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Original Article

HPTLC Method Development and Validation of Cilnidipine and Metoprolol Succinate in Combined Dosage Form

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ABSTRACT

Introduction and Objectives: The present work involves development and validation of HPTLC method for simultaneous estimation of Cilnidipine and Metoprolol Succinate in their combined tablet dosage form. **Method:** In HPTLC method, Silica Gel G60 F254 TLC plate as the stationary phase and a mobile phase of Toluene: Chloroform: Methanol: Glacial acetic acid (45: 25: 25: 5 v/v/v/v) was used to resolve CIL and METO. CIL and METO were quantified at 231 nm. The proposed method weas validated according to International Conference on Harmonization. **Result and Discussion:** Two well-separated and sharp peak for CIL and METO were obtained at R_f values of 0.70 ± 0.01 and 0.34 ± 0.005 respectively. The linearity range obtained for HPTLC method were 100-500 ng/spot and 500-2500 ng/spot for CIL and METO respectively. **Conclusion:** Method validation was found to be accurate, specific and precise.The developed method was successfully applied for estimation of CIL and METO in combined tablet formulation.

Key words: Cilnidipine, Metoprolol succinate, HPTLC, Tablets, Simultaneous estimation, Method validation.

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INTRODUCTION

Cilnidipine is a dual blocker of L-type voltage gated calcium channels in sympathetic nerve terminals that supply blood vessels and is used in treatment of hypertension. It also dilates efferent and afferent arterioles. Chemically it is described as 2-Methoxyethyl (2E)-3-Phenyl-2 propen-1-yl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3,5-pyridine dicarboxylate. Metoprolol Succinate, β-1 selective receptor blocker, is competitive antagonist of catecholamines at peripheral adrenergic neuron leading to decreased cardiac output. It is used in management of acute myocardial infection, angina pectoris, heart failure and hypertension. Chemically it is described as Bis[(2RS)-1-[4-(2-Methoxy ethyl)phenoxy]-3-[(1-methyl) amino]propan- 2-ol] butanedioate. Metoprolol is official in BP 2009 and USP 2007. Potentiometric titration method is given in BP 2009[1] and liquid chromatography method is official in USP 2007.[2]

Literature survey reveals that no analytical method has been developed for estimation of cilnidipine and metoprolol succinate, however it was found that Spectrophotometric[3-6] RP-HPLC[7] and HPTLC[8] methods for cilnidipine alone and in combination with other drug are available and also Spectrophotometric[9-19] HPLC[20-28] HPTLC[29-32] method for metoprolol alone and in combination with other drugs are available. No analytical method till date has been published for simultaneous estimation of cilnidipine and metoprolol succinate. Although, a dosage form consisting of cilnidipine and metoprolol succinate in combination is being marketed. Therefore, in present work HPTLC method for simultaneous analysis of cilnidipine and metoprolol succinate has been devloped.

MATERIALS AND METHODS

Chemicals and Reagents

Cilnidipine was obtained as gift sample from J.B. Chemicals and Pharmaceuticals Pvt. Ltd., Ankleshwar and Metoprolol succinate was obtained as gift sample from Zydus Cadila, Ahemdabad. Aluminium based silica gel 60 F_{254} plates (Merck) were purchased from Anchrom Technologist, Mumbai. Cilacar M tablet were purchased from local pharmacy. The analytical grade chloroform, toluene methanol and Glacial acetic acid were purchased from Thomas Baker. All reagents and chemicals used were of analytical grade.

Insrtumentation

Analysis was performed on 10×10 cm aluminium based silica gel 60 F_{254} plates (Merck, supplied by Anchrom Technologist, Mumbai). Samples were applied on plates by Linomat-V semiautomatic sample applicator with the help of Hamilton Syringe (100 µl). TLC plates were developed in Camag twin-trough developing chamber (20×20 cm). Densitometry was performed on TLC scanner 4.

UV-800 Spectrophotometer was used to determine detection wavelength. Hot air oven (Shital Scientific Ltd.) was used to dry silica plates. Pipettes (Borosil) of 1, 2, 10 and 25 ml, Volumetric flasks (Borosil) of 10, 25, 100 ml capacity were used. All weighing was carried out using Reptech electronic weighing balance

Preparation of standard stock solution
Standard stock solution

Accurately weighed Cilnidipine (10 mg) and Metoprolol Succinate (50 mg) were transferred into 10 ml volumetric flask separately, dissolved and diluted up to mark with methanol to give stock solutions having strength of 1000 µg/ml of Cilnidipine and 5000 µg/ml of Metoprolol Succinate.

Combined standard solution

Combined solution of Cilnidipine (100 µg/ml) and Metoprolol succinate (500 µg/ml) was prepared by diluting standard stock solution (1.0 ml) of each with methanol in 10 ml volumetric flak. Volume was made up to the mark with methanol.

Chromatographic separation

The chromatographic separation was performed on silica gel 60 F_{254} aluminium plates (10×10 cm) as stationary phase and Toluene: Methanol:

Chloroform: glacial acetic acid (45: 25: 25: 5 v/v/v/v) as mobile phase. TLC plates were prewashed with methanol and activated in an oven at 105ºC for 30 min prior to chromatography. The working standard/sample solutions were applied on TLC plate in the form of bands of 6 mm width using a Camag Linomat 5 semi automatic sample applicator. A constant application rate of 0.1 µl/s was employed and space between two bands was fixed automatically. Ascending development to 90 mm was performed in Camag (20×20 cm) twin trough glass chamber saturated with the mobile phase for 30 min at room temperature. The developed TLC plate was air dried and scanned between 200 to 400 nm using Camag TLC scanner IV. Both drug showed reasonably good response at 231 nm keeping the slit dimension of 4×0.30 mm and scanning speed of 20 mm/s.

Selection of mobile phase

Chloroform, Toluene, Methanol, Glacial acetic acid in different ratio were tried to achieve good separation. Mobile phase has been developed in such a ratio which provides optimum polarity for proper migration, separation and resolution Cilnidipine and Metorpolol Succinate.

Selection of detection wavelength

Solution of CIL (10 µg/ml) and METO (50 µg/ml) were scanned between 200-400 nm using UV-visible spectrophotometer. Wavelength was selected from the overlay spectra of above solutions.

Preparation of Calibration Curve

Different volumes of combined standard solution 1, 2, 3, 4 and 5µl were spotted on TLC plate to obtain concentrations of 100, 200, 300, 400 and 500 ng/spot of Cilndipine and 500, 1000, 1500, 2000 and 2500 ng/spot of Metoprolol Succinate respectively. Solutions were spotted and analyzed by HPTLC under stated chromatographic condition. The graph of peak area versus respective concentration was plotted.

Analysis of tablet formulation

Total 20 tablets were accurately weighted and triturated with glass mortar and pestle. The powder equivalent to 10 mg of CIL and 50 mg of METO was taken in 10 ml volumetric flask; mobile phase was added and the flask was kept in an ultrasonic bath for 10 min. Volume was made upto the mark with mobile phase. From this solution, 1 ml was transferred to another 10 ml volumetric flask. The volume was made up to mark and the solution was filtered through 0.45 micro membrane filter. 3 µl of diluted solution was spotted on TLC plate and analyzed under optimized chromatographic conditions. The areas of resulting peak were measured at 231 nm.

Validation of HPTLC method

Linearity: The linearity response was determined by analyzing 5 independent levels of calibration curve in the range of 100-500 ng/spot for Cilnidipine and 500-2500 ng/spot for Metoprolol Succinate. The calibration curve for Cilnidipine and Metoprolol Succinate were constructed by plotting peak area versus respective concentration. The mean area with its standard deviation and % relative standard deviation of peak were calculated.

Precision

Set of three different concentrations in three replicates of mixed standard solutions of CIL and METO were prepared. All the solutions of CIL and METO were analyzed on the same day in order to record any intraday variation study. For interday study three different concentrations of the mixed standard solutions in linearity range were analyzed on three consecutive days. For repeatability studies of peak area and sample application, three replicates of single concentration were analyzed.

Recovery studies

Recovery studies were carried out by adding standard drug solution to pre analyzed sample solution at three different levels 80, 100, 120%. Chromatograms were developed and peak areas noted at each level of the amount, three determinations were carried out.

LOD and LOQ

The LOD (Limit of Detection) was estimated from the set of 6 calibration curves used to determine method linearity. The LOD may be calculated as

$$LOD = 3.3 \times \frac{S.D.}{Slope}$$

Where,

S.D.=Standard deviation of the response

Slope=Mean slope of calibration curves

The LOQ (Limit of Quantitation) was estimated from the set of 6 calibration curves used to determine method linearity. The LOQ may be calculated as

$$LOQ = 10 \times \frac{S.D.}{Slope}$$

Where,

S.D. = Standard deviation of the response

Slope = Mean slope of calibration curves

RESULT AND DISCUSSION

Different mobile phase containing different ratios of toluene, methanol and chloroform was tried (Table 1). Finally optimized mobile phase was Methanol: Chloroform: Toluene: Glacial acetic acid (45:25:25:5). The optimum wavelength for detection used was 231 nm (Figure 1). The retention factors of CIL and METO was found to be 0.70 ± 0.01 and 0.34 ± 0.005 respectively (Figure 2).

Straight line calibration graphs were obtained in range 100-500 ng/spot for CIL and 500-2500 ng/spot for METO. (Table 2). 3-D chromatogram is shown in Figure 3. The calibration plots obtained for CIL (Figure 4) and METO (Figure 5). The proposed method was evaluated by assay of commercially available tablets containing CIL and METO. The % assay was found to be 101.36 ± 0.48 and 100.03 ± 0.75 (Table 3).

For accuracy, all the recovery values of CIL (Table 4) and METO (Table 5) were within ± 5%. Intraday precision data for CIL and METO were found in range 0.581-0.694 and 0.411-0.659 (Table 6). Interday precision data for CIL and METO were found in range 1.435-1.803 and 1.723-1.878 (Table 7). Repeatability of peak area (Table 8) for CIL and METO showed %RSD of 0.490 and 0.585 respectively. Repeatability data for sample application for CIL and METO showed %RSD of 0.510 and 0.680 respectively (Table 9). LOD and LOQ data are tabulated in Table 10. Summary of validation parameters is depicted in Table 11.

CONCLUSION

HPTLC method was developed and validated for simultaneous estimation of Cilnidipine and Metoprolol succinate which consisted of Toluene: Chloroform: Methanol: Glacial acetic acid (45:25:25:5 v/v/v/v) as mobile phase. Saturation time was kept 30 min. The drugs were separated at Rf value of 0.70 ± 0.011 for Cilnidipine and 0.34 ± 0.005 for Metoprolol Succinate. Cilnidipine and Metoprolol succinate showed linearity in the range of 100-500 ng/spot and 500-2500 ng/spot with correlation coefficient of 0.9954 and 0.9991 respectively. The method was found to be accurate, precise and specific.

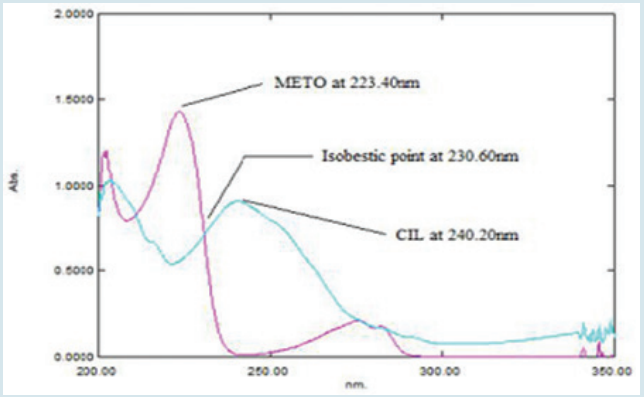

Figure 1: Selection of wavelength.

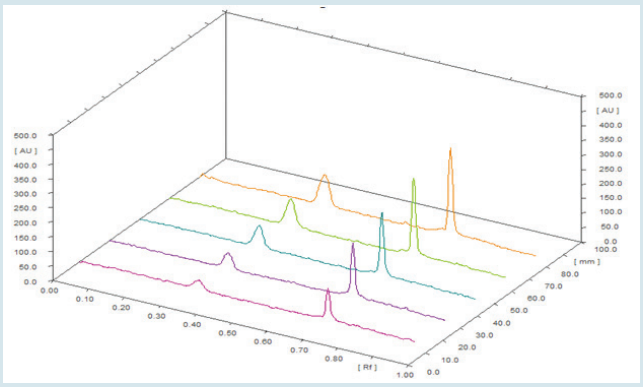

Figure 3: 3-D chromatogram of CIL and METO showing linearity.

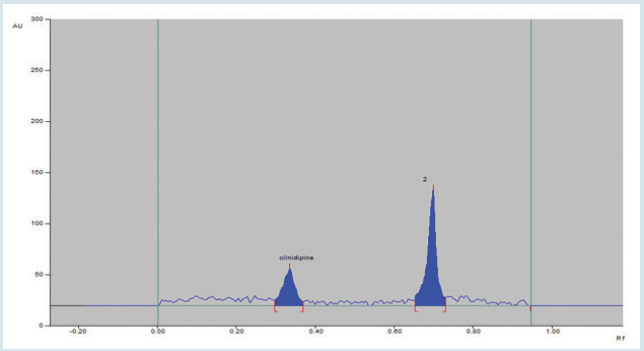

Figure 2: Densitogram showing Retention factors of CIL and METO.

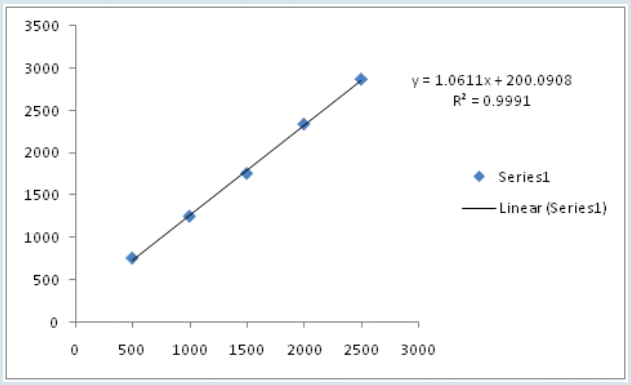

Figure 4: Calibration Curve of CIL.

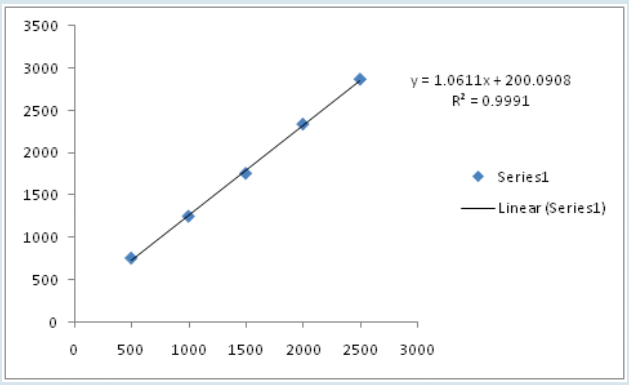

Figure 5: Calibration Curve of METO.

Table1: Trials for selection of mobile phase

Mobile phase	R_f value	Inference
Methanol (100)	Cilnidipine-0.96 Metoprolol succinate- 0.91	Poor Seperation
Chloroform (100)	Cilnidipine-0.94 Metoprolol succinate- 0.86	Poor Seperation
Toluene	-	No spot detected
Methanol: Toluene (90:10)	Cilnidipine-0.91 Metoprolol succinate- 0.79	Separation was not good and Rf value was out of range
Methanol: Toluene (70:30)	Cilnidipine–0.86 Metoprolol succinate-0.63	Rf value was out of range
Methanol: Toluene (60:40)	Cilnidipine-0.80 Metoprolol Succinate-0.56	Rf value was out of range
Chloroform: Toluene (90:10)	Cilnidipine-0.87 Metoprolol Succinate- 0.73	Separation was not good and Rf value was out of range
Chloroform: Toluene (70:30)	Cilnidipine-0.78 Metoprolol Succinate-0.52	Not proper separation
Chloroform: Toluene (60:40)	Cilnidipine-0.76 Metoprolol Succinate-0.46	Seperation was good but Rf value was not proper
Methanol: Chloroform: Toluene (35:35:30)	Cilnidipine-0.78 Metoprolol Succinate-0.43	Seperation was good but Rf value was not proper
Methanol: Chloroform: Toluene (25:25:50)	Cilnidipine-0.73 Metoprolol succinate-0.36	Seperation was proper but tailing was observed in metoprolol
Methanol: Chloroform: Toluene: Glacial acetic acid (45:25:25:5)	Cilnidipine-0.70 Metoprolol Succinate-0.34	Separation was proper

Table 2: Linearity data of CIL and METO

CIL			METO		
Conc. (ng/spot)	Mean ± S.D. (n=3)	% RSD	Conc. (ng/spot)	Mean ± S.D. (n=3)	% RSD
100	1254.36 ± 10.60	0.845	500	755.416 ± 5.61	0.743
200	1866.85 ± 11.14	0.597	1000	1248.87 ± 8.20	0.656
300	2364.09 ± 14.51	0.613	1500	1754.02 ± 12.51	0.713
400	2824.32 ± 111.41	0.404	2000	2335.65 ± 20.94	0.896
500	3263.00 ± 16.32	0.500	2500	2864.79 ± 16.53	0.577

Table 3: Assay of Marketed formulation (Cilacar-M tablet)

Actual Conc. (ng/spot)		Mean conc. obtained ± S.D.		% Conc. Of Label claim	
CIL	METO	CIL	METO	CIL	METO
300	1500	304.10 ± 5.65	1500.51 ± 25.99	101.36	100.03

Table 4: Recovery study of CIL

Conc of CIL in tablet (µg/ml)	Conc. Of std. CIL spiked (µg/ml)	Total conc. of CIL (µg/ml)	Mean area ± S.D. (n=3)	Conc. Recovered	% Recovery
200	0	200	1823.80 ± 29.45	201.43	100.71
200	160	360	2620.13 ± 24.00	159.84	99.90
200	200	400	2812 ± 27.069	198.38	99.19
200	240	440	3021.90 ± 28.91	240.52	100.21

Table 5: Recovery study of METO

Conc of METO in tablet (µg/ml)	Conc. Of std. METO spiked (µg/ml)	Total conc. of METO (µg/ml)	Mean area ± S.D. (n=3)	Conc. Recovered	% Recovery
1000	0	1000	1269.8 ± 17.54	1004.38	100.43
1000	800	1800	2114.03 ± 16.25	795.6	99.46
1000	1000	2000	2326.20 ± 27.29	995.47	99.54
1000	1000	2000	2554.83 ± 20.96	1210.94	100.91

Table 6: Intraday precision data for CIL and METO

CIL			METO		
Conc. (ng/spot)	Mean area ± S.D. (n=3)	%RSD	Conc. (ng/spot)	Mean area ± S.D. (n=3)	%RSD
100	1256.87 ± 8.727	0.694	500	764.033 ± 5.040	0.659
300	2351.52 ± 13.671	0.581	1500	1753.373 ± 11.309	0.645
500	3242.07 ± 30.351	0.936	2500	2864.223 ± 11.785	0.411

Table 7: Interday precision data for CIL and METO

CIL			METO		
Conc. (ng/spot)	Mean area ± S.D. (n=3)	%RSD	Conc. (ng/spot)	Mean area ± S.D. (n=3)	%RSD
100	1237.193 ± 25.757	1.783	500	753.84 ± 15.104	1.777
300	2327.03 ± 33.413	1.435	1500	1732.87 ± 32.54725	1.878
500	3208.527 ± 57.870	1.835	2500	2824.43 ± 48.68488	1.723

Table 8: Repeatability of peak area measurement for CIL and METO

CIL			METO		
Conc. (ng/spot)	Mean area ± S.D. (n=3)	%RSD	Conc. (ng/spot)	Mean area ± S.D. (n=3)	%RSD
300	2357.63 ± 11.556	0.490	1500	1778.13 ± 10.237	0.585

Table 9: Repeatability of sample area application for CIL and METO

CIL			METO		
Conc. (ng/spot)	Mean area ± S.D. (n=3)	%RSD	Conc. (ng/spot)	Mean area ± S.D. (n=3)	%RSD
300	2349.133 ± 12.005	0.590	1500	1764.933 ± 12.008	0.680

Table 10: LOD and LOQ data of CIL and METO

Parameters	CIL	METO
LOD	4.936001	4.936001
LOQ	27.18213	82.3701

Table 11: Summary of validation parameters

Parameter	CIL	METO
Linearity range (ng/spot)	100-500	500-2500
Correlation Coefficient	0.9954	0.9991
Repeatability		
Peak area measurement	0.490	0.585
Sample application	0.590	0.680
Intraday precision (%RSD, n=3)	0.581-0.694	0.411-0.659
Interday precision (%RSD, n=3)	1.435-1.803	1.723-1.878
Accuracy (%Recovery)	99.19-100.21	99.46-100.91
LOD (µg/ml)	4.936001	4.936001
LOQ (µg/ml)	27.18213	82.3701

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CONFLICT OF INTEREST

The author have no conflict of interest to declare.

ABBREVIATION USED

HPTLC: High Performance Thin Layer Chromatography; **CIL:** Cilnidipine; **METO:** Metoprolol; **LOD:** Limit of Detection; **LOQ:** Limit of Quantification.

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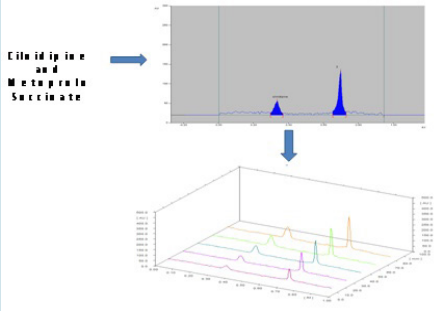
PICTORIAL ABSTRACT



SUMMARY

- A simple, precise and accurate HPTLC method was developed for the estimation of Cilnidipine and Metoprolol succinate in combined dosage form.
- The drugs were satisfactorily resolved at R_f value 0.70 ± 0.01 for Cilnidipine and 0.34 ± 0.005 for Metoprolol succinate.
- The accuracy and reliability of the proposed method was determined by evaluating various validation parameters like linearity, precision, accuracy according to ICH guidelines.

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