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Zero order and First order Derivative Spectrophotometric methods for determination of Cisapride in Pharmaceutical formulation

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Abstract: Simple, fast and reliable derivative spectrophotometric methods were developed for determination of Cisapride in bulk and pharmaceutical dosage forms. The solutions of standard and the sample were prepared in methanol. The quantitative determination of the drug was carried out using the zero order derivative values measured at 275 nm and the first order derivative values measured at 264 nm (n=6). Calibration graphs constructed at their wavelengths of determination were linear in the concentration range of Cisapride using 4-24 µg.mL-1 (r^2 = 0.9998 and r^2 = 0.9998) for zero order and first order derivative spectrophotometric method. All the proposed methods have been extensively validated as per ICH guidelines. There was no significant difference between the performance of the proposed methods regarding the mean values and standard deviations. Developed spectrophotometric methods in this study are simple, accurate, precise, sensitive to assay of Cisapride in tablets.
Keywords: Cisapride, Derivative spectrophotometric, Zero order derivative spectrum, First order derivative spectrum.

1. INTRODUCTION

Cisapride is a gastro pro- kinetic[1] drug which act as an agonist at the pre-synaptic $5HT_4$[1,3] receptor & act as antagonist at $5HT_3$[1,3] receptors. The stimulation mediates release of acetyl-choline & its prokinetic action is blocked by atropine[1]. Cisapride is chemically cis-4-amino-5-chloro-N-[1-(3-(p-florophenyl)propyl]-3-methoxy-4piperidinyl]-o-anisamide[4] (**Fig.1**). Its molecular formula is $C_{23}H_{29}ClFN_3O_4$ and its molecular weight is 465.95.it is freely soluble in acetone, methanol and insoluble in water. Its melting point is 109.8 ^{0}c[4,7]. It is official in E.P[5] & B.P.[6]

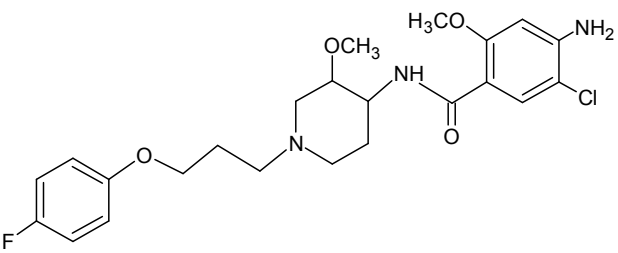

Figure 1. Chemical structure of Cisapride

Cisapride which is officially not available in U.S. as it is withdrawn on jan2000,[4,6,7]due to its side effects in the patients suffering from the cardiac arrthymias and hepato disorders, but it is official drug in Europe and U.K. In 1998 U.K. committee of safety medicine [4,6,7]as contraindicated to the patients with arrthymias. European society has recommended to use cisapride for gastro-oesophageal reflux disease. Regulatory authorities of India has not been announced to with draw because of its therapeutic use. It's very efficient the patients who are not responding to the metoclopramide. Cisapride does not have any dopaminergic[1] effect.

Literature survey reveals that, only bioanalytical methods by HPLC and few Spectrophotometric methods were found using human plasma and urine for the quantitative estimation of Cisapride in bulk drug and pharmaceutical formulations.[8-13]

2. EXPERIMENTAL

2.1. MATERIALS AND METHODS

Cisapride pure compound was kindly supplied by Intas Labs Pvt. Ltd., Dehradun, India and was used without further purification. All chemicals and reagents used were of analytical grade and were purchased from Merck Chemicals, India.

2.2. INSTRUMENTATION

For all the spectrophtometric methods, Shimadzu model 1700 double beam UV-VIS spectrophotometer with spectral bandwidth of 1.8nm, wavelength accuracy of 2 nm and a pair of 1 cm matched quartz cells of 10 mm optical path length was used.

2.3. PREPARATION OF STANDARD AND SAMPLE SOLUTIONS:

Stock solution of 1000 µg.mL-1of Cisapride was prepared in methanol, for zero order and first order derivative spectrophotometric analysis. The standard solutions were prepared by dilution of the stock solution with methanol in a concentration range of 4, 8, 12, 16, 20 and 24 $\mu g.mL^{-1}$ with methanol for zero order and first order derivative spectrophotometric methods. Methanol was used as a blank solution.

2.3. ASSAY PROCEDURE:

A total of 20 tablets of Cisapride were opened and the contents were weighed and mixed. Accurately weighed and powdered. An aliquot of powder equivalent to the weight of 1 tablet was accurately weighed and transferred to volumetric flask and was dissolved in 100 ml of methanol and made up to the volume with HPLC grade methanol. The solutions were filtered through a 0.45 µm nylon filter and sonicated for about 15 min and then volume made up with methanol. This solution was filtered to remove any insoluble matter. The filtrate was collected in a clean flask. Appropriate dilutions were made to obtain 12 $\mu g.mL^{-1}$ with methanol from stock solution for both zero order and first order derivative spectrophotometric methods. **Figure 2.**

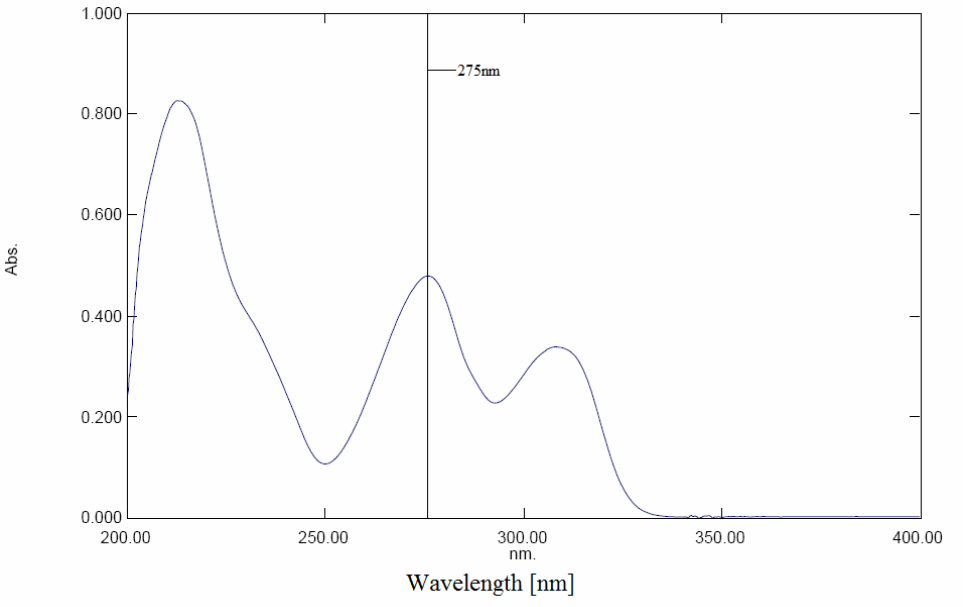

Figure 2. Zero order derivative spectrum of 12 µg.mL-1 Cisapride in methanol

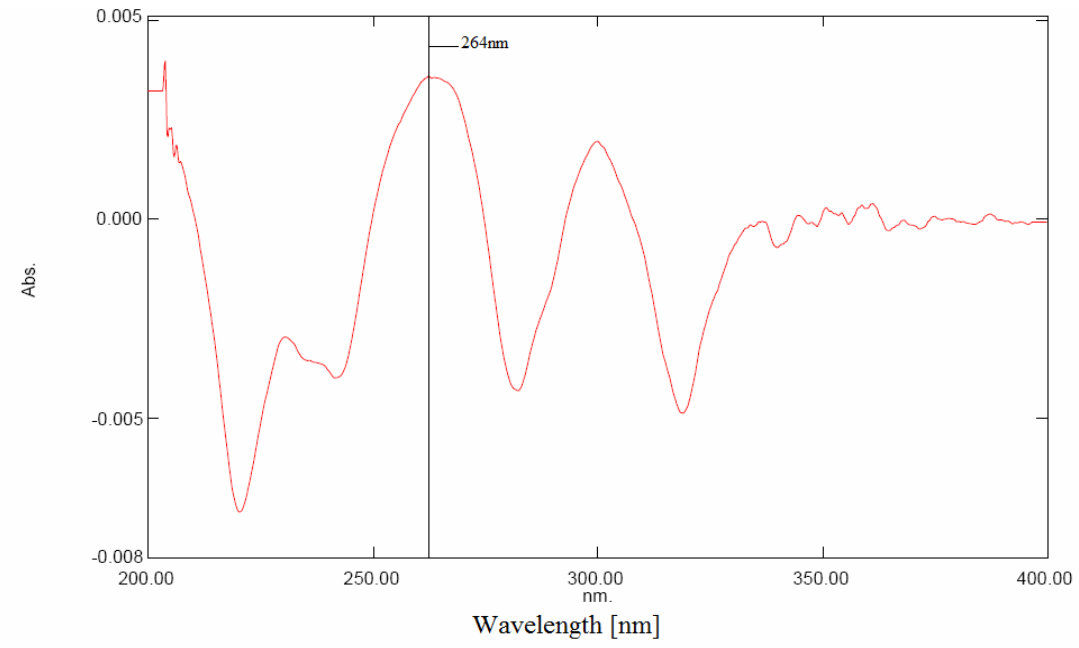

Figure 3. First order derivative spectrum of 12 µg.mL-1 Cisapride in methanol

Table I : Stastical data for the calibration graphs for determination of Cisapride by proposed methods

Parameters	**Zero order derivative**	**First order dwrivative**
Linearity range (4-24 µg.ml^{-1})	4-24	4-24
r ^{2}± S.D.	0.9998	0.9998

[a]n=6

Table II: Results of Intra and Inter Day Precision

Parameters	**Intra Day Precision**		**Inter Day Precision**	
	S.D	**% RSD**	**S.D**	**% RSD**
Zero derivative	0.0483	0.0482	0.0488	0.0489
First derivative	0.7327	0.7357	0.1133	0.1137

[a]n=6 [b]Average of one concentrations 12 µg.Ml^{-1}

3. RESULTS AND DISCUSSION

The zero order and first order derivative spectra for Cisapride were recorded at the wavelength of 275 nm and 264 nm respectively [Fig. 2-3].

3.1. LINEARITY AND RANGE:

Under the experimental conditions described, the graph obtained for zero order and first order derivative spectra showed linear relationship. Regression analysis was made for the slope, intercept and correlation coefficient values. The regression equations of calibration curves were y = 0.04x + 0.0067 (r2 = 0.9998) at 275 nm for zero order derivative spectrophotometry and y = 0.001x + 0.006 (r2 = 0.9998) for first order derivative spectrophotometry. The range was found to be 4-24 µg.mL^{-1} for both zero order and first order derivative spectrophotometric methods. (Table I).

Table III: Data of recovery studies

Actual concentration ($\mu g.ml^{-1}$)	Observed concentration ($\mu g.ml^{-1}$)	Recovery (%)	% RSD
Zero order derivative spectrophotometric method			
12	11.95	99.58	0.020
12.6	12.62	100.15	0.009
13.6	13.58	99.85	0.010
First order derivative spectrophotometric method			
12	12.03	100.25	0.009
12.6	12.57	99.76	0.010
13.6	13.59	99.92	0.010

Table IV : Assay results for the determination of Cisapride in pharmaceutical formulation

Parameters	Tablet brand name	Drug Content (%)	% RSD
Zero order derivative	Ciza 10mg	100.03	0.564
First order derivative	Ciza 10mg	99.93	0.377

[a]n=6, Average of three concentrations 12 µg Ml^{-1}

Table V : Summary of validation parameters

Parameter	Zero derivative method	First derivative method
Wavelength (nm)	275	264
Linearity range ($\mu g.Ml^{-1}$)	4-24	4-24
Correlation coefficient	0.9998	0.9998
Limit of detection ($\mu g.Ml^{-1}$)	0.048	0.952
Limit of quantitation ($\mu g.ml^{-1}$)	0.146	2.886
Mean recovery %	99.86	99.97
Precision(%±RSD) repeatability Inter day	0.0482 0.0489	0.7357 0.1137

3.2. PRECISION:

To determine the precision of the method, Cisapride solutions at a concentration of 12 $\mu g.mL^{-1}$ were analyzed each six times for both zero order and first order derivative spectrophotometric methods. Solutions for the standard curves were prepared fresh everyday (Table II).

3.3. SENSITIVITY:

The limit of detection (LOD) and limit of quantification (LOQ) were calculated by using the equations LOD = 3 x σ / S and LOQ = 10 x σ /S, where σ is the standard deviation of intercept, S is the slope. The LOD and LOQ were found to be 0.048$\mu g.mL^{-1}$ and 0.146 $\mu g.mL^{-1}$ respectively for zero order derivative and The LOD and LOQ were found to be 0.952 $\mu g.mL^{-1}$ and 2.886 $\mu g.\ mL^{-1}$ for first order derivative methods respectively.

3.4. RECOVERY:

To study the accuracy of the proposed methods, and to check the interference from excipients used in the dosage forms, recovery experiments were carried out by the standard addition method. This study was performed by addition of known amounts of Cisapride to reanalyzed solutions of commercial tablets (Table III).

3.5. ANALYSIS OF THE MARKETED FORMULATION:

There was no interference from the excipients commonly present in the tablets. The drug content was

found to be 99.91% with a % R.S.D. of 0.19 and 99.97% with a % R.S.D. of 0.11 for zero order and first order derivative spectrophotometric methods respectively. It may therefore be inferred that degradation of Cisapride had not occurred in the marketed formulations that were analyzed by this method. The low % R.S.D. value indicated the suitability of this method for routine analysis of Cisapride in pharmaceutical dosage form (Table IV). The summary of the validation parameters is depicted in (Table V).

4. CONCLUSION

No UV or derivative spectrophotometric methods have been described for the determination of Cisapride. Therefore simple, fast and reliable derivative spectrophotometric methods were developed for the routine determination of Cisapride. The developed methods can be concluded as accurate, sensitive and precise and can be easily applied to the pharmaceutical formulation.

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