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Development and Validation of HPTLC Method for Estimation of Nicardipine Hydrochloride in Injectable Dosage Form

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ABSTRACT :

A simple, accurate, precise and suitable High Performance Thin Layer Chromatography (HPTLC) method was developed and validated for estimation of Nicardipine Hydrochloride in its marketed injectable dosage form. Chromatographic separation of Nicardipine Hydrochloride was achieved on TLC Silica gel 60 F254 plates as a stationary phase using a standardized mobile phase comprising of n-Hexane: Ethyl acetate: Methanol: Ammonia (60:20:20:0.3). Densitometric detection and quantification was carried out at 237 nm. The Retention Factor (Rf) values of Nicardipine Hydrochloride were found to be 0.436 respectively with good resolution and peak shapes. The method was validated in accordance with ICH guidelines for specificity, linearity, precision, recovery, sensitivity and robustness. The method was found to be linear in the concentration range of 10-100 ng/band with the Correlation coefficient value of 0.9999. Mean percent recovery of Nicardipine Hydrochloride sample solutions was found to be 100.32 %. The Limit of Detection (LOD) and Limit of Quantitation (LOQ) values for Nicardipine Hydrochloride were found to be 4 ng/band and 12 ng/band respectively. The proposed method was novel since there wasn't previously a reported HPTLC method for Nicardipine Hydrochloride in its injectable dosage form and was applied successfully for the quantitative analysis of the same. The validated method is convenient, time efficient and extremely suitable for all types of analysis and quality checks to be done for Nicardipine Hydrochloride.

Keywords: High Performance Thin Layer Chromatography (HPTLC), Method Development and Validation.

1.Introduction :

Cardiovascular disease (CVD) is the leading cause of death worldwide, with most deaths attributed to hypertension resulting from coronary heart disease or stroke and more than three quarters of these deaths occurring in low- and middle-income countries. The level of high blood pressure (BP) is directly related to many adverse outcomes, including CVD and kidney diseases[1]. Hypertension is the most common modifiable risk factor for death and disability including stroke, accelerated coronary and systemic atherosclerosis, heart failure and chronic kidney diseases. Lowering the BP with antihypertensive drugs and reducing the target organ damage and prevalence of the occurrence of cardiovascular disease becomes essential[2]. Therefore,diagnosis and effective treatment of HBP is one of the main goals to prevent and reduce its complications, and pharmacological treatment is the cornerstone of hypertension management[3].

A common dihydropyridine calcium channel blocker with proven effectiveness in the treatment of several cardiovascular diseases is nicardipine hydrochloride. A calcium channel blocker of the second generation, nicardipine has been extensively used to treat various cardiovascular diseases such as hypertension, angina pectoris, and subarachnoid hemorrhage. It has proven to be effective in regulating calcium influx and producing vasodilatory effects[4]. Nicardipine hydrochloride produces a significant decrease in systemic vascular resistance. The degree of vasodilation and the resultant hypotensive effects are more prominent in hypertensive patients. In hypertensive patients, nicardipine reduces the blood pressure at rest and during isometric and dynamic exercise. In normotensive patients, a small decrease of about 9 mm Hg in systolic and 7 mm Hg in diastolic blood pressure may accompany this fall in peripheral resistance. An increase in heart rate may occur in response to the vasodilation and decrease in blood pressure, and in a few patients this heart rate increase may be pronounced[5].

1.1. Literature Survey :

Few High-Performance Liquid Chromatography (HPLC) and Ultra High-Performance Liquid Chromatography (UHPLC) methods for estimation of Nicardipine in bulk and tablet dosage forms were reported[6-9]. No HPTLC method was found during the literature survey for the analysis of Nicardipine

in its injectable dosage forms. Hence attempts were made to develop a simple, rapid, precise, and accurate HPTLC method to estimate Nicardipine Hydrochloride in its injectable dosage form. The proposed method was optimized and validated as per the ICH guidelines.

Drug Profile :

The IUPAC name of Nicardipine Hydrochloride is 5-O-[2-[benzyl(methyl)amino]ethyl] 3-O-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate;hydrochloride. (Figure.1) having molecular formula $C_{26}H_{30}ClN_3O_6$. Nicardipine hydrochloride is a greenish-yellow, odourless, crystalline powder that melts at about 169°C. It is freely soluble in chloroform, methanol and glacial acetic acid, sparingly soluble in anhydrous ethanol, slightly soluble in n-butanol, water, 0.01 M potassium dihydrogen phosphate, acetone and dioxane, very slightly soluble in ethyl acetate, and practically insoluble in benzene, ether and hexane. It has a molecular weight of 515.99 g/mol.

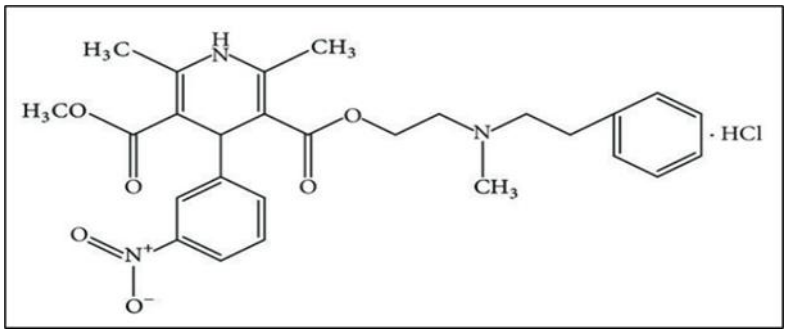

Figure No. 1 : Chemical Structure of Nicardipine Hydrochloride

2. Instrumentation Work :

2.1. Chemicals, reagents and materials :

Nicardipine Hydrochloride standard having potency 99.5% was obtained from Central Drugs Testing Laboratory (CDTL), Mumbai. Niczaar ampoules 10mg/10ml (Nicardipine Hydrochloride, USP) manufactured by Chuzaar Pharmaceuticals Pvt.Ltd were procured from the local market. TLC Silica gel 60 F254 plates (20×10 cm) from Sigma-Aldrich. Methanol was from Merck Life Science Pvt.Ltd. n-Hexane extrapure AR Grade, 99% and Ammonia Solution extrapure AR Grade, 30% from Srichem laboratories and Ethyl acetate from rankem was used. Nylon membrane filter (0.45 µm) were obtained from Axiva Sichem Pvt. Ltd.

2.2. Instrumentation and Chromatographic Conditions :

CAMAG Linomat 5 sample applicator (CAMG, Muttenz, Switzerland) with nitrogen aspirator and CAMAG Hamilton Bonaduzschwetzmicrosyringe (100µl) were used for applying bands on pre-coated Silica gel 60 F254 HPTLC plates (20×10cm) with a thickness of 250µm from Sigma-Aldrich. CAMAG twin trough glass chamber was saturated with mobile phase comprising of n-Hexane: Ethyl acetate: Methanol: Ammonia (60:20:20:0.3) for 25 minutes. Activation of plates was done at 140 °C for 15 min on CAMAG TLC Plate Heater III. Sample spotting was done in the form of narrow bands having length 8 mm at a constant rate of 15 nl/s using a nitrogen aspirator. In order to avoid edge effect, the application positions X and Y were kept at the distance of 8 mm and 20 mm respectively. Distance between two bands was kept 20 mm. Chromatogram was developed in a linear ascending manner up to the run distance of 80 mm. Drying of plates was carried out in hot air stream using an air dryer in a wooden chamber having adequate ventilation. Plates were scanned at 237 nm for spectro densitometric quantification of the separated components using CAMAG TLC Scanner 4 equipped with deuterium lamp by keeping the sensitivity at auto mode, during which the slit dimension was 6.0 mm × 0.3 mm and scanning speed was 100 nm/s. Evaluation of peak areas was carried out using CAMAG visionCATS software version 3.0. Sartorius Analytical Balance was used for all weighing's.

2.3. Selection of wavelength of maximum absorbance :

20 ug/ml solution of Nicardipine Hydrochloride solution was scanned in the range of 200.0 to 400.0 nm using CAMAG TLC Scanner 4. Nicardipine showed maximum absorbance at 237 nm as shown in Fig. 2. Hence the same wavelength was selected for the analysis of Nicardipine Hydrochloride.

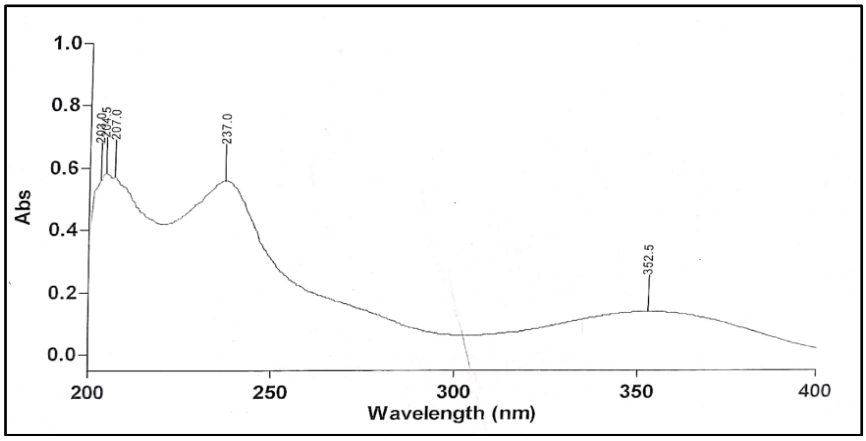

Figure No. 2. UV spectra of Nicardipine Hydrochloride.

2.4. Diluent Preparation :

100% HPLC grade methanol was used to dissolve Nicardipine Hydrochloride in standard solutions as well as sample preparations.

2.5. Preparation of Standard Solution :

5 mg of Nicardipine Hydrochloride standard was accurately weighed and transferred into a 100 ml volumetric flask. 50 ml of diluent was added and sonicated for around 15 minutes. The volume was made up to the mark with the help of diluent which finally gives 50µg/ml of Nicardipine Hydrochloride standard solution.

2.6. Preparation of Sample Solution :

5ml of Niczaar Injection ampoule containing Nicardipine Hydrochloride solution was transferred into a 100 ml Volumetric flask. The solution was then filled up to the mark by adding the diluent and sonicating it for around 15 minutes so as to prepare the sample solution containing 50µg/ml of Nicardipine Hydrochloride.

3. Method Optimization :

Pre-coated Silica gel 60 F254 plates were used for the separation of Nicardipine by considering its chemical nature and polarity. Initial trials were carried out using mobile phase containing Acetonitrile: Methanol: n-butanol: Glacial acetic acid in the ratio 60:20:20:0.1 % v/v/v with a chamber saturation period of 15 minutes. In this trial the Rf value observed was 0.917 including a broad peak shape. Hence, this trial was not taken into consideration. The chromatogram of this trial is indicated in Figure 3.

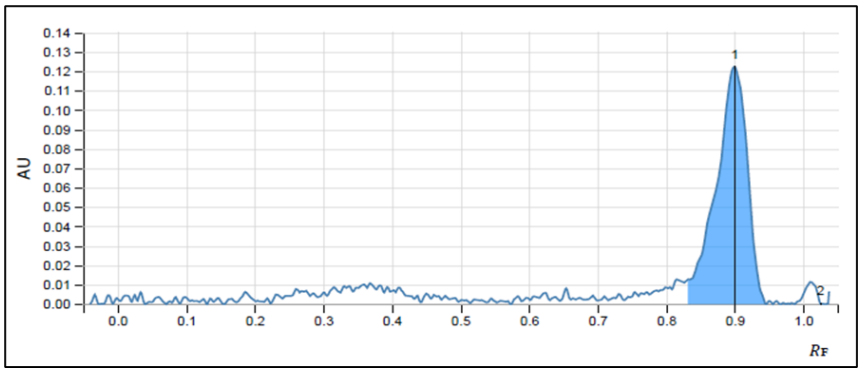

Figure No. 3 : 1st Trial of Nicardipine Hydrochloride Standard Solution.

Second trial was carried out out using a completely different mobile phase consisting of n-Hexane: Ethyl Acetate: Ethanol: Ammonia in the ratio of 60:10:30:0.5 % v/v/v with a chamber saturation time of 20 minutes. Although the trial's peak shape was good, but the observed Rf value was observed around 0.753. For this particular reason, the trial was not accepted. The chromatogram of this trial is indicated in Figure 4.

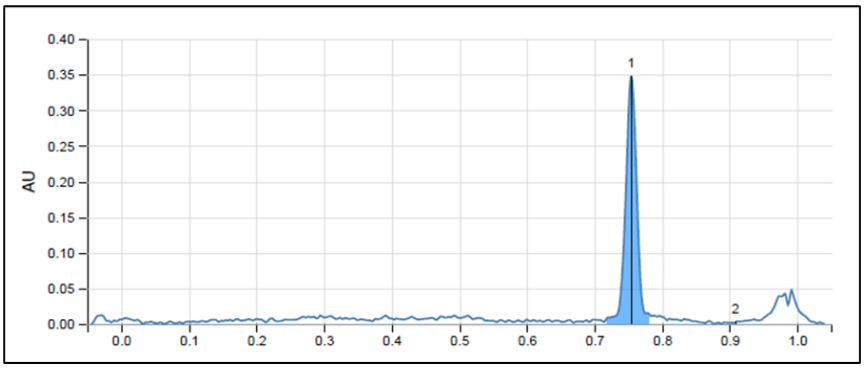

Figure No. 4. 2nd Trial of Nicardipine Hydrochloride Standard Solution

Final trial was conducted by changing the mobile phase comprising of n-Hexane: Ethyl acetate: Methanol: Ammonia in a ratio of 60:20:20:0.3 % v/v/v with a chamber saturation time of 25 minutes. Under these conditions, the peak was eluted with a good peak shape and the Rf value observed was 0.436 respectively and all the parameters were within the limit as per the system suitability parameters. Hence, this mobile phase was selected for the chromatographic analysis of Nicardipine Hydrochloride as indicated in Figure 5.

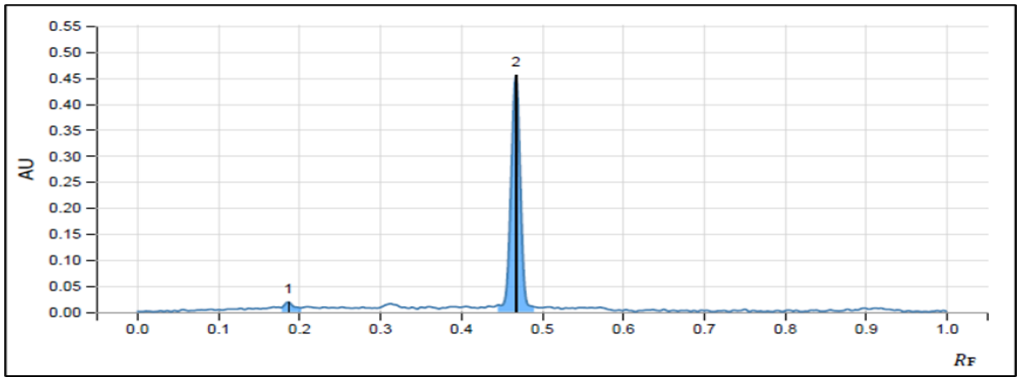

Figure 5 : Optimized Trial of Nicardipine Hydrochloride Standard Solution

4. Method Validation :

Validation of the developed HPTLC method was done by checking the parameters such as specificity, linearity, precision, accuracy, Limit of Detection (LOD), Limit of Quantitation (LOQ) and robustness as per ICH Q2 (R1) guidelines.

4.1. System Suitability :

System suitability tests are an integral part of liquid chromatographic methods. They are used to confirm that the chromatographic system's detection sensitivity, resolution, and reproducibility are sufficient for the intended analysis. Peak resolution, theoretical plate count, peak tailing, and capacity are just a few examples of factors that have been examined to assess the applicability of the employed method.

The system suitability was evaluated and analyzed to check the system performance by developing and scanning six replicate bands of a reference standard solution of 50ng/bands. A single band of blank preparation was used for making standard solutions in the HPTLC system. The chromatograms were recorded to evaluate SST parameters such as the %RSD of the Rf value and area. The Rf value of Nicardipine was found to be 0.436, and the %RSD of the SST parameters was within the acceptable criteria. The data on system suitability is summarised in Table 1.

Table No. 1 : System Suitability Data of Nicardipine

Sr. No.	Area	Rf Value
1.	0.00518	0.00436
2.	0.00521	0.00439
3.	0.00517	0.00436
4.	0.00515	0.00432
5.	0.00518	0.00435
6.	0.00516	0.00438
Mean	0.00518	0.00436
S.D.	2.16E-0.5	0.00141
%RSD	0.687	0.247

4.2. Specificity :

Specificity is the ability of the analytical method to distinguish between the analyte(s) and the other components in the sample matrix. In case of an HPTLC method, it is assured by complete separation of peak(s) of analyte(s) from other peaks originated from the sample matrix.
Standard and sample solutions of Nicardipine Hydrochloride were analysed for demonstrating the specificity of the method. By comparing the Rf value and spectrum of the band with that of standard, the band for Nicardipine was confirmed. The spectrum was compared in three different regions of the bands viz., peak start (S), peak apex (M), and peak end (E), for determining the peak purity of Nicardipine. Blank, standard, and sample chromatograms are represented in figure No. 6,7&8 respectively.

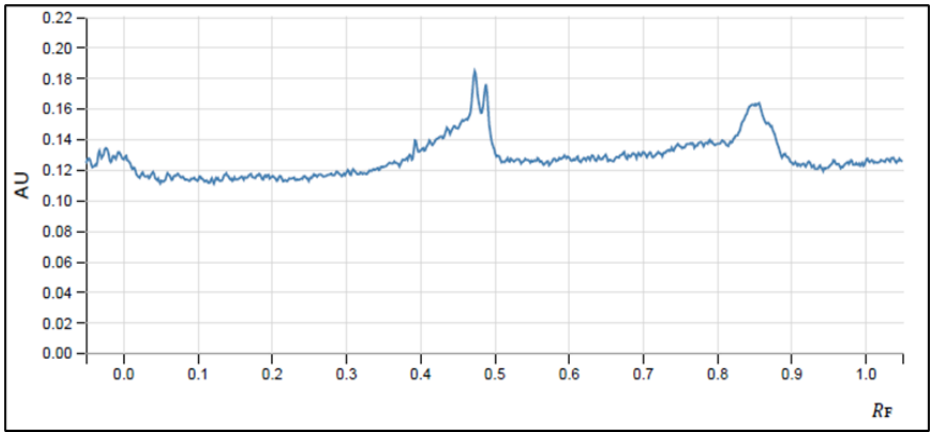

Figure No. 6 : HPTLC Densitogram of Blank Solution

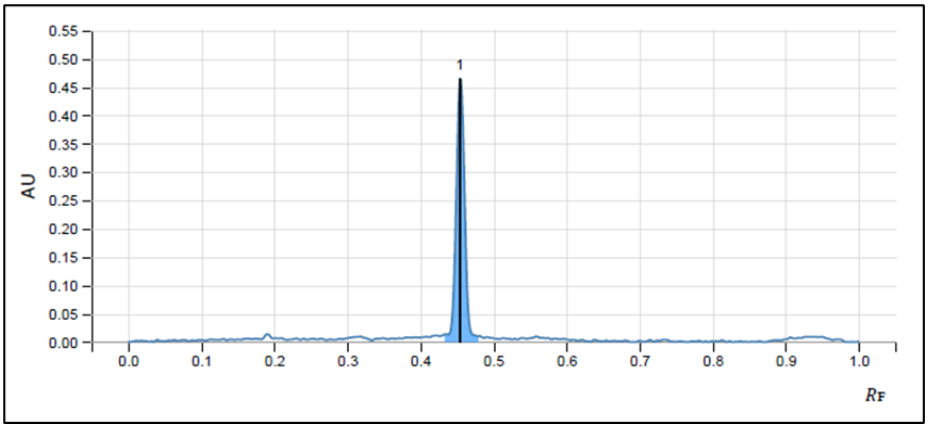

Figure No. 7: HPTLC Densitogram of Standard Solution

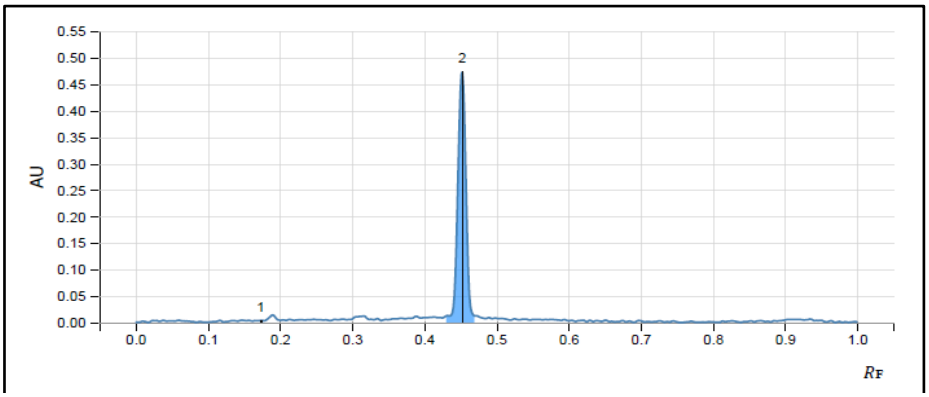

Figure No. 8 : HPTLC Densitogram of Sample Solution.

4.3. Linearity :

Linearity is the method's ability to obtain test results, which are directly proportional to the concentration of the analyte in the sample. Linearity studies on Nicardipine were performed in the concentration range of 10-100 ng/band by applying seven different concentrations of mix standard solution of Nicardipine. The linearity graph of peak areas verses concentrations was plotted to assess the linearity. The three-dimensional densitogram for Nicardipine.Hcl linearity is shown in Fig. 9. The plot of peak areas verses respective concentrations is shown in Fig. 10 and the results of Nicardipine linearity is shown in Table 2.

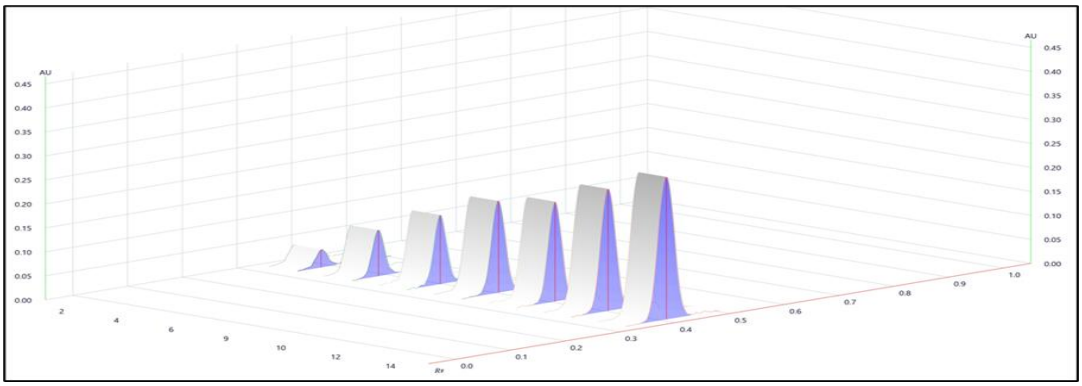

Figure 9. Three-dimensional densitogram for linearity of Nicardipine at 237 nm.

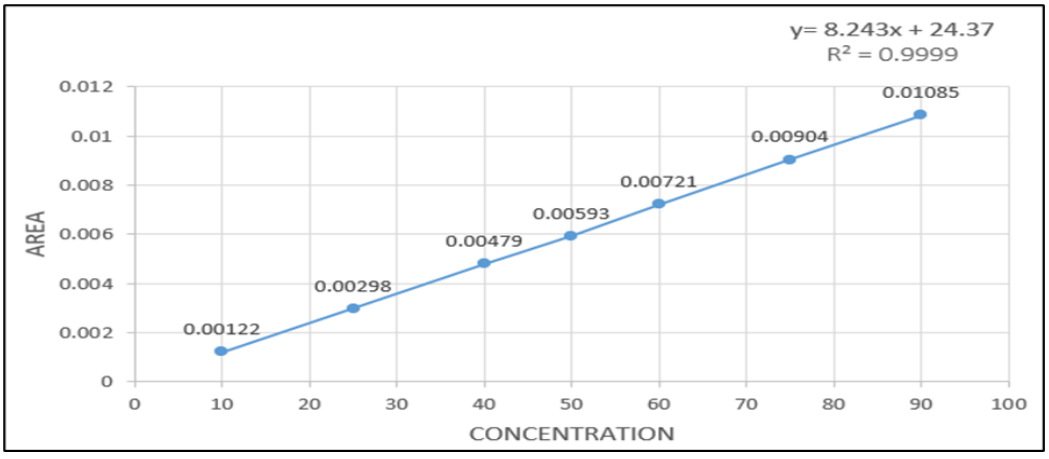

Figure.10 : Calibration Curve of Nicardipine Hydrochloride.

Table No. 2 : Linearity Studies of Nicardipine Hydrochloride.

Concentration (ng/band)	Area
10	0.00122
25	0.00298
40	0.00479
50	0.00593
60	0.00721
75	0.00904
100	0.01095

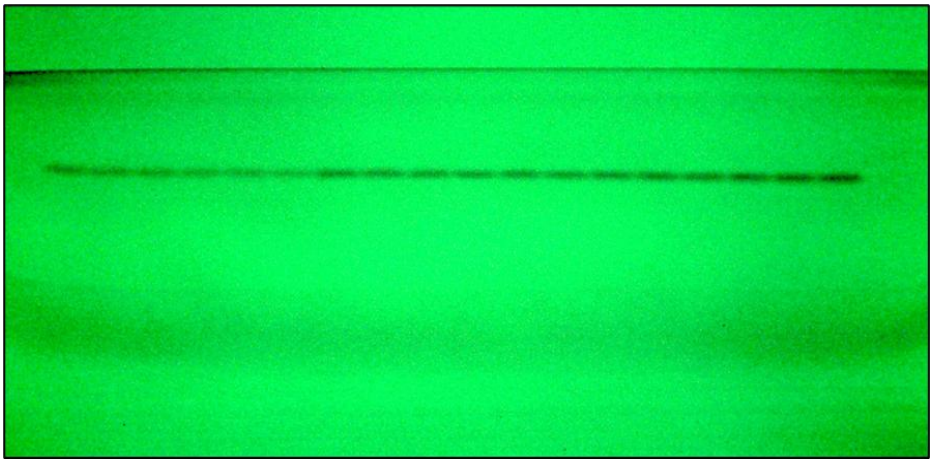

Figure.11 : Image of HPTLC Plate taken at 285 nm

4.4. Precision :

Precision is the agreement between replicate measurements of the same sample. The precision of analytical procedure expresses the closeness of agreement between series of measurements obtained from multiple sampling of the same homogenous samples under the prescribed conditions. It is expressed as relative standard deviations of replicate measurements.

Precision of the proposed method was determined in terms of repeatability and intermediate precision. % RSD for repeatability was determined by applying 50 ng/band of Nicardipine Hydrochloride standard solution six times. % RSD for intraday precision was determined by analysing 25, 50 and 75 ng/band Nicardipine standard solution each applied thrice on the plate. Interday precision was determined by analysing 25, 50 and 75 ng/band Nicardipine standard solution each applied thrice on the plate on different days over a period of one week. The results of repeatability and intermediate precision studies of Nicardipine Hydrochloride are depicted in Table 3 and 4 respectively.

Table No. 3. Precision Data of Nicardipine as Repeatability

Concentration (ng/band)	**Peak Area**
50	0.00526
50	0.00528
50	0.00523
50	0.00521
50	0.00527
50	0.00524
Average (n=6)	0.00523
SD	3.14E-0.5
%RSD	0.326

Table No. 4. Intermediate Precision Data of Nicardipine Hydrochloride

Concentration (ng/band)	Intraday Precision			Interday Precision		
	Area	S.D.	%RSD	Area	S.D.	%RSD
25	0.00298	1.52E-05	0.515475331	0.00237	1.43E-05	0.537
50	0.00582	3.51E-05	0.799638802	0.00516	3.13E-05	0.763
75	0.00903	5.73E-05	0.921483942	0.00931	5.95E-05	0.978

4.5. Accuracy :

The accuracy of an analytical procedure expresses the closeness of the agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found. The accuracy of the method is the closeness of the measured value to the true value for the sample.

Accuracy of the method was established by using standard addition method. Known amount of standard was added to pre-analyzed formulation at three different levels (110, 120 and 130 %). Recovery studies were conducted by performing three determinations at each level and mean % recovery was calculated and reported. The results of accuracy studies of Nicardipine Hydrochloride are exhibited in Table 5.

Table No.5 : Accuracy studies of Nicardipine Hydrochloride

% Level	Amount of STD spiked (ng/band)	Amount recovered (ng/band)	% Recovery	Mean % Recovery	% RSD
100	50	50.36			
100	50	50.77	100.53 %		0.5324
100	50	50.46			
110	55	51.63			
110	55	51.78	99.32 %		0.2457
110	55	51.88			
120	60	52.62			
120	60	52.33	100.65 %		0.3765
120	60	52.54		100.32 %	
130	65	53.75			
130	65	53.66	100.07 %		0.4392
130	65	53.05			

4.6. Sensitivity Data :

The ICH indicates that LOD (which they call DL, the detection limit) can be calculated as LOD = 3.3σ / S, and the limit of quantification (which they call QL, the quantitation limit) LOQ = 10σ / S. Where ‘s’ is the slope of the calibration curve and ‘σ’ is the standard deviation of the regression response. The values of the detection limit and quantification limit are calculated from calibration curve data. LOD and LOQ values are presented in the Table No. 6.

Table No. 6 : Sensitivity Data of Nicardipine Hydrochloride

Regression Statistics	
Linear Range	10 – 100 ng/band
Regression Equation	8.243x + 24.37
Slope	8.243x
Intercept	24.37
R^2	0.9999
Standard Deviation	4.576
LOD	0.246 ng/band
LOQ	0.437 ng/band

4.7. Robustness :

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters which provides an indication of its reliability during the normal usage. Robustness of the proposed method was evaluated by changing the volume of mobile phase in the range of ±5 ml, saturation time in the range of ±5 min and distance travelled by the solvent front in the range of ±5 mm. The results of Robustness of the proposed method for analysis of Nicardipine are displayed in Table No. 7.

Table No. 7. Robustness Data of Nicardipine Hydrochloride

Change in mobile phase ratio (60:20:20:0.3) v/v/v/v ± 2ml in n-Hexane and Methanol)					
Ratio (ml)	Rf value	Area	Average Area	S.D.	% RSD
(58:20:18:0.3)	0.432	0.00537	0.00535	1.37E-05	0.358 %
(60:20:20:0.3)	0.436	0.00534			
(62:20:22:0.3)	0.438	0.00536			
Change in chamber saturation time (25 minutes ± 2 minutes)					
Time	Rf value	Area	Average Area	S.D.	% RSD
23	0.452	0.00563	0.00566	2.25E-05	0.532 %
25	0.457	0.00566			
27	0.459	0.00568			

Change in distance travelled by solvent front (± 5 ml)					
Distance (mm)	Rf value	Area	Average Area	S.D.	% RSD
75	0.433	0.00534	0.00586	5.86E-06	0.15
80	0.481	0.00598			
85	0.479	0.00519			
Change in volume of Mobile Phase (20 ml ± 5ml)					
Volume (ml)	Rf value	Area	Average Area	S.D.	% RSD
15	0.62	0.00543	0.00545	5.79E-06	0.13
20	0.66	0.00545			
25	0.69	0.00548			

4.8. Analysis of Pharmaceutical Formulation :

Under optimised chromatographic conditions, analysis of Nicardipine Hydrochloride in Injectable formulation was carried out. Six replicate bands of 50ng/band of standard solution and six replicate bands of 50ng/band of sample solution were analysed in the HPTLC system. The %assay, mean, S.D., and %RSD were calculated and studied as per the ICH guidelines acceptance criteria. The %assay by analysis of Nicardipine Injectable formulation was found to be 99.98%. Assay results are tabulated in Table No.8.

Table No. 8. Assay results of Nicardipine Hydrochloride formulation.

Sr. No.	Weight of Standard (mg)	Sample Weight (equivalent to 10mg/10ml of Nicardipine)	Mean area of Standard at 237nm	Area of sample at 237nm	% Assay
1.	5.57	10.32	0.00647	0.00535	99.98
2.		10.38		0.00544	99.95
3.		10.42		0.00531	99.98
4.		10.45		0.00548	99.96
5.		10.35		0.00569	99.99
6.		10.47		0.00546	99.97
Mean 99.98					
S.D. 5.63E-05					
% 0.3872					RSD

5. Results and Discussion :

The developed HPTLC method for Nicardipine provided results with a mobile phase of n-Hexane: Ethyl Acetate: Methanol: Ammonia (v/v/v/v) using HPTLC silica gel F254 plates. A linear relationship was observed by plotting a calibration curve which included a range of concentrations theory, establishing the linear dynamic range for the method. Nicardipine depicted a constant linear response between the ranges of 10-100 ng/band. The corresponding linear regression coefficient was found to be 0.9999 respectively. Results for parameters such as repeatability and intermediate precision data are shown in Tables 1 and 3. The developed method was found to be precise as the %RSD values were found to be 0.326% (within range) as per the (ICH Q2(R1) Guidelines. The sensitivity of the method was derived from the trendline equation and regression coefficient obtained. Limit of Detection (LOD) was found to be 4 ng/band whereas the Limit of Quantitation (LOQ) obtained was 6 ng/band which indicated the sensitivity of the method developed. The proposed method showed adequate percentage of recovery i.e. between 98-102%. All 3 concentrations were spiked with the required known amount of standard as per the concentration of each and hence the percent recovery was estimated. The results depicting recovery/accuracy of the method are given in Table 5.

6. Conclusion :

The proposed HPTLC method was validated successfully with respect to ICH guidelines and was found to be simple, accurate and precise for the quantification of Nicardipine in Injectable Formulations without interference of excipients. All validation parameters were found to be within their acceptance limits. The method offers better resolution between drug and excipients and higher sensitivity. No HPTLC method was reported earlier for analysis of Nicardipine Hydrochloride in Injectable Dosage Form; hence this method is worthwhile. Using this method can be highly beneficial due to easy sample preparation, method's high capacity and method's flexibility to run qualitative and quantitative assays at a time. Hence the method can be routinely used for analysis of Nicardipine Hydrochloride in its Injectable formulations.

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