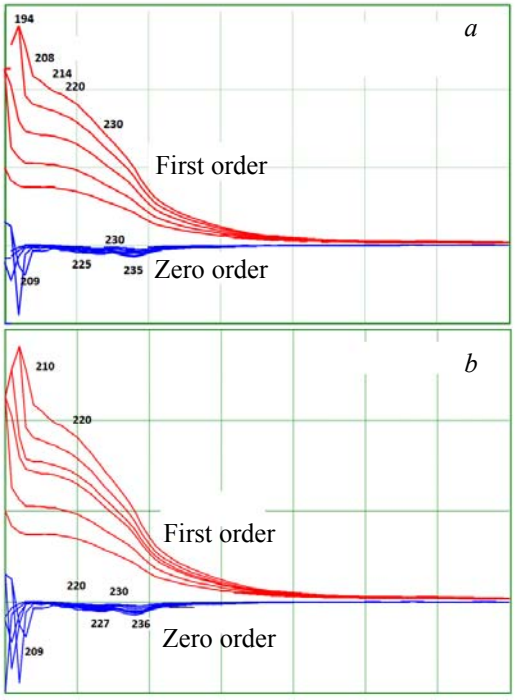


Fig. 2. Zero-order and first-order derivative UV overlay spectra of trandolapril in phosphate buffer pH 2.0 (a) and in 0.1 N HCl (b).

LOD and LOQ of the method were established using calibration standards. LOD and LOQ were calculated as $3.3\sigma/s$ and $10\sigma/s$, respectively, as per ICH definitions, where σ is the mean standard deviation of the replicate determination under the same conditions as the sample analysis in the absence of the analyte (blank

determination), while *s* is the sensitivity, namely, the slope of the calibration graphs. LOD and LOQ values for all method variants **3**, **7**, and **8** were found to be 1.23, 2.01, 0.88 μg/mL and 4.00, 6.09, and 2.66 μg/mL, respectively.

Precision was investigated by analyzing three different concentrations of trandolapril (10.0, 20.0, and 30.0 μg/mL) in three independent repeats on the same day (to evaluate intraday precision) and on three consecutive days (to evaluate inter-day precision). These intraday and inter-day precision data, represented as relative standard deviation (RSD%), are shown in Table 2. The RSD% values in the intraday and the inter-day precision study were found to be less than 1.73 and 2.11%, respectively, for method variants **3**, **7**, and **8,** indicating good precision of the method.

TABLE 2. Validation Parameters for the Proposed Method

Accuracy	Concentration (μg/mL)±S.D.; RSD%					
Conc. of drug taken, μg/mL	Spiked drug conc. μg/mL (%)*	Calculated % Recovery by method variants				
		3		**7**	**8**	
10.0	15.0 (50%)	95.7±0.27;0.28%		95.3±1.01;1.05%	95.7±1.03;1.08%	
10.0	20.0 (100%)	98.2±0.95;0.96%		98.6±1.04;1.05%	97.8±1.61;1.65%	
10.0	25.0 (150%)	102.2±1.13;1.27%		98.8±1.79;1.81%	97.6±1.24;1.27%	
Precision	Concentration (μg/mL)±S.D.#; RSD% with method variants **3**, **7**, and **8****					
Conc. taken, μg/mL	Intra-day (*n*=3)			Inter-day (*n*=3)		
	3	**7**	**8**	**3**	**7**	**8**
10.0	9.4±0.08;0.85	8.30±0.11;1.32	9.4±0.15;1.57	9.5±0.20;2.11	8.4±0.15;1.78	9.3±0.12;1.29
20.0	19.6±0.05;0.26	19.18±0.16; 0.83	18.0±0.12;0.66	18.5±0.15;0.81	19.3±0.24;1.24	18.1±0.28;1.55
30.0	28.5±0.05;0.17	27.0±0.12;0.44	29.9±0.52;1.73	29.5±0.62;2.10	28.9±0.56;1.93	30.0±0.62;2.07
LOD, μg/mL (method variant)	1.23 (**3**); 2.01 (**7**); 0.88 (**8**)					
LOQ, μg/mL (method variant)	4.00 (**3**); 6.09 (**7**); 2.66 (**8**)					

*Diluted degraded drug solution (10.0 μg/mL) mixed with equal volumes of the standard drug solutions with concentrations of 20.0, 30.0, and 40.0 μg/mL.

**Calculated as a mean of measurements in triplicate (n = 3).

#Calculated as: SD/mean ×100.

The stability indicating the potential of the developed methods was evaluated by fortifying a pre-neutralized, equal-volume mixture of stress-degraded solutions of trandolapril prepared under conditions of acidic and alkaline hydrolysis. The original drug concentration in all the stressed solutions was the same, i.e., 10.0 μg/mL. This pre-analyzed degraded drug solution mixture of trandolapril was suitably diluted to obtain the unspiked drug solution (original concentration 10.0 μg/mL). The assessment of the accuracy of the developed methods was carried out by spiking the excess drug (50, 100, and 150%), to pre-analyzed degraded drug solution samples (10.0 μg/mL). Accuracy was determined as mean % recovery and RSD%. Excellent recovery values were for method variants **3**, **7**, and **8** ranging from 95.3–102.2% (Table 2), thereby indicating good accuracy for the method (Fig. 3).

Robustness gives the measure of the repeatability of an analytical method, which is assessed by evaluating the effect of small variances in experimental conditions such as heating temperatures (±2°C). Three replicate determinations at six different concentration levels of the drugs were carried out at ambient temperature (29°C), and at 27 and 31°C (room temperature ±2°C). The intraday %RSD values for method variants **3**, **7**, and **8** were found to be less than 1.73%, indicating that the proposed method variants have reasonable robustness. Additionally, the stability of the final sample solutions was examined by their absorbance values/peak amplitudes, and responses were found to be stable for at least 6 h at room temperature.

The analysis for trandolapril was carried out on the marketed oral tablet formulation of the drug (Mavik®; label claim 2 mg; Lupin Pharmaceuticals) by the proposed three method variants in triplicate, and the results are shown in Table 4. The percentage recovery was found for the range from 90–97% with %RSD less than 2.1%, which shows close agreement between the results obtained by the proposed method variants and the label claim.

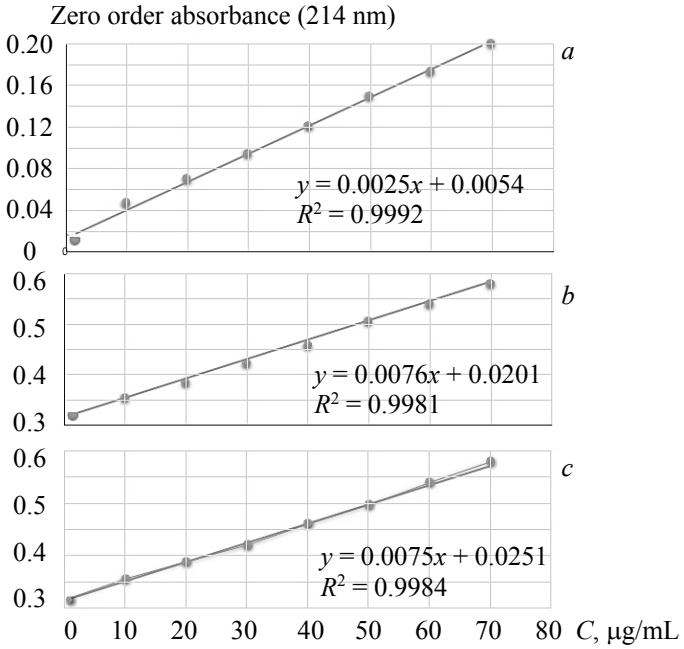


Fig. 3. Standard plots of trandolapril with method variants **3** (a), **7** (b), and **8** (c).

TABLE 3. Robustness at Different Temperatures for the Proposed Methods for Analysis of Valbenazine Tosylate

Method variant	Mean ± SD*	RSD (%)**
3	0.426 ± 0.05	0.12
7	0.215 ± 0.03	0.14
8	0.115 ± 0.02	1.73

*Calculation as mean of measurements in triplicate for three temperatures 29, 31, and 27ºC.
**Calculated as the relative standard deviation from mean value at 29, 31, and 27ºC.

TABLE 4. Recovery Studies from Marketed Drug Formulation (Label claim, 2 mg)

Method variant	Mean recovery(mg)±S.D*; %RSD	%Recovery±S.D; %RSD
3	1.96 ± 0.03; 1.53%	96.63 ± 1.47%; 1.52%
7	1.89 ± 0.04; 2.12%	89.91 ± 1.90%; 2.11%
8	1.97 ± 0.04; 2.03%	97.72 ± 1.98%; 2.03%

* Average of three determinations.

Conclusions. This work describes the development of three rapid, sensitive and inexpensive method variants for zero- and first-order derivative spectrophotometric estimation of trandolapril in bulk as well as in its marketed tablet formulation. A comprehensive exploration of all pertinent wavelength regions in the zero-order and first-order derivative spectra of trandolapril was carried out to select the three method variants **3**, **7**, and **8**. The methods were validated in terms of sensitivity, reproducibility, precision, accuracy, robustness, and solution stability for ≥6 h returning excellent validation characteristics. Excellent recovery of the drug was obtained from its force-degraded solutions, suggesting the stability-indicating nature of the method and its potential applicability in the presence of routine degradation products. Further, the proposed method variants were successfully used to quantify the drug in its marketed tablet formulation with good recoveries, suggesting that the method is well suited for routine drug analysis without any interference from the formulation excipients. These methods can be explored further for analysis of the drug in other formulations containing varied excipients.

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