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Research Article

APPLICATIONS OF COLORIMETRIC METHODS FOR THE DETERMINATION OF CINITAPRIDE HYDROGEN TARTARATE IN DRUG FORMULATIONS

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ABSTRACT

Six simple and sensitive spectrophotometric methods (A, B, C, D, E and F) have been developed for the quantitative estimation of cinitapride in bulk drug and pharmaceutical dosage forms. Method A and B is based on the oxidation followed by coupling reaction of cinitapride with 1, 10 phenanthroline and 2, 2' bipyridyl in presence of ferric chloride to form orange-red colored chromogens respectively. Methods are based on the diazotization of cinitapride with nitrous acid followed by its coupling *in situ* with N-(1-naphthyl) ethylenediamine dihydrochloride to form pinkish purple colored chromogen(C), with phloroglucinol to form orange colored chromogen (D), with diphenylamine to form pink colored chromogen (E) and with chromo tropic acid to form orange colored chromogen (F) respectively. The results of analysis for the six methods have been validated statistically and by recovery studies.

Keywords: CNT, Spectrophotometric

INTRODUCTION

Cinitapride[1-2], chemically 4-amino-*N*-[3-(Cyclohexan-1-yl-methyl)-4-piperidinyl]-2-ethoxy-5-nitrobenzamide has the molecular formula $C_{21}H_{30}N_4O_4$ and molecular weight 402.49 $g.mol^{-1}$ .Cinitapride is a drug that has against action to the serotoninergic 5-HT_2 and D_2 dopaminergic receptors that has been indicated in the gastro esophageal reflux and in the functional disorders of gastrointestinal motility treatment. The therapeutic effect of cinitapride lies on the capacity of increasing lower esophageal sphincter tone and has strong gastro kinetic activity, which generates significant increases in the gastric emptiness; besides, through the serotoninergic system it stimulates the intestinal activity. The use of cinitapride is efficient and safe in treatment of patients with disorders in the gastric emptiness related to gastro esophageal reflux and functional dyspepsia as well as in individuals that present irritable bowel syndrome with constipation and abdominal pain. Literature survey reveals a polarographic[3] method for its determination. Further, a fast, sensitive and selective method for measuring plasma cinitapride using LC-MS/MS with positive ion electrospray ionization using multiple reaction-monitoring (MRM) mode to quantify cinitapride in human plasma using respridone as the internal standard is also reported [4].To best of our knowledge, there is no work in the literature reported about the spectrophotometric method for the analysis of cinitapride in biological fluids or pharmaceutical formulations. Hence, the authors has made an attempt to develop few simple and rapid spectrophotometric methods [5-7] for the estimation of cinitapride in the bulk drugs and in pharmaceutical formulations.

MATERIALS AND METHODS

All spectral measurements were made on Shimadzu 1700 UV-Visible spectrophotometer with matching glass and quartz cells. The chemicals used were of analytical grade. All the aqueous solutions were prepared in double distilled water The commercial tablets were procured from local market. The gift sample of CNT was obtained from Chromo labs, Hyderabad.

Working standard of drug solution

About 100 mg of CNT was accurately weighed and dissolved in 20.0 mL of methyl alcohol in 100.0 mL of volumetric flask and diluted upto the mark with methyl alcohol (1 mg/mL). The final concentration of CNT was brought upto 100.0 µg/mL with methyl alcohol.

Sample preparation

A commercial tablet from different batches of a brand was analyzed by the proposed methods. Sufficient tablets of formulation each containing 1 mg of CNT were accurately weighed and powdered. Weight of tablet powder equivalent to 100 mg of drug was taken in 40 ml of methyl alcohol and shaken for 15.min, filtered into 100 ml volumetric flask through cotton wool and the remaining amount of methyl alcohol was added through tablet powder to make upto 100.0 mL. Final concentration of CNT was brought upto 100 µg/mL with methyl alcohol

Method A

Aliquots of CNT ranging from 0.2-1.0 mL (1 mL = 100µg/mL) were transferred into a series of 10.0 ml

volumetric flasks. To each flask 1.0 ml of aqueous solution of ferric chloride (0.5%w/v) and 1.0 ml of methanolic solution of 2-2'bipyridyl (0.25%w/v) were added, heated on a water bath for 25 minutes and then cooled to room temperature. The final volume was made upto 10.0 ml with distilled water. The absorbance of the orange red colored species formed was measured at 522.5 nm against the reagent blank and Beer's law obeyed in the concentration range of 2-10 µg/mL. The absorbance of reaction product at 522.5 nm remained stable for more than 3 hours. The amount of CNT in the sample solution was computed from calibration curve

Method B

Aliquots of CNT ranging from 0.1-5.0 mL (1 mL = 100µg/mL) were transferred into a series of 10.0 mL volumetric flasks. To each flask 0.5 ml of aqueous solution of ferric chloride (0.05%) and 0.5 ml of methanolic solution of 1, 10 phenanthroline (0.3%w/v) were added, heated on a water bath for 25 minutes and then cooled to room temperature. The final volume was made upto 10.0 ml with distilled water. The absorbance of the orange red colored species formed was measured at 510 nm against the reagent blank and Beer's law was obeyed in the concentration range of 1-5 µg/mL. The absorbance of reaction product at 510 nm remained stable for more than 3 hours. The amount of CNT in the sample solution was computed from calibration curve

Method C

Aliquots of CNT ranging from 0.4-2.0 mL (1 mL = 100 µg/mL) were transferred into a series of 10.0 mL volumetric flasks. To each flask 1.5 mL of hydrochloric acid (5N) and 0.5 mL of sodium nitrite(0.4%w/v) were added and kept aside for 10 min.Then 1 mL of aqueous solution of ammonium sulphamate (2% w/v) was added and solution was shaken thoroughly. After 2 min. 1 mL of methanolic coupling reagent, N-1-(naphthyl) ethylene diamine dihydrochloride (0.4%w/v) was added and diluted to mark with distilled water. The absorbance of pinkish purple colored species formed was measured at 533 nm against reagent blank and beer's law was obeyed in the concentration range of 4-20 µg/mL The absorbance of reaction product at 533 nm remained stable for more than 3 hrs. The amount of CNT present in the sample was computed from calibration curve

Method D

Aliquots of CNT ranging from 0.4-2.0 mL (1 mL = 100 µg/mL) were transferred into a series of 10.0 mL volumetric flasks. To each flask 1.0 mL of hydrochloric acid (5N) and 1.0 mL of sodium nitrite(0.2%w/v) were added and kept aside for 10 min.Then 1 mL of aqueous solution of ammonium sulphamate (2% w/v) was added and solution was shaken thoroughly After 2 min. 1 mL of methanolic coupling reagent, phloroglucinol (0.2%w/v) was added and diluted to mark with distilled water. The absorbance of orange colored species formed was measured at 438.6 nm against reagent blank and Beers law was obeyed in the concentration range of 4-20 µg/mL. The absorbance of reaction product at 438.6 nm remains stable for more than 3 hours. The amount of CNT in the sample solution was computed from the calibration curve

Method E

Aliquots of CNT ranging from 0.2-1.0 mL (1 mL = 100 µg/mL) were transferred into a series of 10.0 mL volumetric flasks. To each flask 1.0 mL of hydrochloric acid (5N) and 1.0 mL of sodium nitrite (0.2%) were added and kept aside for 10 min. Then 1 mL of aqueous solution of ammonium sulphamate (2% w/v) was added and solution was shaken thoroughly. After 2 min. 1 mL of methanolic coupling reagent, diphenylamine (0.2%w/v) was added and diluted to mark with distilled water. The absorbance of pink colored species formed was measured at 533.2 nm against reagent blank and Beer's law was obeyed in the concentration range of 2-10 µg/mL The absorbance of reaction product at 533.2 nm remained stable for more than 3 hrs. The amount of CNT present in the sample was computed from calibration curve

Method F

Aliquots of CNT ranging from 1.0-5.0 mL (1 mL = 100 µg/mL) were transferred into a series of 10.0 mL volumetric flasks. To each flask 1.0 mL of hydrochloric acid (5N) and 1.0 mL of sodium nitrite(0.2%) were added and kept aside for 10 min.Then 1 mL of aqueous solution of ammonium sulphamate (2% w/v) was added and solution was shaken thoroughly. After 2 min. 1 mL of methanolic coupling reagent, chromo tropic acid (0.2%w/v) was added and diluted to mark with distilled water. The absorbance of orange colored species formed was measured at 509.2 nm against reagent blank and Beer's law was obeyed in the concentration range of 10-50 µg/mL.The absorbance of reaction product at 509.2 nm remained stable for more than 3 hrs. The amount of CNT present in the sample was computed from calibration curve.

RESULTS AND DISCUSSIONS

The optical characteristic such as beer's law limits, sandell's sensitivity, molar extinction co-efficient, percent relative standard deviation (calculated from eight measurement containing $3/4^{th}$ of the amount of the upper beer's law limits) were calculated and the results are summarized in Table 1.Regression characteristic like slope,intercept,correlation co-efficient and percentage range of errors (0.05 and 0.01 confidence limits) were also calculated and are shown in Table1.

Table 1: Optical characteristics and precision

Parameter	Method A	Method B	Method C	Method D	Method E	Method F
λmax(nm)	522.5	510	533	438.6	533.2	509.2
Beer's law limits(µg/mL)(c)	2-10	1-5	4-20	4-20	2-10	10-50
Molar absorptivity (lit.mol^{-1}cm^{-1})	4.1x10^4	7.7x10^4	0.18x10^4	0.17x10^4	2.3x10^4	9.3x10^4
Sandell's sensitivity (µg.cm^{-2}/0.001 absorbance unit)	0.016	0.021	0.0625	0.0625	0.031	0.017
Regression equation(Y*)						
Slope(b)	0.99x10-1	0.1751	0.1180	0.0424	0.0770	0.0201
Intercept(a)	-0.016	0.0476	-0.7930	0.0220	-0.0949	0.0810
Correlation coefficient(r)	1.0026	1.0010	1.0011	0.9999	0.9999	0.9995
% RSD	0.2493	0.5555	0.1700	0.0820	0.3862	0.2145
Range of errors** confidence limits with 0.05 levels	± 0.0012	±0.0026	±0.00075	±.00106	±.00045	±0.00153
Confidence limits with 0.01 levels	± 0.0017	±0.0039	±0.00119	±.00157	±0.0016	±0.00226

*Y=bC+a, where C is the concentration of Cinitapride in µg/mL and Y is the absorbance at the respective λmax . ** For eight measurements.

Table 2: Assay and recovery of Cinitapride in pharmaceutical dosage form

Pharmaceutical dosage form	Labelled amount (mg)	Amount obtained by the Proposed methods(mg)						Reference UV method	Percentage recovery by the Proposed methods					
		A	B	C	D	E	F		A	B	C	D	E	F
T1	1.0	0.99	0.98	0.98	0.99	0.98	0.99	0.99	99.58	99.55	99.65	99.39	99.36	99.52
T2	1.0	0.98	0.99	0.98	0.98	0.99	0.98	0.98	99.09	98.89	98.81	99.58	99.89	99.65

T1 and T2 are tablets from different batches (Cintapro,Cadila Health Care Ltd,Ahmedabad)

Commercially available formulation of cinitapride was successfully analysed by the proposed methods and results are presented in Table 2.To evaluate validity and reproducibility of the methods, fixed amounts of drug were added to the pre-analysed formulations. These results of percentage recovery are summarized in Table-2.There is no interference of additives and excipients in the proposed analytical methods. The proposed spectrophotometric methods for estimation of cinitapride are simple, sensitive accurate and precise and can be used in routine estimation of this drug in bulk as well as in pharmaceutical formulation.

CONCLUSION

The results indicate that the proposed methods are simple,accurate,precise and economical for the estimation of cinitapride in bulk and in formulations

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