Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6, Issue 4, 2014

Original Article

EXTRACTIVE SPECTROPHOTOMETRIC METHOD DEVELOPMENT AND VALIDATION FOR THE ESTIMATION OF CINITAPRIDE TARTRATE IN BULK AND PHARMACEUTICAL FORMULATIONS

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Received: 13 Mar 2014 Revised and Accepted: 27 Mar 2014

ABSTRACT

Objective: The aim of the present investigation was to develop two novel highly sensitive, selective, accurate and simple extractive spectrophotometric methods for the determination of Cinitapride tartrate (CNP) in its dosage forms and to validate them as per ICH guidelines.

Methods: These methods are based on complex formation of CNP with cobalt thiocynate (Method A) and methyl orange (Method B) which can be estimated at absorption maxima of 620 and 430 nm respectively. The factors affecting the reaction in both the methods were carefully studied and optimized.

Results: Linearity was obtained in concentration range of 6 to 30 µg/mL and 6 to 18 µg/mL, with correlation coefficient of 0.9999 and 0.9996 for method A and B respectively. Recovery was in the range of 99.41 –100.61%. The value of standard deviation and % RSD were found to be < 1.2 % which shows that the methods are highly accurate and precise.

Conclusion: The proposed methods were successfully applied for the determination of CNP in its bulk form and pharmaceutical formulations with good accuracy. Hence, these methods can be used for the routine quality control of CNP in its dosage forms.

Keywords: Cinitapride tartrate, Extractive Spectroscopy, Cobalt thiocynate, Methyl orange.

INTRODUCTION

Cinitapride tartrate[1, 2] (CNP) chemically 4-amino-*N*-[3-(Cyclohexan-1-yl-methyl)-4-piperidinyl]-2-ethoxy-5-nitrobenzamide (Figure 1), is a gastrointestinal agent belonging to the chemical classification of benzimidazole derivatives. It is a gastroenteric prokinetic agent acting via complex, but synergistic effects on serotonergic HT_4 (stimulation) and 5- 5-HT_2 (inhibition) receptor and dopaminergic D_2 (inhibition) receptors in the neuronal synapses of the myenteric plexus.

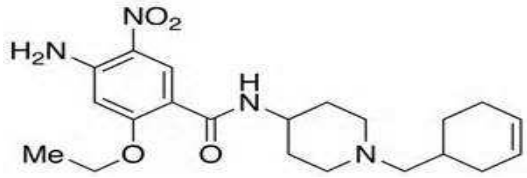


Fig. 1: Structure of CNP

Literature survey reveals that a few UV-Visible spectrophotometric[3-7], HPTLC[8], RP-HPLC[9-11], LC-MS/MS[12] methods have been reported for the estimation of CNP either in isolation or in combination of other drugs like pantaprazole[6, 10] and omeprazole[7, 11]. However the analytically important functional groups of the drug have not been fully exploited for the sensitive and precise determination of drug. Hence, the aim of the present work was to develop simple, rapid, economic and accurate method for the estimation of the drug in bulk and pharmaceutical formulations and to validate it as per ICH Guidelines[13].

MATERIALS AND METHODS

Instruments:

A Systronics Double beam UV visible spectrophotometer 2201 with 1 cm matched quartz cells was used for all spectral and absorbance measurements. A Systronics digital p^H meter was used for all p^H measurements.

Preparation of Reagents:

All the chemicals and reagents used were of analytical grade and solutions were prepared in double distilled water. The procedures for preparation of the various reagents were mentioned below.

Method A

CTC solution (2.5×10^{-1}M) Prepared by dissolving 7.25 gm of cobaltous nitrate and 3.8 gm of ammonium thiocyanate in 100 mL of distilled water. Buffer solution (P^H 2.0): Prepared by mixing 306 mL of trisodium citrate (0.1M) with 694 mL of HCl (0.1M) and the P^H was adjusted to 2.0.

Method B

Methyl orange (Fluka: 0.2% w/v, 6.11×10^{-3}M): Prepared by dissolving 200 mg of Methyl orange in 100 mL of distilled water and washed with chloroform.

Acid phthalate buffer: To 200 mL volumetric flask 50 mL of potassium hydrogen phthalate buffer (Prepared by dissolving 40.846 g of potassium hydrogen phthalate in 100 mL of water) and 0.1 mL of concentrated HCl were added. The volume was made up to mark with water.

Preparation of standard drug solution

The working standard solution (1.0 mg/mL) of CNP was prepared by dissolving 100 mg of the drug in 100 mL of water. This stock solution was further diluted with the same solvent to get 100 µg/mL of working standard solution.

Preparation of sample solution

20 commercially available tablets from different batches of a brand were procured from the local market. These tablets were transferred to a mortar and thoroughly ground. From this, tablet

powder equivalent to 10 mg was taken in to a 100 mL volumetric flask and was made up to mark with water.

Procedure for estimation:

Based on the results obtained in different trials the following procedures were recommended for the determination of CNP in bulk and pharmaceutical dosage formulations.

Method A:

Into a series of 125 mL separating funnels, CNP standard solution (100µg/mL) ranging from 0.6 to 3.0 mL was transferred and the volume in all separating funnels was adjusted to 2.0 mL with water. Then 4.0 mL of buffer (pH 2.0) and 5.0 mL of CTC were added. The total volume in each separating funnel was adjusted to 15.0 mL with distilled water. To each separating funnel 10 mL of nitrobenzene was added and contents were shaken for 5 min. The two phases were allowed to separate and the absorbance of the separated nitrobenzene layer was measured at 620 nm against a reagent blank. The amount of CNP was deduced from its Beer-Lambert's plot.

Method B:

To a series of 10 mL volumetric flasks, CNP standard solution (100 µg/mL) ranging from 0.6 to 1.8 mL was transferred and the volume in each volumetric flask was adjusted to 5.0 mL with water. Then 2.0 mL of methyl orange dye was added and mixed well. The complex formed was extracted into 10 mL chloroform. The absorbance was measured at 430 nm against the reagent blank. The amount of CNP present in the given sample solution was computed from its calibration curve.

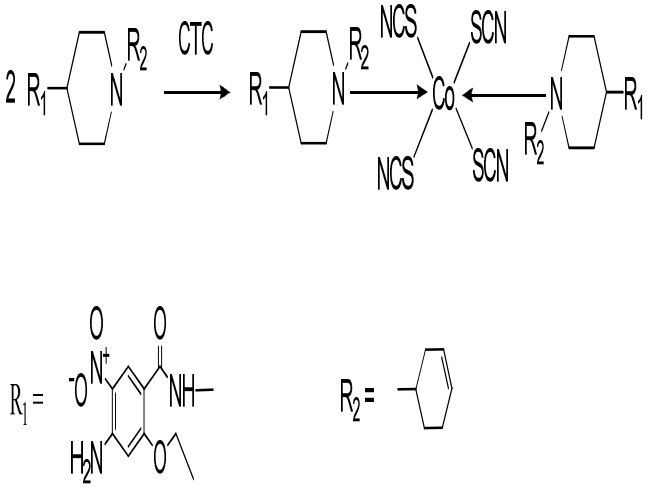
RESULT AND DISCUSSIONS

Method A:

Cobalt-thiocyanate can be utilized as a valuable chromogenic reagent for the detection and determination of tertiary amino compounds and phenothiazines. The coloured species formed is the coordination complex of the drug (electron donor) and the central metal atom of cobalt-thiocyanate, which is extracted in to non-aqueous solvents (usually nitrobenzene) from aqueous solution.

The green coloured complex formed between CNP and CTC can be attributed to presence of cyclic tertiary nitrogen in CNP. The probable sequence of reactions is presented in scheme no 1.

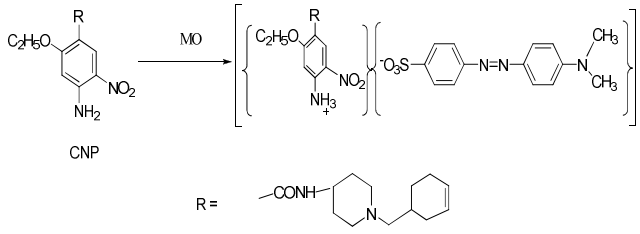
Reaction for CNP



Scheme: 1

Method B

As CNP has an amino group it forms ion association complex with acidic dyes MO. The proposed structure of ion association complex is shown in scheme no 2.



Scheme : 2

In order to ascertain the optimum wavelength of maximum absorption (λ max), the spectra were scanned in the wavelength region of 400 – 800 nm against a corresponding reagent blank. The reagent blank absorption spectrum of each method was recorded against solvent employed in each method. The results were graphically presented in the Figs. 2, 3.

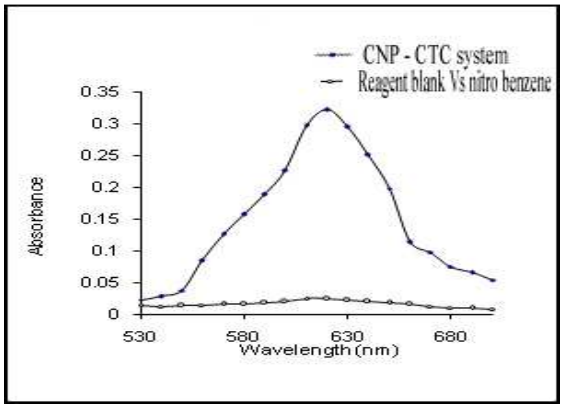


Fig. 2: Absorption spectra of CNP – CTC system and its reagent blank.

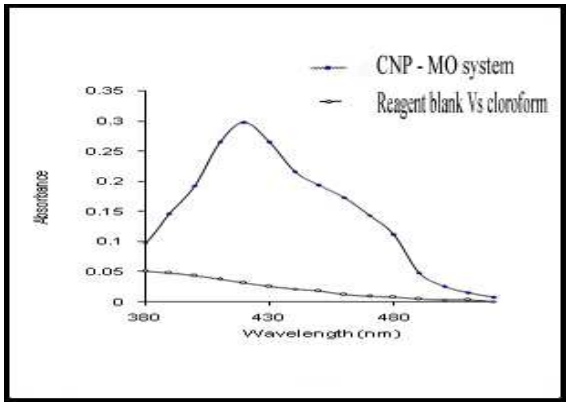


Fig. 3: Absorption spectra of CNP – MO system and its reagent blank.

The beer's plots of these systems were recorded (fig. 4, 5). Beer's law limits, molar absorptivity, sandell's sensitivity and optimum photometry range (fig. 6, 7) for CNP in each method developed with mentioned reagents were calculated. Least square regression analysis was carried out for getting the slop, intercept and correlation coefficient values. These were recorded in Table 1.

Interference studies were conducted to see the influence of excipients with proposed methods. The accuracy of the methods were evaluated by estimating the amount of CNP in previously analyzed samples to which known amounts of CNP was spiked. The results of accuracy were given in Table 2. Some of the commercial available formulations were procured from the local market and analyzed by the developed methods and the results comply with the labelled claim (Table 2).

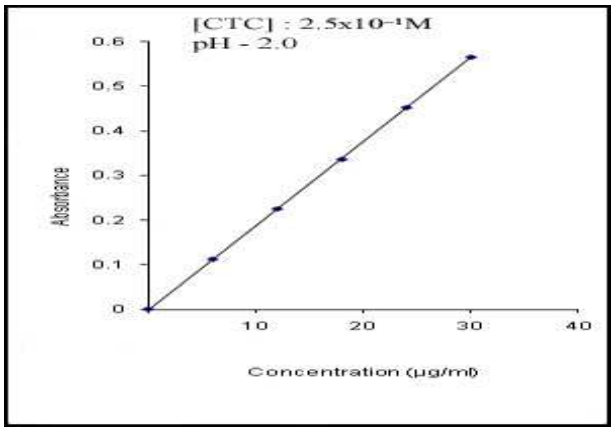


Fig. 4: Beer's plot of CNP – CTC system.

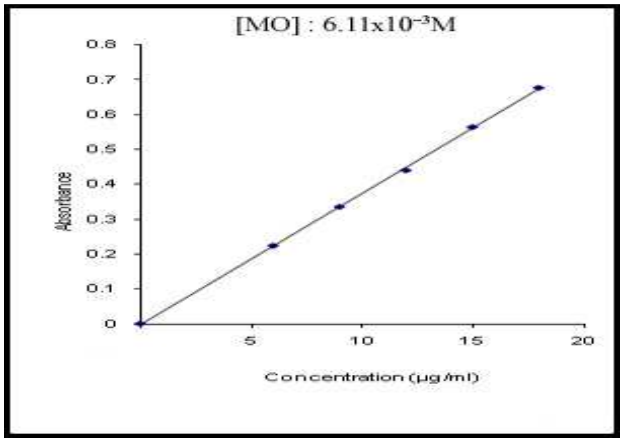


Fig. 5: Beer's plot of CNP – MO system

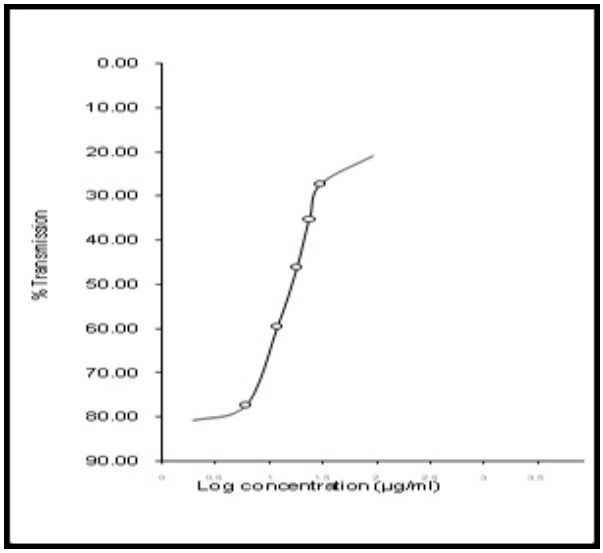


Fig.6: Ringbom plot of CNP – CTC system.

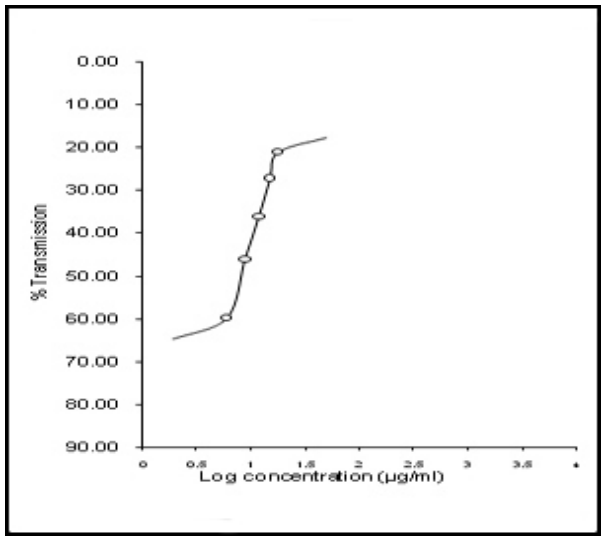


Fig. 7: Ringbom plot of CNP – MO system

Table 1: Optical characteristics and regression analysis parameters, precision and accuracy of the proposed methods for CNP

Parameter	M_1	M_2
λ_{max} (nm)	620	430
Beer's law limits (µg/mL)	6-30	6-18
Molar absorptivity (L. mole^{-1} cm^{1})	9.7 x 10^3	1.9 x 10^4
Detection limit (µg/mL)	0.165	0.335
Sandell's sensitivity (µg /cm ^{2}/0.001 absorbance unit)	0.0533	0.0267
Optimum photometric range (µg/mL)	8-40	5-50
Regression equation (Y = a+ bc):		
Slope (b)	0.0188	0.0376
Standard deviation of slope (S_b)	5.2 x 10^{-5}	3.2 x 10^{-5}
Intercept (a)	-0.0009	-0.0021
Standard deviation of intercept (S_a)	0.0009	0.0038
Standard error of estimation (S_e)	0.0013	0.0047
Correlation coefficient (r)	0.9999	0.9996
% Relative standard deviation*	0.1816	0.1824
% Range of Error (Confidence limits)*		
0.05 level	0.1905	0.1914
0.01 level	0.2988	0.3022
% Error in bulk samples**	0.0917	0.0913

* Average of six determinations** Average of three determinations.,

Table 2: Assay and Recovery of CNP in bulk forms

Method	Amount added (mg)	Proposed Method			% recovery by proposed methods**±S.D
		Amount found* (mg) ±S.D	t (value)	F (Value)	
M_A	5	4.94 ± 0.011	0.674	1.62	99.41 ±0.79
	10	10.05 ± 0.014	0.421	1.621	100.2± 0.85
M_B	5	5.01 ± 0.122	0.153	2.474	100.9 ± 0.61
	10	9.91 ± 0.057	0.075	1.104	100.61 ± 1.01

CONCLUSION

The proposed methods are economic, simple, sensitive, reproducible and accurate. Hence these can be used for the routine analysis of CNP in bulk as well as in its pharmaceutical preparations.

ACKNOWLEDGEMENT

The authors are thankful to Darwin labs pvt Ltd, A.P, India for providing gift sample of Cinitapride, Management of Siddhartha Academy General and Technical Education and Principal of our college for providing required facilities to carry out this research work.

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