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Hypothesis testing for the validation of the kinetic spectrophotometric methods for the determination of lansoprazole in bulk and drug formulations via Fe(iii) and Zn(ii) chelates

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Point and interval hypothesis tests performed to validate two simple and economical, kinetic spectrophotometric methods for the assay of lansoprazole are described. The methods are based on the formation of chelate complex of the drug with Fe(III) and Zn(II). The reaction is followed spectrophotometrically by measuring the rate of change of absorbance of coloured chelates of the drug with Fe(III) and Zn(II) at 445 and 510 nm, respectively. The stoichiometric ratio of lansoprazole to Fe(III) and Zn(II) complexes were found to be 1 : 1 and 2 : 1, respectively. The initial-rate and fixed-time methods are adopted for determination of drug concentrations. The calibration graphs are linear in the range 50–200 μg ml^{-1} (initial-rate method), 20–180 μg ml^{-1} (fixed-time method) for lansoprazole-Fe(III) complex and 120–300 (initial-rate method), and 90–210 μg ml^{-1} (fixed-time method) for lansoprazole-Zn(II) complex. The inter-day and intra-day precision data showed good accuracy and precision of the proposed procedure for analysis of lansoprazole. The point and interval hypothesis tests indicate that the proposed procedures are not biased.

Keywords: lansoprazole; metal chelate; kinetic determination; drug formulations; spectrophotometry; interval hypothesis; point hypothesis

Introduction

Lansoprazole (L), 2-({3-Methyl-4-(2,2,2-trifluroethoxy)-2-pyridyl) methyl} sulfinyl benzimidazole, is a new substituted benzimidazole compound that effectively decreases gastric acid secretion via inhibition of gastric H^+, K^+-adenosine triphosphatase. Like omeprazole, lansoprazole is thought to be a weak inducer of hepatic cytochrome P450. It is an important alternative to omeprazole and H_2 receptor antagonists in acid-related disorders. In addition to its efficacy in healing or maintenance treatment, it may provide more effective symptom relief than other comparator agents.[1] The drug is acid labile and administered in the form of enteric-coated granules in capsules.

Control of the contents of commercially available medication is stringent; pharmaceutical companies have been using analytical methods to determine the purity of their products. Several methods have been reported for the determination of lansoprazole in biological fluids and pharmaceutical dosage forms. These methods are HPLC,[2–5] HPTLC,[6–7] capillary electrophoresis[8] and electroanalytical methods.[9–10]

Few spectrophotometric methods[11–12] have also been presented for quantification of the cited drug. It was determined by reacting with p-dimethylaminobezaldehyde in acidic medium.[13] Meyyanathan *et al*. have reported[14] two spectrophotometric methods. One method was based on the reaction of lansoprazole with acetyl chloride in the presence of 1% $CuSO_4$ solution. The resulting yellowish-red chromogen exhibited absorption peak at 478.5 nm. Beer's Law was obeyed in the concentration range 100–600 μg ml^{-1}. In the second method, lansoprazole was treated with methylbenzothiazolinone hydrazone in the presence of Ce(IV) resulting in the formation of a coloured chromogen, which absorbed maximally at 491 nm. The folin ciocalteu reagent[15] has also been used for determination of cited drug in the concentration range 0.5–5.0 μg ml^{-1} at 654 nm. The ion pair complex[16] formed between lansoprazole and bromocresol green can be extracted with organic solvent, which absorb maximally at 420 nm. The assay was carried out in the concentration range 1–20 μg ml^{-1}. The quantification of lansoprazole was made possible by reacting it with vanillin in acidic medium.[17]

Kinetic methods have been used for assay of drugs in pharmaceutical formulations as some specific advantages are involved, namely: (1) selectivity due to measurement of the evolution of the absorbance with time of reaction instead of measure of a concrete absorbance value; (2) possibility of no interference of the coloured and/or turbidity background of the sample. In

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the literature, no kinetic spectrophotometric method has been reported yet for determination of lansoprazole. Therefore, there is a need to develop a simple and fast kinetic method.

The present work describes two spectrophotometric methods for the determination of lansoprazole in pharmaceutical formulations based on the formation of complexes with Fe (III) and Zn(II). The methods were validated statistically.

Experimental

Apparatus

All spectral and absorbance measurements were made on spectronic $20D^+$ spectrophotometer (Milton Roy, Iryland, Pennsylvania USA), with 1 cm matched glass cells.

Materials and reagents

Lansoprazole was kindly provided by Cipla Ltd. (Mumbai, India), and was used as received. Four different pharmaceutical preparations such as Lancus (Cadila Pharma), Lansofast (Zydus Alidac), Lanzol (Cipla Ltd.) and Propilan (Glenmark) were purchased from the local market. All other reagents used were of analytical reagent grade.

Standard solutions

(i) Ferric chloride solution, 4.93×10^{-2} M, was prepared in ethanol and standardized.[18]
(ii) Zinc chloride solution, 8.0×10^{-2} M, was prepared in ethanol.
(iii) Standard solution of lansoprazole (3 mg ml^{-1}) was prepared in ethanol and further diluted according to need.

Lansoprazole solution was freshly prepared and used within 5 h.

Recommended procedures

Method A

Accurately measured aliquots containing 0.5 mg–2 mg from standard solution of lansoprazole were transferred into a 10-ml volumetric flask followed by 0.8 ml of $FeCl_3$ solution, and diluted to the volume with ethanol. The mixture was shaken well and transferred to the spectrophotometric cell (within 1 min) and evolution of the absorbance was measured at 445 nm with time for 35 min.

The initial rate of the reaction was calculated as tangent to the kinetic curve at different concentrations. The calibration graphs were constructed by plotting (1) the logarithm of the initial rate of the reaction *vs* the logarithm of the molar concentration of lansoprazole; and (2) the absorbance measured at a fixed time of 5 min against the concentration of lansoprazole. Its content was estimated either from the calibration curves or corresponding calibration equations.

Method B

Into a series of 10-ml volumetric flasks, volumes equivalent to 1.2–3.0 mg of lansoprazole were pipetted, 1.8 ml of $ZnCl_2$ solution was added to each flask, and the volume of the flask was brought up to the mark with ethanol. The evolution of absorbance was recorded as a function of time at 510 nm against the reagent blank prepared simultaneously at room temperature.

The initial rate of reaction at different concentrations was obtained from slope of the absorbance time curve. The calibration curves were obtained by plotting (1) logarithm of the initial rate of the reaction *vs* logarithm of the molar concentration of lansoprazole; and (2) the absorbance measured at a fixed time of 15 min against the lansoprazole concentration. The content of the drug was computed either from the calibration curves or regression equations.

Analysis of capsules

The content of the capsules (enteric coated granules) were accurately weighed and finely powdered. The amount of the powder equivalent to 150 mg of lansoprazole was dissolved in 40 ml of ethanol and allowed to stand for a few minutes and filtered on Whatmann No. 42 filter paper. The residue was completely washed with ethanol. The filtrate was diluted to 50 ml with ethanol. This solution is further diluted according to need. The assay of lansoprazole was completed by following the recommended procedures.

Results and Discussion

Organic compounds have long been utilized as analytical reagents for the determination of metal ions via formation of metal complexes. However, the binary complexes of lansoprazole with metal ions have not yet been studied, although they may be of biological significance. These may affect the bioavailibility of the cited drug, as certain metal ions are present in relatively appreciable concentrations in biological fluids. At room temperature, the chelation reactions of lansoprazole with Fe(III) and Zn(II) were slow and the intensity of the colour increased with time. Therefore, kinetically based methods were elaborated for quantification of the drug. The various experimental parameters affecting the metal chelate formation were optimized.

The equilibrium for the chelation reaction between lansoprazole and Fe(III) was reached in about 35 min. To study the effect of the concentration of Fe(III), aliquots containing 2.0 mg of the drug were pipetted into a series of 10 ml standard flasks followed by varying volumes (0.1–1.0 ml) of 4.93×10^{-2} M reagent and diluted to volume with ethanol. The absorbance was measured after 35 min of mixing. The maximum absorbance was obtained with 0.6 ml of the reagent. Higher volume of Fe(III) yielded no change in absorbance and hence, 0.8 ml was chosen as the optimum value for all measurements.

To establish the optimum experimental conditions for method B, the cited drug (300 μg ml^{-1}) was allowed to react with varying volumes (0.2–2.0 ml) of 0.08M zinc chloride solution. The absorbance at 510 nm was measured at a fixed time of 25 min. It is apparent from that, that the absorbance increased with increasing volume of $ZnCl_2$ solution and became constant at 1.5 ml; further addition caused no change in absorbance. Therefore 1.8 ml was adopted in the final solution proving to be adequate for maximum concentration of lansoprazole used in kinetic determination.

Reaction stoichiometry

The combining ratio between metal ion and lansoprazole was established by the Job's method of continuous variation[19] and limiting logarithmic method.[20] Figures 1 and 2 indicated the formation of 1 : 1 lansoprazole : Fe(III) and 2 : 1 lansoprazole : Zn(II) complexes. The beads of the strong cation exchange resin in Na^+ form were placed in the ethanolic solution of the complex to

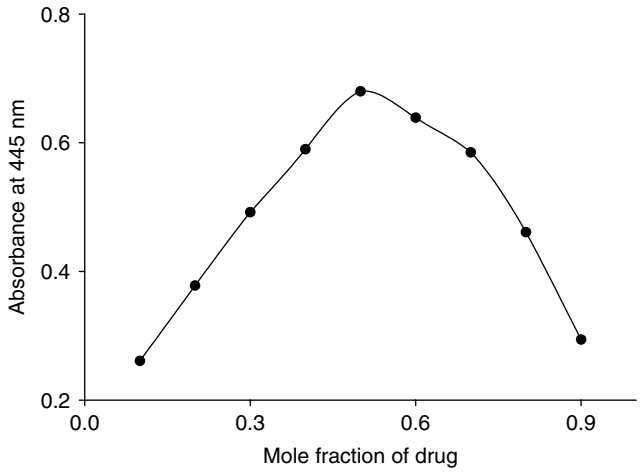


Figure 1. Job's plot for the lansoprazole and Fe(III) complex (each 1.5412×10^{-2} M).

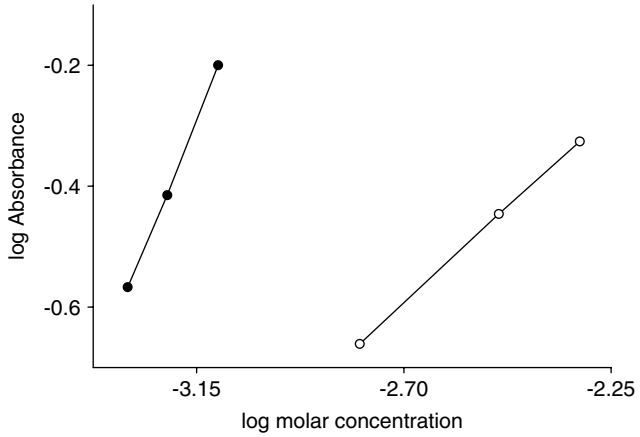


Figure 2. Determination of the molar ratio between lansoprazole and Zn(II) by the limiting logarithmic method. (●) Constant $ZnCl_2$ concentration and variable lansoprazole concentration, (○) Constant lansoprazole concentration and variable $ZnCl_2$ concentration.

ascertain the ionic nature. The results suggested positive charge on lansoprazole-Fe(III) complex and no charge on lansoprazole-Zn(II) complex. Based on the literature background[21] and our experimental findings, the reaction mechanisms are proposed and given in Schemes 1 and 2.

Kinetic study of the reaction

The initial rates of the reactions were determined by measuring the slope of the initial straight line of the absorbance-time curves. The rate of the reaction was found to be dependent on the concentration of lansoprazole. The rates were followed at room temperatures: (1) with various concentrations of lansoprazole in the concentration range of 0.05–0.2 mg ml^{-1}, keeping Fe(III) concentration constant and high (method A); and (2) keeping a constant and high concentration of Zn(II) and varying the lansoprazole concentration in the range of 0.12–0.3 mg ml^{-1} (method B).

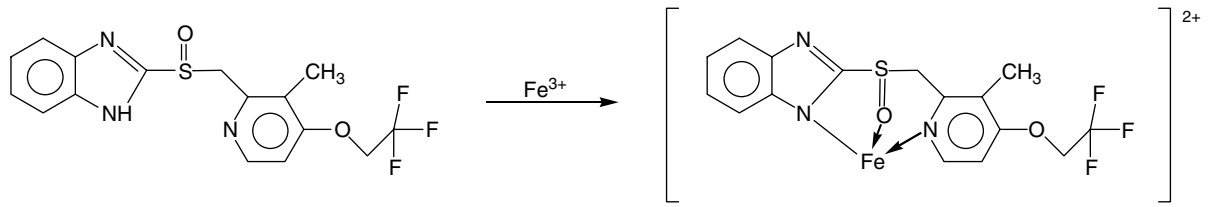
Figure 3 and 4, obtained by applying methods A and B, reveal the fact that the rate increases with increasing lansoprazole concentration. The reaction rates obey Eqn (1):

$$\text{rate} = \Delta A/\Delta t = K' \,[\text{lansoprazole}]^n \qquad (1)$$

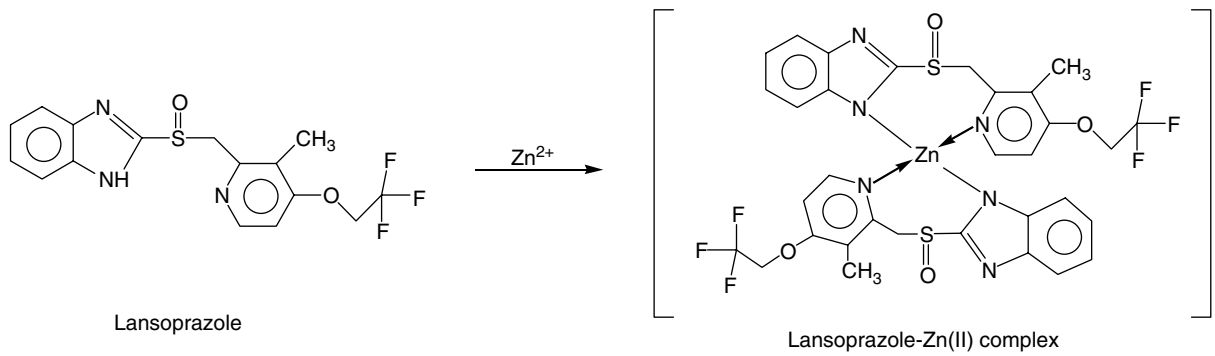
where K' is the pseudo-order constant of the reaction and n is the order of the reaction. Equation (1) is transformed into logarithmic Eqn (2) as:

$$\log\ (\text{rate}) = \log\ K' + n\ \log\,[\text{lansoprazole}] \qquad (2)$$

Regression of log rate versus log [lansoprazole] give the regression Eqns (3) and (4):



Scheme 1. Reaction between Lansoprazole and Fe(III).



Scheme 2. Reaction between Lansoprazole and Zn(II).

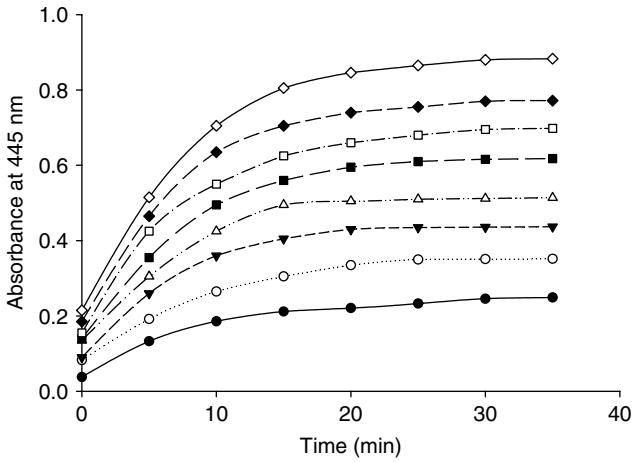


Figure 3. Absorbance *vs.* time graph for the reaction between lansoprazole and Fe(III), showing the dependence of the reaction on lansoprazole concentration (●) 1.353×10^{-4} M (○) 1.624×10^{-4} M (▼) 2.166×10^{-4} M (▽) 2.707×10^{-4} M (■) 3.248×10^{-4} M (□) 3.790×10^{-4} M (◆) 4.331×10^{-4} M (◇) 5.414×10^{-4} M.

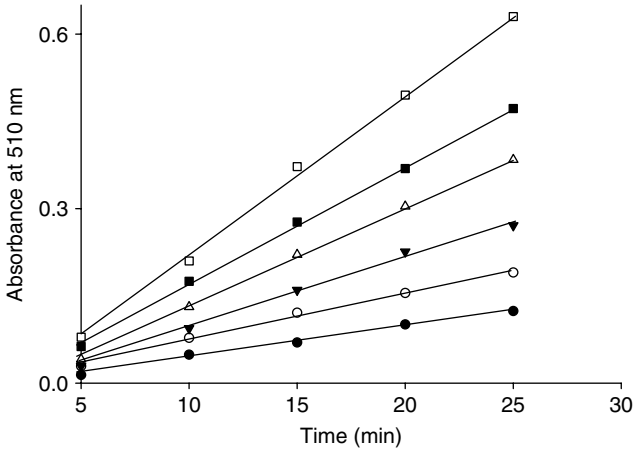


Figure 4. Absorbance *vs* time graph for the reaction between lansoprazole and Zn(II), showing the dependence of the reaction on lansoprazole concentration (●) 3.248×10^{-4} M (○) 4.060×10^{-4} M (▼) 4.872×10^{-4} M (▽) 5.685×10^{-4} M (■) 6.497×10^{-4} M (□) 7.309×10^{-4}.

(1) For method A,

$$\log(\text{rate}) = 2.861 + 1.191 \times \log[\text{lansoprazole}] \quad (\gamma = 0.9977) \qquad (3)$$

(2) For method B,

$$\log(\text{rate}) = 4.723 + 2.007 \times \log[\text{lansoprazole}] \quad (\gamma = 0.9972) \qquad (4)$$

Regression Eqns (3) and (4) also indicate that the reaction is first order with respect to the lansoprazole concentration for method A and a second order reaction kinetics with respect to the drug concentration for method B.

Under the optimum experimental conditions, quantification of the cited drug was carried out using an excess of Fe(III) and Zn(II) with respect to initial concentration of lansoprazole by methods A and B, respectively. Therefore pseudo-zero order condition was obtained with respect to Fe (III) and Zn (II) concentrations. However, the rates are related to lansoprazole concentration in a pseudo-order condition as follows:

$$\text{rate} = K'[\text{lansoprazole}] \quad \text{method A}$$
$$\text{rate} = K'[\text{lansoprazole}]^2 \quad \text{method B}$$

The regression analysis indicated linear relationship between log rate and log molar concentration of drug. The calibration curves were found to be linear over the concentration ranges 50–200 μg ml^{-1} and 120–300 μg ml^{-1} for methods A and B, respectively. The high value of correlation coefficient (γ) pointed towards good linearity of both the calibration curves. The confidence intervals[22] for intercept and slope were calculated using relations $\pm\, t\, S_a$ and $\pm\, t\, S_b$ and found to be 3.395×10^{-2}; 4.568×10^{-2} and 5.663×10^{-2}; 1.310×10^{-1} for methods A and B, respectively which showed high reproducibility of the proposed methods. The detection limits[23] were calculated using Equation (5)

$$\text{Detection limit} = [S_o^2(n\text{-}2)/(n\text{-}1)]^{1/2}(t/b) \qquad (5)$$

where n is the number of samples; b is the slope of line of regression; *t*- is the Student's *t*- value at 95% confidence level and S_o^2 is the variance of regression lines obtained with pure lansoprazole.

The detection limits were found to be 0.03 and 0.02 μg ml^{-1} for methods A and B, respectively. At lower concentrations it was difficult to get the accurate slope of the absorbance-time curve, indicating that the detection can be done at the specified concentration levels. The low value of variance (3.299×10^{-4} and 6.542×10^{-4} for methods A and B) obtained in each method indicated the negligible scattering of data points around the line of best fit.

Fixed-time method

At a preselected time, absorbance was measured. The calibration curve of absorbance *vs* initial concentration of lansoprazole was obtained for each method at a fixed time of 5, 15 and 25 min. The linear concentration range, molar absorptivity, regression equation, correlation coefficient and variance are given in Table 1. It is evident from Table 1 that the slope increases with time and that the most acceptable values of correlation coefficient and intercept are obtained at a fixed time of 5 min and 15 min for methods A and B, respectively and therefore, selected as the most suitable time intervals for determination.

Precision

Repeatability was determined by assaying six samples of 80, 120 and 160 μg ml^{-1} using lansoprazole-Fe(III) system for initial-rate and fixed-time methods, respectively. For lansoprazole-Zn(II) system, six replicate determinations of 120, 150 and 210 μg ml^{-1} were performed utilizing initial-rate and fixed time methods, respectively. The results are summarized in Table 2.

Reproducibility was evaluated by determining four different lansoprazole concentrations in triplicate over a period of six days. Results of inter-day reproducibility are given in Table 3. The inter-day and intra-day precision data showed good accuracy and precision of the proposed procedures for analysis of lansoprazole.

Table 1. Optical characteristics and statistical data of regression equations at different fixed times for proposed methods

	Fixed-time method					
	Method A			Method B		
Parameters	5 min.	15 min.	25 min.	5 min.	15 min.	25 min.
Calibration range ($\mu g\ ml^{-1}$)	20–180	20–180	20–180	90–210	90–210	90–210
Calibration equation	$A = 2.891 \times 10^{-2} + 2.745 \times 10^{-3}C$	$A = 6.525 \times 10^{-2} + 3.980 \times 10^{-3}C$	$A = 5.734 \times 10^{-2} + 4.527 \times 10^{-3}C$	$A = -1.790 \times 10^{-2} + 2.767 \times 10^{-4}C$	$A = -5.260 \times 10^{-2} + 1.153 \times 10^{-3}C$	$A = -0.173 + 2.533 \times 10^{-3}C$
$\pm t\ S_a$	1.30×10^{-2}	4.48×10^{-2}	2.51×10^{-2}	4.94×10^{-3}	1.18×10^{-2}	2.26×10^{-2}
$\pm t\ S_b$	8.43×10^{-5}	2.89×10^{-4}	1.62×10^{-4}	5.21×10^{-5}	1.25×10^{-3}	2.38×10^{-4}
Correlation coefficient (γ)	0.9987	0.9949	0.9986	0.9884	0.9986	0.9972
Molar absorptivity (lit $mol^{-1}\ cm^{-1}$)	1.09×10^{3}	1.72×10^{3}	1.87×10^{3}	6.01×10^{1}	3.28×10^{2}	5.60×10^{2}
Variance ($\mu g\ ml^{-1}$)	6.504×10^{-5}	5.570×10^{-4}	1.936×10^{-4}	5.433×10^{-6}	4.543×10^{-4}	1.076×10^{-4}

Table 2. Intra-day assay: accuracy and precision of proposed methods using initial-rate and fixed-time procedures

Method A						Method B					
Initial-rate method			Fixed-time method			Initial-rate method			Fixed-time method		
Amount ($\mu g\ ml^{-1}$)			Amount ($\mu g\ ml^{-1}$)			Amount ($\mu g\ ml^{-1}$)			Amount ($\mu g\ ml^{-1}$)		
Taken	Found	RSD (%)	Taken	Found	RSD (%)	Taken	Found	RSD (%)	Taken	Found	RSD (%)
80.0	79.78	0.82	80.0	80.09	0.88	120.0	120.25	0.72	120.0	119.93	0.48
120.0	119.74	0.91	120.0	118.75	0.79	150.0	150.14	0.62	150.0	148.65	0.96
160.0	159.71	0.49	160.0	160.19	0.72	210.0	210.27	0.32	210.0	210.02	0.60

Table 3. Inter – day assay: accuracy and precision of proposed methods using initial – rate and fixed time procedures

Method A						Method B					
Initial-rate method			Fixed-time method			Initial-rate method			Fixed-time method		
Amount ($\mu g\ ml^{-1}$)			Amount ($\mu g\ ml^{-1}$)			Amount ($\mu g\ ml^{-1}$)			Amount ($\mu g\ ml^{-1}$)		
Taken	Found	RSD (%)	Taken	Found	RSD (%)	Taken	Found	RSD (%)	Taken	Found	RSD (%)
80.0	80.14	0.90	80.0	79.37	0.57	120.0	120.56	0.66	120.0	120.39	0.91
120.0	119.99	0.39	120.0	119.61	0.45	150.0	148.63	0.87	150.0	148.50	0.62
160.0	160.43	0.42	160.0	158.85	0.53	210.0	210.37	0.37	210.0	208.80	0.52

Table 4. Point hypothesis: comparison of the proposed method A with the reference method at 95% confidence level

	Initial-rate method				Fixed-time method				Reference method	
Formulation	(%)[a] Recovery	(%)[a] RSD	*t*- value[b]	*F*- value[b]	(%)[a] Recovery	(%)[a] RSD	*t*- value[b]	*F*- value[b]	(%)[a] Recovery	(%)[a] RSD
Lancus	99.82	0.60	0.550	3.45	99.46	0.55	0.791	2.95	99.67	0.32
Lansofast	99.95	0.60	0.543	2.80	99.69	0.53	0.415	2.18	99.80	0.36
Lanzol	100.09	0.66	0.832	4.56	99.76	0.57	0.273	3.42	99.84	0.31
Propilan	100.10	0.65	0.773	4.83	100.22	0.43	1.681	2.09	99.86	0.30

[a] Average of six independent analyses.
[b] Theoretical *t*- and *F*- value at 95% confidence level is 1.812 and 5.05, respectively.

Table 5. Point hypothesis: comparison of the proposed method B with the reference method at 95% confidence level

	Initial-rate method				Fixed-time method				Reference method	
Formulation	(%)[a] Recovery	(%)[a] RSD	*t*- value[b]	*F*- value[b]	(%)[a] Recovery	(%)[a] RSD	*t*- value[b]	*F*- value[b]	(%)[a] Recovery	(%)[a] RSD
Lancus	99.78	0.36	0.400	1.20	99.95	0.36	0.531	1.21	99.84	0.32
Lansofast	99.93	0.39	1.692	2.85	99.67	0.46	0.248	4.06	99.62	0.22
Lanzol	99.98	0.35	1.737	2.65	99.64	0.32	0.155	2.25	99.69	0.21
Propilan	100.08	0.52	0.357	4.87	99.95	0.46	0.206	3.86	100.00	0.24

[a] Average of six independent analyses.
[b] Theoretical *t*- and *F*- value at 95% confidence level is 1.812 and 5.05, respectively.

Table 6. Interval hypothesis: comparison of the the proposed methods with the reference method at 95% confidence level

	Method A				Method B			
	Initial-rate method		Fixed-time method		Initial-rate method		Fixed-time method	
Formulation	Lower limit (θ_L)	Upper limit (θ_U)	Lower limit (θ_L)	Upper limit (θ_U)	Lower limit (θ_L)	Upper limit (θ_U)	Lower limit (θ_L)	Upper limit (θ_U)
Lancus	0.994	1.009	0.993	1.003	0.996	1.003	0.997	1.005
Lansofast	0.996	1.007	0.994	1.004	1.000	1.006	0.997	1.004
Lanzol	0.997	1.008	0.994	1.004	0.999	1.006	0.997	1.003
Propilan	0.997	1.008	0.999	1.008	0.997	1.005	0.996	1.004

Acceptance limit: ($\theta_L = 0.98$ and $\theta_U = 1.02$).

As an additional demonstration of accuracy, recovery experiments were carried out by standard addition technique. In this method, a fixed amount of pure lansoprazole was added to pre-analyzed commercial dosage forms at 80%, 100% and 120% of the initial concentration and the content was determined by the proposed procedures. The results observed were in the range 98.67–100.27% and 98.23–100.25% using initial-rate and fixed-time methods, respectively. It is apparent from the results that common excipients present in dosage forms did not interfere with the determination.

The proposed methods have been successfully applied to the determination of lansoprazole in some commercial preparations. The results obtained by proposed procedures were compared to those of reference method.[14] The Student's *t*- and *F* – values at 95% confidence level did not exceed the theoretical values (Tables 4 and 5) indicating no significant difference between accuracy and precision of the two methods.

The interval hypothesis[24] was also applied to judge the reliability of the proposed procedures. For this it was decided that a bias expressed as a proportion of the reference mean of ±2% is acceptable.

$$-0.02\mu_1 < (\mu_2 - \mu_1) < 0.02\mu_1 \quad (6)$$

Equation (6) can also be written as

$$0.98 < \mu_2/\mu_1 < 1.02 \quad (7)$$

Which can be generalize to

$$\theta_L < \mu_2/\mu_1 < \theta_U \quad (8)$$

Where θ_L and θ_U are lower and upper acceptance limits, respectively. The limits of this confidence interval can be calculated as the two roots of the quadratic Eqn (8)

$$\theta^2(X_1{}^2 - S_p{}^2 t^2_{tab}/n_1) - 2\theta\, X_1\, X_2 + \theta^2(X_2{}^2 - S_p{}^2 t^2_{tab}/n_2) = 0 \quad (8)$$

Where

$$a = X_1{}^2 - S_p{}^2 t^2_{tab}/n_1$$
$$b = -2\, X_1\, X_2$$
$$c = X_2{}^2 - S_p{}^2\, t^2_{tab}/n_2$$

The values of θ_L and θ_U of the confidence interval can be obtained as

$$\theta_L = -b - (b^2 - 4ac)^{1/2}/2a$$
$$\theta_U = -b + (b^2 - 4ac)^{1/2}/2a$$

At 95% confidence level the different set of results are summarized in Table 6. It is concluded based on these intervals that the proposed procedures are not biased, as true bias is smaller than ±2%.

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