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Research Article

New Spectrophotometric Methods for the Assay of Cinitapride Hydrogen Tartrate (A Gastroprokinetic Drug)

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Abstract

Cinitapride hydrogen tartrate is a gastroprokinetic drug and acts against serotoninergic 5-HT2 and D2 dopaminergic receptors indicated for the gastroesophageal reflux and also for the treatment of functional disorders of gastrointestinal motility. New spectrophotometric methods (D_0 and D_1) have been developed and validated for the estimation of Cinitapride hydrogen tartrate tablets in acetate buffer (pH 4.0) and phosphate buffer (pH 5.0) using SHIMADZU Model No. UV – 1800 double beam spectrophotometer with 1 cm quartz cells. All the methods were validated as per ICH guidelines. The proposed methods are applied to the Cinitapride marketed formulations and the methods were found to be simple, precise and accurate.

Keywords: Cinitapride; Spectroscopy; Acetate Buffer; Phosphate Buffer; Validation; ICH Guidelines

Introduction

Cinitapride hydrogen tartrate (CAS 66564-14-5) is a gastroprokinetic drug (Figure 1) typically used for the treatment of gastrointestinal motility disorders such as gastroesophageal reflux disease, non-ulcer dyspepsia and delayed gastric emptying [1]. It is chemically 4-amino-*N*-[1-(cyclohex-3-en-1-ylmethyl) piperidin-4-yl]-2-ethoxy-5-nitrobenzamide; 2, 3-dihydroxy butanedioic acid ($C_{25}H_{36}N_4O_{10}$; Mo. wt. 552.57 g/mol) with pKa 9.74. It acts as an agonist at 5-HT1 and 5-HT4 receptors and as an antagonist of the 5-HT2 receptors [2,3].

Literature survey reveals that Cinitapride was estimated by different analytical techniques such as LC-MS [4], HPLC [5-8] and spectrophotometry [9-16] in pharmaceutical formulations as well as biological fluids. In the present study the authors have chosen two different buffers and two different spectrophotometric techniques i.e., zero order (D_0) and first order derivative (D_1) for the assay of Cinitapride hydrogen tartrate tablets and the methods were validated [17].

Figure 1: Chemical structure of Cinitapride hydrogen tartrate.

Materials and Methods

A double beam spectrophotometer (SHIMADZU Model No. UV – 1800) with 1 cm quartz cells was used for the present study and all the solutions were scanned at 200-400 nm range. The buffer solutions chosen such as acetate buffer (pH 4.0) and phosphate buffer (pH 5.0) were prepared as per IP 2010.

- **Preparation of Acetate buffer (pH 4.0)**: 2.86 ml of glacial acetic acid and 1.0ml of a 50% w/v solution of sodium hydroxide were transferred in to a 1000ml volumetric flask and the volume was made up to volume with distilled water, sonicated and filtered.
- **Preparation of Phosphate buffer (pH 5.0)**: 6.8g of potassium dihydrogen phosphate was transferred in to a 1000ml volumetric flask and the volume was made up to volume with distilled water, sonicated and filtered.

Procedure

A stock solution of Cinitapride hydrogen tartrate was prepared by dissolving 25 mg of API in methanol in a 25 ml volumetric flask (1000 µg/ml) and sonicated. A working standard solution (100 µg/ml) was prepared from which a series of diluted solutions (0.5-60 µg/ml) were prepared with acetate buffer (pH 4.0) and phosphate buffer (pH 5.0) as per the requirement.

Method validation

Zero order spectroscopy (D_0)

A series of Cinitapride hydrogen tartrate solutions 0.5-60 µg/ml were prepared using different buffer solutions such as acetate buffer (pH 4.0) (Method I) and phosphate buffer (pH 5.0) (Method II) and scanned against their reagent blank (200-400 nm). Cinitapride hydrogen tartrate has shown λ_{max} at 266.60 nm and 266.80 nm in Method I and Method II. A calibration curve was drawn by taking the concentration on the X-axis and their respective absorbance on Y-axis for both the methods.

First order derivative spectroscopy (D_1)

The individual zero order spectra of Cinitapride hydrogen tartrate obtained in Method I and Method II were converted into their first order derivative spectra with the help of inbuilt software of the instrument. The resultant derivative spectra for Method III and Method IV have shown both maxima and minima and therefore the amplitude was chosen for the computation work. A calibration curve was drawn by plotting the amplitude value on the y-axis against concentration for Method III and Method IV.

Intraday precision studies were performed (n = 6) at different time intervals on the same day and interday precision studies were performed (n = 3) on three consecutive days (Day 1, Day 2 and Day 3) and the statistical parameters were evaluated. Accuracy studies were carried out by standard addition method for Method I, Method II, Method III and Method IV.

Assay of Cinitapride tablets

Cinitapride hydrogen tartrate is available as tablets with brand names Cintapro (Label claim: 1 mg) (Zydus Cadila), Cinmove (Label claim: 1 mg) (Cipla Ltd), Kinpride (Label claim: 1 mg) (Dr. Reddy's Labs) etc. 20 tablets of two different brands were procured from the local pharmacy store and the assay was carried out. 20 tablets of each brand were weighed, powdered and powder equivalent to 25 mg Cinitapride hydrogen tartrate was transferred to two different 25 ml volumetric flask and sonicated after the addition of methanol. The contents were filtered and the dilutions were made with the buffers as per the requirement and the percentage of purity was calculated from the linear regression equation obtained from the calibration curve for all the proposed methods.

Results and Discussion

Two new spectrophotometric methods of Zero order (D_0) (Method I and Method II) and another two new spectrophotometric methods of first order derivative (D_1) (Method III and Method IV) were developed for the assay of Cinitapride hydrogen tartrate in acetate buffer (pH 4.0) and phosphate buffer (pH 5.0). A review of the previously published methods for the determination of Cinitapride hydrogen tartrate were shown in table 1.

Method validation

Zero order spectroscopy (D_0)

The absorption spectrum of Cinitapride hydrogen tartrate have shown at λ_{max} at 266.60 nm in acetate buffer (pH 4.0) (Method I) and 266.80 nm in phosphate buffer (pH 5.0) (Method II) respectively (Figure 2). Cinitapride hydrogen tartrate obeys Beer-Lambert's law over the concentration range 0.5-60 µg/ml for both Method I

Table 1: Literature survey.

Liquid chromatographic methods			
Mobile phase	**Linearity (µg/ml)**	**Detection wavelength (nm)**	**Ref**
0.1% formic acid in water, acetonitrile	5-100	268	[5]
Acetonitrile, phosphate buffer	12.55- 45.18	260	[6]
Acetonitrile, phosphate buffer	20-120	264	[7]
10mM ammonium acetate, methanol, acetonitrile	1-35	260	[8]
Spectrophotometric methods			
Reagent	Linearity (µg/ml)	λ_{max} (nm)	Ref
0.1N HCl	6-14	266	[9]
Sodium nitrite, 1M HCl, sulfamic acid, - 0.5% resorcinol, 20% NaOH, - 0.5% 1-benzoylacetone, 20% NaOH, - 0.5% 8-hydroxyquinoline, 20%NaOH	 2-32 1-24 1-20	 442 465 552	[10]
Dimethyl sulphoxide Nitrous acid	10-50 1-5	401 552	[11]
Methanol	5-40	260	[12]
Cobalt thiocyanate Methyl orange	6-30 6-18	620 430	[13]
Picric acid Citric acid- acetic anhydrate system	8-40 4-20	410 565	[14]
Bromocresol green Bromothymol blue	5-40 2-10	414 416	[15]
Ferric chloride and Nitrous acid	-	-	[16]
Zero order and Derivative spectroscopy Acetate buffer (pH 4.0) Phosphate buffer (pH 5.0)	 0.5-60 0.5-60	266.60 (Method I) 266.80 (Method II) 255.75-277.80 (Amplitude) (Method III) 255.75-276.82 (Amplitude) (Method IV)	Present methods

and Method II (Table 2). Calibration curves were drawn by taking the concentration of the drug on the x-axis and the corresponding absorbance on the y-axis. The linear regression equations are found to be y = 0.0655x + 0.0104 (R^2 = 0.9994) and y = 0.0553x + 0.0146 (R^2 = 0.9997) in acetate buffer (pH 4.0) (Method I) and phosphate buffer (pH 5.0) (Method II) respectively (Figure 3).

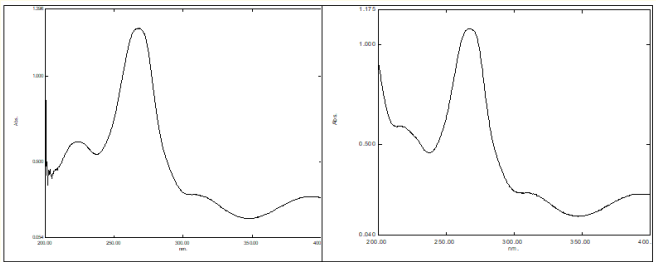


Figure 2: Absorption spectra of Cinitapride hydrogen tartrate (D_0).

Table 2: Linearity (Zero order spectroscopy) (D_0).

Conc. (µg/ml)	Method I (λ_{max} 266.60 nm)	Method II (λ_{max} 266.80 nm)
0.5	0.0440	0.0504
1	0.0712	0.0690
2	0.1331	0.1226
5	0.3359	0.3313
10	0.6814	0.5607
20	1.2802	1.0797
40	2.6899	2.2445
50	3.3179	2.7852
60	3.8799	3.3295

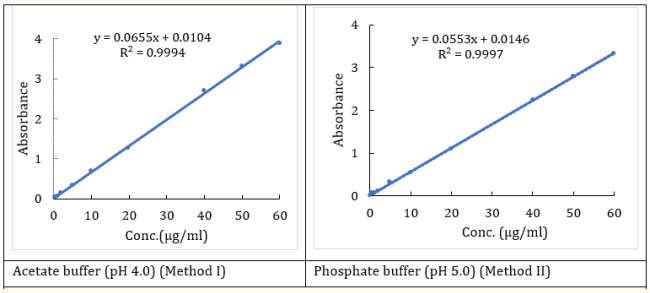


Figure 3: Calibration curve of Cinitapride hydrogen tartrate (D_0).

First order derivative spectroscopy (D_1)

The first derivative absorption spectra of Cinitapride hydrogen tartrate in acetate buffer (pH 4.0) (Method III) and phosphate buffer (pH 5.0) (Method IV) were shown in figure 4. Cinitapride hydrogen tartrate obeys Beer-Lambert's law over the concentration range 1-60 µg/ml in both Method III and Method IV (Table 3). Calibration curve was drawn by taking the concentration on the x-axis and the corresponding amplitude on the y-axis. The linear regression equations are found to be y = 0.0066x - 0.0055 (0.999) and y = 0.0053x - 0.0005 (0.9992) in acetate buffer (pH 4.0) (Method III) and phosphate buffer (pH 5.0) (Method IV) respectively (Figure 5).

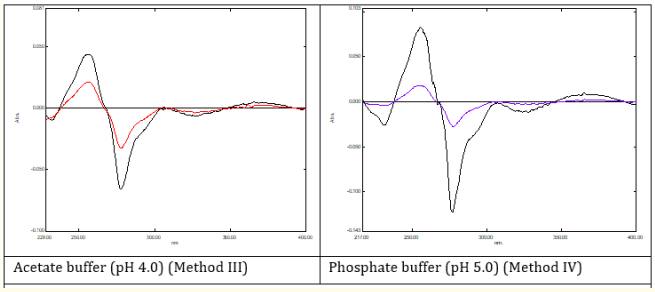
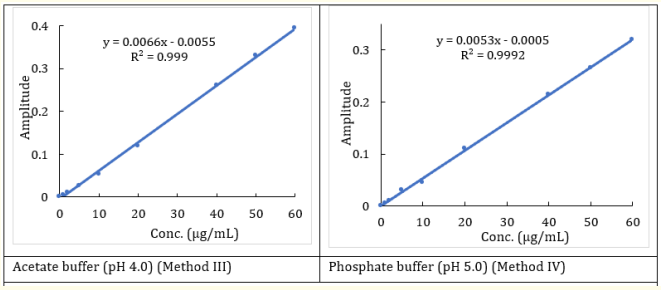


Figure 4: Derivative absorption spectra of Cinitapride hydrogen tartrate (D_1).

Table 3: Linearity (Derivative spectroscopy) (D_1).

Conc. (µg/ml)	Method III			Method IV		
	Minima (277.80 nm)	Maxima (255.75 nm)	Amplitude	Minima (276.82 nm)	Maxima (255.75 nm)	Amplitude
1	0.003	0.002	0.005	0.003	0.002	0.005
2	0.007	0.004	0.011	0.006	0.004	0.01
5	0.016	0.010	0.026	0.018	0.012	0.03
10	0.03s2	0.021	0.053	0.027	0.018	0.045
20	0.066	0.044	0.12	0.066	0.044	0.11
40	0.143	0.098	0.26	0.122	0.083	0.215
50	0.197	0.145	0.33	0.164	0.101	0.265
60	0.222	0.172	0.394	0.201	0.132	0.32



Acetate buffer (pH 4.0) (Method III) | Phosphate buffer (pH 5.0) (Method IV)

Figure 5: Calibration curve of Cinitapride hydrogen tartrate (D_1).

In all the methods (Method I, II, III and IV) the percentage RSD in precision (Intraday and Interday) and accuracy studies was found to be less than 2.0 indicating that the methods are precise and accurate. The Optical characteristics of the proposed methods were shown in table 4.

Table 4: Optical characteristics.

Parameters		Method I	Method II	Method III	Method IV
Linearity (µg/ml)		0.5-60	0.5-60	1-60	1-60
λ_{max} (nm)		266.60	266.80	255.75-277.80	255.75-276.82
Molar extinction coefficient (litre/mole/cm^{-1})		3.7649×10^{4}	3.0983×10^{4}	-	-
Sandell's sensitivity (µg/cm^2/0.001 absorbance unit)		0.0147	0.0561	-	-
Slope		0.0655	0.0553	0.0066	0.0053
Intercept		0.0104	0.0146	0.0055	0.0005
Correlation coefficient		0.9994	0.9997	0.9990	0.9992
Precision (%RSD)	Intraday	0.53-0.94	0.54-0.62	0.07-0.61	0.42-0.82
	Interday	0.71-0.86	0.41-0.72	0.42-0..74	0.31-0.68
Accuracy (% RSD) (< 2.0)		0.79-0.82	0.76-0.98	0.34-0.68	0.29-0.89

Table 5: Assay (Label claim: 1.0 mg).

Brand	Method I		Method II	
	Zero order spectroscopy (D_0)			
	Observed amount (mg)	% Recovery	Observed amount (mg)	% Recovery
I	0.9499	94.99	0.9130	91.30
II	0.9405	94.05	0.9037	90.37
	Method III		Method IV	
	Derivative spectroscopy (D_1)			
I	0.9772	97.72	0.9339	93.39
II	0.98	98.00	0.948	94.80

*Mean of three replicates.

Assay of formulations (Tablets)

The percentage of purity of Cinitapride hydrogen tartrate is found to be 94.05-94.99, 90.37-91.30, 97.72-98.00 and 93.39- 94.80 for Method I, Method II, Method III and Method IV respectively (Table 5) and no interference of excipients was observed.

Conclusion

The proposed new spectrophotometric methods are validated for the estimation of Cinitapride hydrogen tartrate and found to be simple, precise and accurate and all these methods can be applied successfully for the assay of Cinitapride hydrogen tartrate in tablet dosage forms.

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