Research Article

DEVELOPMENT AND VALIDATION OF REVERSE PHASE HIGH PERFORMANCE LIQUID CHROMATOGRAPHY METHOD FOR SIMULTANEOUS ESTIMATION OF CINITAPRIDE AND OMEPRAZOLE IN COMBINED CAPSULE DOSAGE FORM

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ABSTRACT

A reverse phase high performance liquid chromatography (RP-HPLC) method for the simultaneous estimation of Cinitapride Hydrogen Tartrate (CNT) and Omeprazole (OMP) in combined capsule dosage form was developed and validated. The determination was carried out on a Lichrospher® 100, RP-18e (5 µm), Merck Ltd., India, 250 mm L × 4.6 mm ∅ in size column using mobile phase in gradient mode as Methanol: Water (95: 05 v/v). The flow rate was 1.2 ml/min with detection wavelength at 276 nm. The retention time for OMP was 1.978 and for CNT was 3.325 min. CNT and OMP showed a linear response in the concentration range of 0.75-3.75 µg/ml and 5-25 µg/ml respectively. The correlation coefficient r^2=0.9993 for CNT and r^2=0.9990 for OMP. The results of analysis have been validated statistically and by recovery studies. The average percentage recoveries obtained for CNT and OMP was found to be 98.97% and 99.22% respectively.

Keywords: RP-HPLC, Cinitapride hydrogen tartrate, Omeprazole.

INTRODUCTION

Day to day numbers of newer drugs and their formulations either in single or in combined dosage forms were marketed. Combination of CNT and OMP was approved in 12th May - 2010 by CDSCO India & manufactured and marketed by Zydus Cadila Healthcare as Burpex capsule (20 mg OMP and 3 mg CNT). Combination is used in treatment of gastric ulcer, gastro esophageal reflux disease (GERD) & Dyspepsia not responding to OMP alone.

OMP is substituted Benzimidazole, (RS)-6-methoxy-2-((4-methoxy-3,5dimethylpyridin-2-yl) methylsulfinyl)-1H-benzoimidazole (Figure 1) that function as proton pump inhibitor. It is anti-secretory drug effective for rapid healing peptic ulcer and corrosive esophagitis.[1-6] CNT is Benzamide class of drug, 4–Amino–N-[1-(3cyclohexen-1-ylmethyl)-4-piperidinyl]-2-ethoxy-5-nitrobenzamide Hydrogen L-(+)-tartrate (Figure 2) that function as pro-kinetic agent and antiemetic.[7,8]

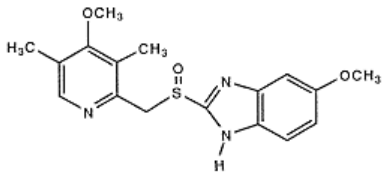

Figure 1: Chemical Structure of OMP

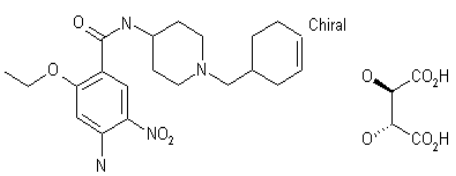

Figure 2: Chemical Structure of CNT

OMP is official in Indian Pharmacopoeia, British Pharmacopoeia, U.S. Pharmacopoeia[9-11] while CNT is not official in any pharmacopoeia. Deep literature survey reveals that numbers of analytical methods are reported for the estimation of OMP and CNT in single dosage forms. Reported methods for estimation of OMP are RP-HPLC[12-17], LC-MS[18-20], Spectrophotometry[21-23], Spectrofluometry[24] and similarly for estimation of Cinitapride are RP-HPLC[25-27], LC-MS[28], HPTLC[29], Spectrophotometry[30], Colorimetric assay[31-33] and Area Under Curve method.[34]

We could not trace reverse phase high performance liquid chromatography method for the estimation of these two drugs in combined dosage forms. So, the rational of work is to develop and validate simple, sensitive, specific, accurate and precise RP-HPLC method for the estimation of these two drugs in combined capsule dosage form.

MATERIALS AND METHODS

Apparatus and Instruments

- HPLC: Make & Model: Young - Linn Clarity 9100 HPLC System

Degasser: Vacuum Degasser YL – 9101

Pump: Quaternary Pump YL – 9110

Detector: PDA detector YL – 9160

Column: Lichrospher® 100, RP-18e (5 µm), Merck Ltd., India, 250 mm L × 4.6 mm ∅ in size

Temperature: Ambient

Pressure: 1000 - 3000 psi

- Double beam UV-visible spectrophotometer (Shimadzu, Model 1800) having two matched quartz cells with 1 cm light path

- Electronic analytical balance, Shimadzu AUX-220
- Ultrasonicator
- Borosilicate Volumetric flask – 10, 25, 50, 100 ml
- Borosilicate Pipettes – 1, 2, 5, 10 ml
- All instruments and glass wares were calibrated.

Reagents and Standards

- Omeprazole IP (Gift sample – Sunrise Remedies Pvt. Ltd, Ahmedabad)
- Cinitapride Hydrogen Tartrate (Gift sample – Zydus Cadila Health Care, Ahmedabad)
- Combined capsule formulations (BURPEX) were procured from Indian market.
- Methanol for Chromatography Lichrosolv® (Merck Pvt. Ltd., Mumbai)
- Water for Chromatography Lichrosolv® (Merck Pvt. Ltd., Mumbai)
- Sartorius Filter Paper 0.2 micron (Sartorius, Germany)

Method

Selection of Analytical Wavelength

The standard solutions of CNT (10 µg/ml) and OMP (10 µg/ml) in Methanol were scanned separately in the UV region of 200 to 400 nm and the overlain spectra were recorded. Isoabsorptive point at 276 nm which is selected as wavelength for measurement in HPLC, depicted in Figure 3.

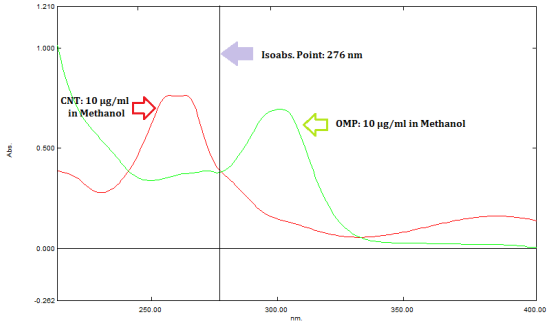

Figure 3: Overlay UV spectra of CNT (10 µg/ml) and OMP (10 µg/ml) in Methanol

Preparation of Standard Solutions

Preparation of CNT standard solution

Accurately weighed quantity of CNT 50 mg was transferred into 50 ml volumetric flask, dissolved and diluted up to the mark with methanol to give a stock solution having strength of 1000 µg/ml. Pipette out 5 ml of solution from 1000 µg/ml stock solution and transfer into 50 ml volumetric flask and diluted up to the mark with methanol to give a working standard solution having strength of 100 µg/ml.

Analytical method validation

Validation of developed method was carried out as per ICH Q_2 R_1 guideline.[35] Parameters such as Linearity, Accuracy, Precision, Specificity, LOD, LOQ, Ruggedness and Robustness were taken up as tests for analytical method validation.

Preparation of OMP standard solution

Accurately weighed quantity of OMP 50 mg was transferred into 50 ml volumetric flask, dissolved and diluted up to the mark with methanol to give a stock solution having strength of 1000 µg/ml. Pipette out 5 ml of solution from 1000 µg/ml stock solution and transfer into 50 ml volumetric flask and diluted up to the mark with methanol to give a working standard solution having strength of 100 µg/ml.

Chromatographic Conditions

- HPLC Model : Young - Linn Clarity 9100 HPLC System
- Stationary Phase : Lichrospher® 100, RP-18e (5 µm), Merck Ltd., India, 250 mm L × 4.6 mm ∅ in size
- Mobile Phase : Methanol: Water (95:05 v/v)
- Flow rate : 1.2 ml/min
- Detection Wavelength : 276 nm
- Temperature : Ambient
- Run time : 8 minutes
- Injection volume : 20 µl

Preparation of Calibration Curves

Pipette out 5 ml of the working standard solution of CNT (100 µg/ml) diluted up to 50 ml, from this 0.75, 1.5, 2.25, 3 and 3.75 ml was transferred into a series of 10 ml volumetric flasks, to this working standard solution of OMP 0.5, 1.0, 1.5, 2.0 and 2.5 ml was transferred and diluted up to the mark with mobile phase (methanol: water 95:5 v/v). Thus final solutions of mixture of CNT and OMP obtained contain 0.75 & 5 µg/ml, 1.5 & 10 µg/ml, 2.25 & 15 µg/ml, 3 & 20 µg/ml and 3.75 & 25 µg/ml respectively. The solutions were injected using Rhenodyne Injector (Fixed Capacity Loop of 20 µl) and chromatograms were recorded. Then, calibration curves were constructed by plotting peak area against concentration of the drug to construct two separate calibration curves for both the drugs.

System Suitability Test

Observed values of Resolution, Column efficiency, Tailing factor were depicted in Table 1.

Linearity and Range

The proposed RP-HPLC shows good linearity in the concentration range of 0.75 to 3.75 µg/ml for CNT and 5 to 25 µg/ml for OMP depicted in Figure 4 and 5. Chromatograms of standard mixture of CNT and OMP depicted in Figure 6 & 7.

Precision

The intraday precision of the developed method was evaluated by analyzing combined samples of different concentrations of CNT and OMP three times on the same day and %RSD was calculated. The inter day precision was evaluated by analyzing combined samples of different concentrations of CNT and OMP on three different days and %RSD was calculated. Repeatability was evaluated by combined standard solutions of CNT (3 µg/ml) and OMP (20 µg/ml) were prepared and analyzed six time on the same day and %RSD was calculated. Results obtained are shown in Table 2.

Accuracy

Accuracy of the method was confirmed by recovery study from marketed formulation at three level of standard addition from 50 % to 150 % of label claim. The results are shown in Table 3 and 4. Recovery greater than 98% with low SD justifies the accuracy of the method.

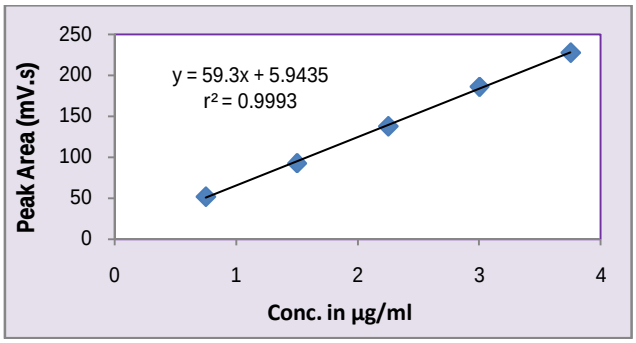

Figure 4: Calibration curve for CNT in Methanol: Water (95: 05 v/v)

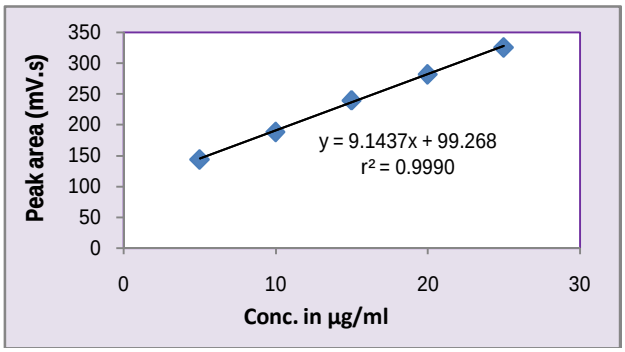

Figure 5: Calibration curve for OMP in Methanol: Water (95: 05 v/v)

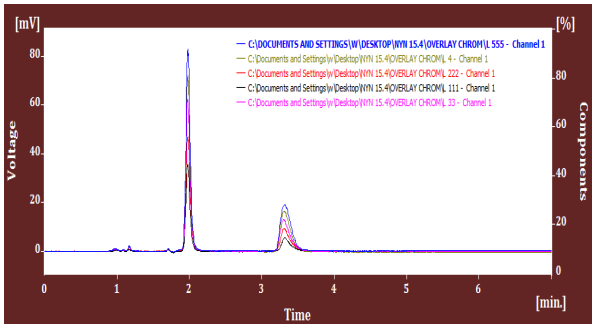

Figure 6: Chromatogram of calibration curve for CNT (0.75-3.75 µg/ml) and OMP (5-25 µg/ml)

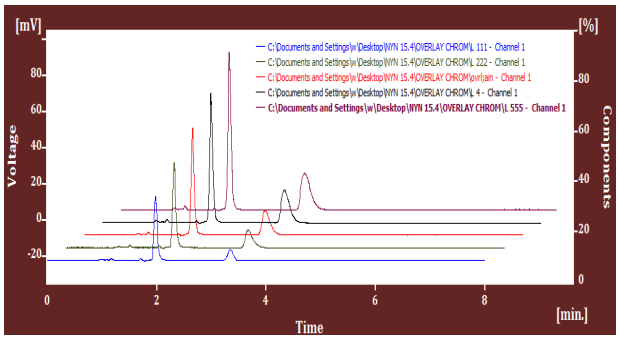

Figure 7: 3D view of Chromatogram of calibration curve for CNT (0.75-3.75 µg/ml) and OMP (5-25 µg/ml)

Specificity

Specificity is the ability to assess unequivocally the analyte in the presence of components that may be expected to be present. Typically, these might include impurities, degrades etc. A solution of placebo in mobile phase was injected and the chromatogram showed no inferring peaks at retention time of the two drugs. The chromatogram of placebo were compared with those acquired from CNT and OMP standards, correlation was good (in terms of t_R and area) indicates the specificity of method. Chromatograms of specificity for CNT and OMP depicted in Figure 8 to 10.

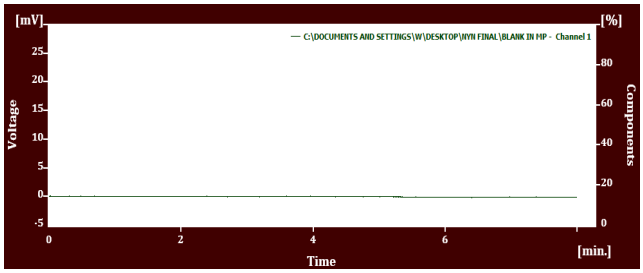

Figure 8: Specificity Chromatogram of Blank Placebo in Methanol: Water (95: 05 v/v)

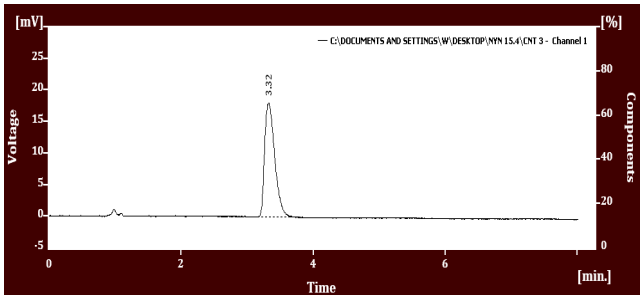

Figure 9: Specificity Chromatogram of standard CNT (3 µg/ml)

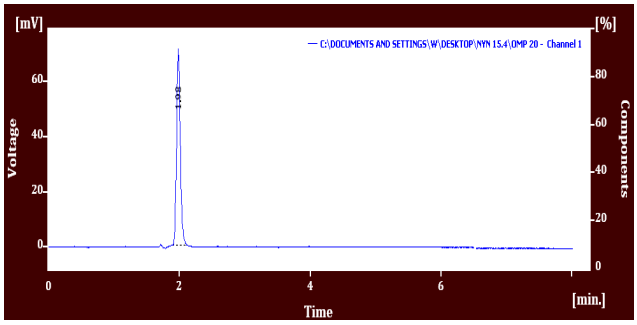

Figure 10: Specificity Chromatogram of standard OMP (20 µg/ml)

LOD and LOQ

Calibration curve of mixture was repeated for 5 times and the standard deviation (SD) of the intercepts was calculated. Then LOD and LOQ were calculated as follows.

LOD=3.3 * SD/slope of calibration curve,

LOQ=10 * SD/slope of calibration curve.

Where, SD = Standard deviation of intercepts

Results obtained are shown in Table 2.

Ruggedness

Ruggedness of the proposed method was determined by analysis of aliquots of sample solution (3 µg/ml CNT and 20 µg/ml OMP) by two analyst using same operational and environmental conditions. Results obtained are shown in Table 5.

Robustness

The Robustness of the method was evaluated by

A) By changing the flow rate by 1.2 ± 0.1 ml/min (1.1 ml/min and 1.3 ml/min).

B) By changing mobile phase ratio by 95 ± 1.0 % (94 and 96 %) for methanol

C) By changing detection wavelength by ± 2 nm (274 nm and 278 nm).

Results obtained are shown in Table 6.

Analysis of marketed formulation by proposed method

Twenty capsules were weighed and average weight of content was determined & the content of capsules was powdered. The powder equivalent to 20 mg of OMP or 3 mg of CNT was transferred in to a 50 ml volumetric flask, dissolved and diluted up to the mark with methanol. The solution was filtered through Sartorius filter paper (0.2 µ). An aliquots of 0.5 ml of this solution was diluted to 10 ml with mobile phase six times.

Each solution was injected using Rhenodyne Injector (Fixed Capacity Loop of 20 µl) and chromatograms were recorded. The peak area of each chromatogram was determined. The concentration of each drug was calculated using calibration curve equation.

The results obtained are shown in Table 7.

Table 1: System Suitability Test Parameter

System Suitability Parameters	Proposed Method		Standard Values
	OMP	CNT	
Retention times	1.978 ± 0.0061	3.325 ± 0.0163	-
Theoretical plates	5342	2369	Greater than 2000
Resolution	7.198 ± 0.517		Greater than 2
Tailing factor	1.217 ± 0.017	1.497 ± 0.038	Not greater than 2.0

Table 2: Summary of Validation parameters

Sr. No.	Validation Parameters	Results		Standard Values
		CNT	OMP	
1	Linearity Range	0.75-3.75 µg/ml	5-25 µg/ml	-
2	Straight line equation	y = 59.3x + 5.9435	y = 9.1437x + 99.268	-
3	Correlation Coefficient	0.9993	0.999	≥ 0.999
4	Precision (% RSD):			≤ 2.0 %RSD
	Repeatability	0.225	0.401	
	Intraday	0.452	0.309	
	Interday	0.717	0.399	
5	Mean % Recovery	98.97	99.22	98 – 102%
6	Specificity	Specific		
7	LOD (µg/ml)	0.050	0.124	-
8	LOQ (µg/ml)	0.152	0.377	-
9	Ruggedness	Complies		≤ 2.0 %RSD
10	Robustness: Changing in Flow rate Changing in Mobile phase ratio Changing in Detection Wavelength	Complies		≤ 2.0 %RSD

Table 3: Recovery of CNT from formulation (BURPEX)

Amount taken (µg)	Amount added (µg)	Total amount of CNT (µg)	Amount of CNT recovered (µg ± S.D.) [n=3]	% Recovery of CNT* ± S.D.
1.5	-	1.5	1.491 ± 0.0100	-
1.5	0.75	2.25	2.229 ± 0.0029	99.07 ± 0.1237
1.5	1.5	3	2.959 ± 0.0076	98.63 ± 0.2524
1.5	2.25	3.75	3.720 ± 0.0215	99.21 ± 0.5726
Average % Mean Recovery				**98.97**

Table 4: Recovery of OMP from formulation (BURPEX)

Amount taken (µg)	Amount added (µg)	Total amount of OMP (µg)	Amount of OMP recovered (µg ± S.D.) [n=3]	% Recovery of OMP* ± S.D.
10	-	10	9.899 ± 0.0532	-
10	5	15	14.917 ± 0.0673	99.45 ± 0.4484
10	10	20	19.875 ± 0.0844	99.37 ± 0.4223
10	15	25	24.711 ± 0.0968	98.84 ± 0.3872
Average % Mean Recovery				**99.22**

Table 5: Ruggedness Data

Ruggedness Study by Analyst - I		
Analyst – I	**CNT**	**OMP**
Mean % Assay* ± SD	99.489 ± 0.5635	98.889 ± 0.5156
% RSD	0.5664	0.521
Ruggedness Study by Analyst – II		
Analyst – II	**CNT**	**OMP**
Mean % Assay* ± SD	99.461 ± 0.7928	99.656 ± 0.2479
% RSD	0.797	0.249

*n=3

Table 6: Robustness results for variations in Method Parameters

Method Parameters	Mean*		S.D.		%RSD	
	CNT	OMP	CNT	OMP	CNT	OMP
Flow rate 1.2 ± 0.1 ml/min	99.957	98.8663	0.91166	0.91572	0.91205	0.92622
% of Methanol 95 ± 1.0 % (v/v)	99.752	99.5823	0.71826	1.10952	0.72004	1.11418
Wavelength ± 2 nm	100.209	99.5703	0.84035	1.09496	0.83859	1.09969

* n=3

Table 7: Analysis of market formulation

Capsule	Label Claim (mg)		Amount Obtained (mg)*		% Assay ± S.D.	
	CNT	OMP	CNT ± S.D.	OMP ± S.D.	CNT	OMP
BURPEX	3	20	2.995 ± 0.0078	19.914 ± 0.1456	99.85 ± 0.261	99.57 ± 0.728

*n=6

RESULTS AND DISCUSSION

A simple, specific, accurate and precise RP-HPLC method has been developed and validated for simultaneous estimation of both these drugs. The chromatographic separation was achieved on Lichrospher® 100, RP-18e (5 µm), Merck Ltd., India, 250 mm L × 4.6 mm ∅ in size column using Methanol: Water (95: 05 v/v) as mobile phase at 276 nm. RP-HPLC method shows linearity in the range of 0.75-3.75 µg/ml for CNT and 5-25 µg/ml for OMP. The correlation coefficient was 0.9993 and 0.9990 found for CNT and OMP respectively. The average percentage recoveries of CNT and OMP for RP-HPLC method are of 98.97% and 99.22% respectively. The average percentage assay results of CNT and OMP for RP-HPLC method are of 99.85% and 99.57% respectively. This is comparable to labeled claim. System suitability test reveal that all system suitability parameters complies with standard values.

CONCLUSION

We have successfully developed a new simple RP-HPLC method for the simultaneous estimation of CNT and OMP combination in mixture using simple mobile phase methanol and water. Rapidity and capability of qualifying very low concentration of respective drugs, made them useful for variety of analyses, including pure drug analysis, assay of formulations and stability studies analysis. The purposed method did not utilize any extraction step for recovering the drug from the formulation excipient matrixes and their by decreased the degree of error, time in estimation of the drugs and the overall cost of the analysis. The method was validated and found to be simple, sensitive, accurate, precise and economical. The proposed method could be applied for routine analysis in quality control laboratories.

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