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Research Article

Spectrophotometric Determination of Cilostazol in Tablet Dosage Form

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Abstract

Purpose: *To develop simple, rapid and selective spectrophotometric methods for the determination of cilostazol in tablet dosage form.*
Methods: *Cilostazol was dissolved in 50 % methanol and its absorbance was scanned by ultraviolet (UV) spectrophotometry. Both linear regression equation and standard absorptivity were calculated and both methods were validated as per ICH guidelines. Cilostazol was determined in tablet dosage form using these validated methods.*
Results: *The λ_{max} of cilostazol was 258.2 nm in 50 % methanol. Beer-Lambert's law was obeyed in the concentration range of 0 – 25 µg/ml and standard absorptivity was 420.2 $dL.g^{-1}.cm^{-1}$. The numerical values for all the validation parameters were within acceptable limits. The results of cilostazol tablet determination by linear regression equation and standard absorptivity methods indicate purity of 100.0 - 102.4 and 98.7 - 101.1 % with standard deviations of 0.611 and 0.592, respectively. Comparing the methods at 99 % confidence limit, the F-test value was found to be 1.065.*
Conclusion: *These validated methods may be useful for routine analysis of cilostazol as bulk drugs, in dosage forms as well as in dissolution studies in the pharmaceutical industry.*

Keywords*: Cilostazol tablets, UV spectrophotometry, Linear regression equation, Standard absorptivity.*

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INTRODUCTION

Cilostazol, whose chemical name is 6-[4-(1-cyclohexyl-1H-tetrazol-5-y1) butoxy]-3, 4-dihydro-2 (1H) – quinolinone (see Fig 1), is a quinolinone derivative that inhibits cellular phosphodiesterase III, and is used for the inhibition of platelet aggregation and as a vasodilator [1-4].

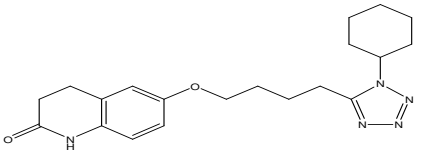

Fig. 1: Structure of cilostazol

The literature reveals that chromatographic methods are employed in the determination of cilostazol in tablet dosage form and human plasma and, to the best of our knowledge, no spectrophotometric method has yet been reported for this compound in tablet form [5-6]. However, the degradation profile and RP-HPLC analysis of cilostazol in tablet dosage form has been reported [7]. Compared to chromatographic methods, spectrophotometric methods are suitable for routine analysis because it is economic, rapid, simple, maintenance-free, and show comparable accuracy and precision with HPLC methods. Therefore, the object of the present work was to develop spectrophotometric methods for the determination of cilostazol in tablet form.

EXPERIMENTAL

Instruments, reagents and chemicals

Ultraviolet spectrophotometer (1700 series, Shimadzu) and UV-VIS double beam spectrophotometer 2201 (Systronics) with 1 cm matched quartz cells were used for the measurement of absorbance. Shimadzu-Ax-200 electronic balance was used for weighing the samples, and class “A” volumetric glassware were used.

Working standard (WS) of cilostazol was a gift from IPCA Laboratories Ltd, Ratlam, MP, India, while Pletoz® 50 tablets (cilostazol tablets 50 mg) manufactured by Hetero Drugs Ltd, Hyderabad were procured from a local pharmacy. Methanol AR grade (Merck, India) and distilled water were used for analytical work.

Linear regression equation method

Stock A (500 µg/ml cilostazol) was prepared from accurately weighed 50 mg cilostazol WS in 50 % aqueous methanol. It was diluted with the solvent to produce Stock B (50 µg/ml); aliquots of Stock B were further diluted to give concentrations of 5, 10, 15, 20 and 25 µg/ml of cilostazol, respectively. These dilutions were scanned from 300 to 200 nm against 50 % aqueous methanol as blank, and their absorbances observed at 258.2 nm.

Standard absorptivity method

Five dilutions of cilostazol were prepared in triplicate and their absorbances were observed at 258.2 nm. From the above observations, the standard absorptivity, A (1%, 1cm), and molar extinction coefficient were calculated.

Validation of methods

As per ICH guidelines [8-9], six dilutions in triplicate were used to validate both methods for linearity, accuracy (by recovery studies-standard addition to pre-analysed samples), repeatability (within day), intermediate precision (days, analyst and instrument variation) and robustness (methanol variation: 45, 50 and 55 %), and statistical parameters were calculated for them.

Quantitative determination

Twenty cilostazol tablets were weighed and finely powdered; a quantity equivalent to 50 mg of cilostazol was dissolved in 100 ml of 50 % aqueous methanol and filtered through

Whatman filter paper no. 41 to give Stock P. Stock P was diluted to obtain Stock Q (50 µg/ml). Aliquots of Stock Q were diluted to obtain sample concentrations in the range of linearity. The absorbance values of these sample solutions were observed in a multi-point calibration curve of quantitative mode at the selected wavelength (258.2 nm) to obtain test sample concentration.

RESULTS

The linear regression equation obtained from analyzing standard solutions of cilostazol is shown in Eq 1.

ABC = 0.2069C - 0.204 …… (1)

It showed an r^2 = 0.9999 where ABC = absorbance, C = concentration (µg/ml), and r^2 = correlation coefficient. The standard absorptivity, A (1%, 1cm), and molar extinction coefficient (ε) for cilostazol were 420.23 $dlg^{-1}cm^{-1}$ and 15527.5 1 $Mol^{-1}cm^{-1}$, respectively (see Table 1). These developed methods were validated for various parameters, viz, accuracy, precision (repeatability, intermediate precision for days, instrument and analysts) and robustness. Statistical analysis (SD, CV, SEx and SEσ) for validation parameters are summarized in Table 2. These parameters were less than one. Thus, these parameters show the suitability of the methods.

Table 1: Standard absorptivity, A (1%, 1cm), and molar extinction coefficient (ε) for cilostazol

Conc. (µg/ml)	Absorbance at 258.2 nm			Standard absorptivity {A (1%, 1cm) = A/bc}		
	I	II	III	I	II	III
5	0.211	0.209	0.210	422.0	418.0	420.0
10	0.422	0.424	0.419	422.0	424.0	419.0
15	0.630	0.628	0.632	420.0	418.7	421.3
20	0.835	0.842	0.840	417.5	421.0	420.0
25	1.052	1.050	1.048	420.8	420.0	419.2

A (1%, 1 cm)* 420.23 $dlg^{-1}cm^{-1}$
ε ** 15527.5 1 $Mol^{-1}cm^{-1}$

** Mean of 15 standard absorptivity determinations;*
***Molar extinction coefficient ε = A (1%, 1cm) Molecular weight/10*

Table 2: Results of validation parameters for cilostazol

Validation parameter	% found* (mean)	SD	CV	SEx	SEσ
Linear regression equation (LRE) method					
Linearity	100.47	0.0106	0.3238	0.0047	0.0033
Accuracy	100.08	0.1603	0.1603	0.0653	0.0460
Precision					
I. Repeatability	100.92	0.0820	0.5056	0.0366	0.0259
II. Intermediate precision					
a. Days	101.13	0.0620	0.4548	0.0277	0.0196
b. Analysts	100.86	0.0540	0.3954	0.0241	0.0170
c. Instruments	100.34	0.6145	0.6625	0.2705	0.1910
Robustness	100.46	0.6733	0.6680	0.3013	0.2130
Standard absorptivity (SA) method					
Accuracy	100.12	0.2216	0.2210	0.0903	0.0636
Precision					
I. Repeatability	99.28	0.1080	0.8556	0.0482	0.0341
II. Intermediate precision					
a. Days	99.84	0.0620	0.4606	0.0277	0.0196
b. Analysts	99.64	0.0500	0.4006	0.0223	0.0158
c. Instruments	99.08	0.5915	0.5840	0.2645	0.1865
Robustness	99.20	0.6697	0.6730	0.2997	0.2120

** mean of six dilutions in triplicate; SD = standard deviation; CV = coefficient of variance; SEx = standard error of mean; and SEσ = standard error of standard deviation.*

Table 3: Results of cilostazol determination in tablets

Conc. (µg/ml) →	% found					
	LRE			SA		
Batch	10	15	20	10	15	20
I	101.70	101.20	100.60	100.40	99.93	99.35
II	102.10	101.50	101.40	100.80	100.30	100.20
III	100.90	100.80	101.20	99.70	99.60	99.95
IV	101.20	102.00	101.50	99.90	100.70	100.03
V	102.40	101.60	100.90	101.10	100.20	99.70
VI	100.00	100.40	100.90	98.70	99.13	99.70
Mean		101.23			99.96	
SD		0.611			0.592	
CV		0.603			0.592	
SEx		0.144			0.139	
SEσ		0.101			0.098	

LRE = linear regression equation method and SA = standard absorptivity method

The validated methods were applied to determine cilostazol in tablet dosage form, and the results were 101.23 % (SD = 0.611) by LRE method, and 99.96 % (SD = 0.592) by SA method. Mean of standard deviation (SEx) and standard error of standard deviation (SEσ) were far less than acceptable limits (see Table 3). Value of coefficient of variance for robustness was within acceptable limits.

DISCUSSION

The linear regression equation and standard absorptivity methods have been validated as per ICH guidelines, and results of validation parameters were within acceptable limits. Cilostazol was estimated by LRE and SA methods in tablet dosage form with standard deviation of 0.611 and 0.592, respectively. On comparing the two methods using the F-test, the calculated value of F (1.065) was substantially less than the theoretical value at 99 % confidence value; therefore, the methods have comparable precision. Impurities or any other interfering substances with λ_{max} close to that of cilostazol (258.2 nm) would adversely affect the accuracy of the developed methods.. Further study on possible interfering substances will need to be carried out.

CONCLUSION

The developed methods for cilostazol are simple, rapid and economical with acceptable accuracy, precision, reproducibility and are robust to slight variations in experimental conditions. Thus, the validated methods may be used for routine analysis of cilostazol as the bulk drug and in tablets and other dosage forms where excipients will not interfere spectrally.

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