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Novel UV-Visible Spectroscopy method for development and validation of nicardipine hydrochloride in bulk form

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ABSTRACT: Nicardipine HCl as Monotherapy or in combination therapy for treating severe Angina and high blood pressure. Its mechanism involves the relaxation of blood vessels, thereby reducing the workload on the heart and lowering blood pressure. İt reduces myocardial oxygen demand by reducing after load and increasing myocardial oxygen supply through coronary vaso dilation. İn present study the solubility and release of the Nicardipine HCl in various solvents was examined based on solubility studies and the choice of solvent was determined by considering its solubility properties. Nicardipine HCl by comparison method. Nicardipine HCl is used to treat Angina, hypertension, arterial relaxation, vasodilation and so on. Currently Nicardipine HCl is marketed in different Novel drug formulations such as Nanoparticles, Capsules, Niosomes, Hydrogels for reducing blood pressure and many analytical techniques were used like HPLC, GC and GC-MS, LC-MS for carrying out the various quantitative and qualitative analyses are some examples of these developments. In this study, Nicardipine HCl was treated with various solvents like Methanol, Phosphate Buffers of PH 3.6 and 6.8. A method was developed and validated with validation parameters like Linearity, Accuracy, Precision, Specificity, LOQ, LOD etc., by using UV-Visible Spectroscopy. Results of the study revealed that Nicardipine HCl gives data about the Linearity, precision, accuracy of Nicardipine HCl gives Linearity 15-55µg/ml, Regression 0.998, LOD, LOQ. By carefully selecting suitable solvents, we successfully established a reliable and efficient method for determining and estimation of Nicardipine HCl by using Spectrophotometric method. Method was developed, optimized and Validated with its parameters

KEYWORDS: Nicardipine HCl; UV-Visible Spectroscopy; ICH.

1. INTRODUCTION

Nicardipine HCL is a chemically 5-O-[2-[benzyl(methyl) amino[ethyl] 3-O-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4 dihydropyridine-3,5-dicarboxylate hydrochloride as shown in Figure 1. It belongs to the Dihydropyridines with molecular weight 516.0 g/mo l[1]. It exhibits solubility in various solvents such as DMSO (1mg/ml), ethanol-water mixtures (25:75 to 70:30), propylene glycol, and methanol. It plays a significant role as geroprotector and also therapeutically active in anti-hypertensive and anti-anginal respectively [4]. Mechanism of action of this drug includes calcium channel blocker. It also shows some adverse affects such as coughing sometimes produces with a pink frothy sputum and Increased urge to urinate during night also produces dark urine [5, 6]. The main aim of this study is to create novel, uncomplicated, highly sensitive, precise, and cost-effective analytical techniques for assessing Nicardipine HCl [7, 8]. In the present work, planning to conduct low cost UV - Visible Spectroscopy technique for the effective quantitative quantification of "Nicardipine hydrochloride" as an active ingredient in bulk [9, 10]. The validation of the methodology followed the ICH Guidelines for assaying the active ingredients [11,12]. The validation encompassed various parameters, including "accuracy", "linearity", "precision", "specificity", "ruggedness", and "robustness" [13, 14]. The Structure of Nıcardıpıne Hydrochloride is shown in figure 1.

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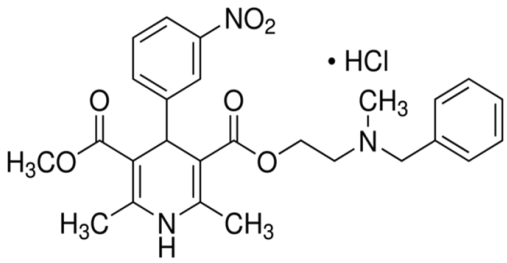

Figure 1. Structure of nicardipine hydrochloride

2. RESULTS

Efforts were undertaken to create and validate a straightforward, reliable, precise, and cost-effective spectrophotometric method for quantifying Nicardipine HCl in bulk, following the guidelines outlined by ICH. The method employed optimized conditions utilizing Phosphate Buffers at pH 3.6 and 6.8, along with Methanol as the solvent. The parameters are shown in Table 1.

Table 1. Parameters

λ max	**235nm**
Solvent used	Methanol, Phosphate Buffer Solution of PH 3.6 and 6.8

2.1 Optimized Parameters: As Shown in table 1. λ max was found to be **235 nm** from the absorption spectrum.

2.2 Validation: Various parameters validated are as follows:

- ❖ Linearity
- ❖ Accuracy
- ❖ Precision
- ❖ Specificity
- ❖ LOD and LOQ

2.2.1 *Linearity:* The linearity values and the respective graphs are shown in Tables 2- 7 and Figures 2- 5 respectively.

Linearity Plot: The linearity plot was shown in figure 6, 7 and table 7

Observation and Inference: Based on the data obtained from the experimental values, a graph gives straight line and obeys Beer - Lambert´S Law.

Conclusion: Regression coefficient value was found to be within the limits.

Table 2 . Linearity Data of Nicardipine HCl In Methanol

Concentration (µg/ml)	Absorbance at 235 nm
0	0
15	0.153
25	0.235
35	0.375
45	0.451
55	0.588

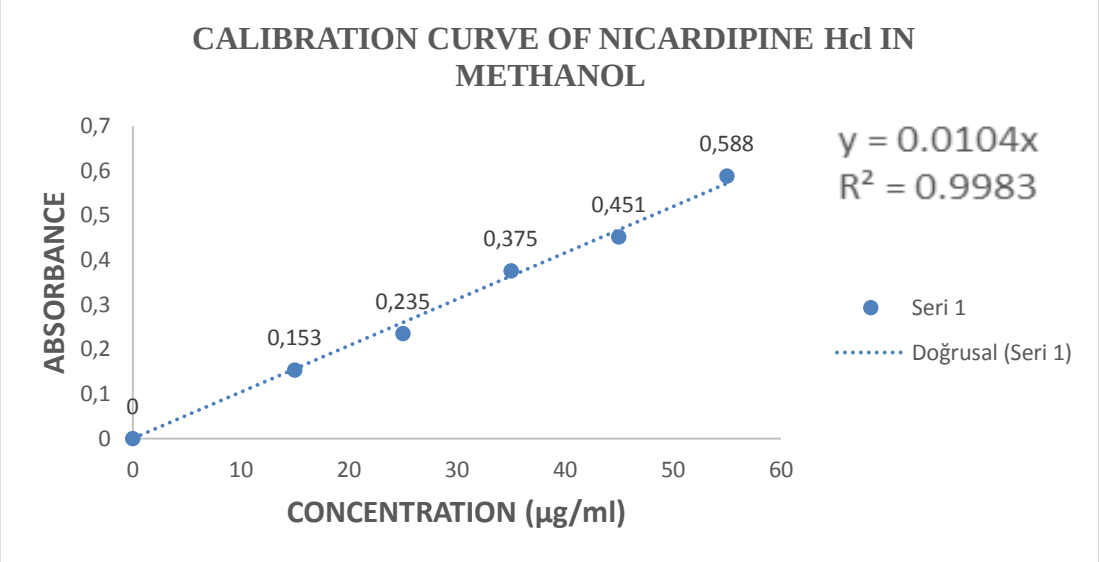

Figure 2. Linearity curve of Nicardipine HCl in methanol

Table 3. Beer- Lambert´S Law Data for Nıcardıpıne HCl In Methanol

Parameters	Nicardipine HCl in Methanol at 235nm
Linearity range	15-55 µg/ml
Correlation coefficient	0.998
Slope (m)	0.0104
Intercept (c)	0.0197

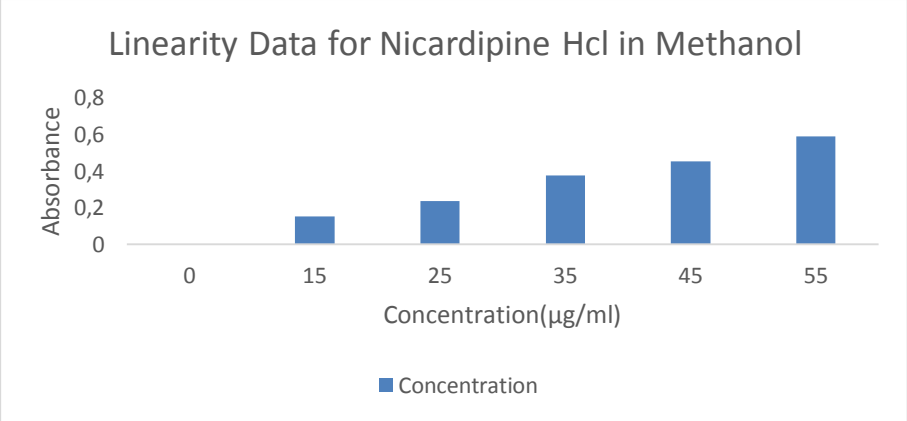

Figure 3. Linearıty Data for Nicardipine HCl In Methanol

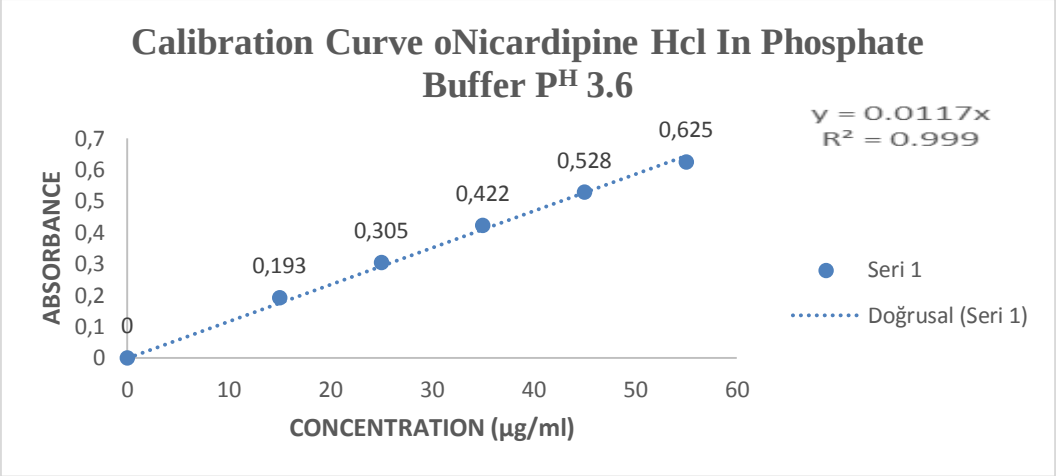

Figure 4. Linearity curve of nicardipine HCl in phosphate buffer of PH 3.6

Table 4. Linearıty Data For Phosphate Buffer of PH 3.6

Concentration (µg/ml)	Absorbance of Nicardipine HCl in Phosphate Buffer of PH 3.6 at 235nm
0	0
15	0.193
25	0.305
35	0.422
45	0.528
55	0.625

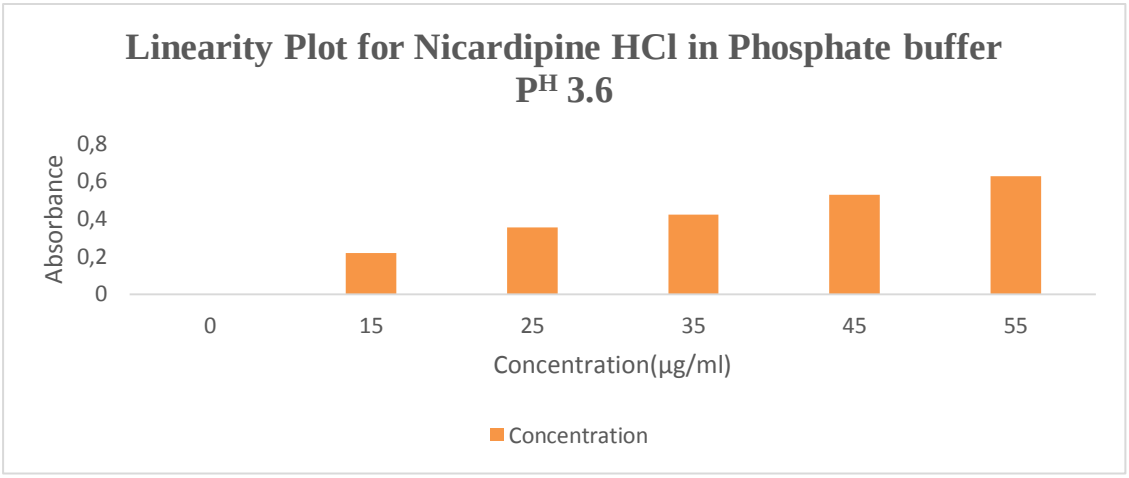

Figure 5. Linearity plot for nicardipine HCl in phosphate buffer PH 3.6

Table 5. Beer- Lambert´s Law Data of Nicardipine HCl in Phosphate Buffer PH 3.6

Parameters	Nicardipine HCl in Phosphate Buffer of PH 3.6 at 235nm
Linearity range	15-55 µg/ml
Correlation coefficient	0.999
Slope (m)	0.0117
Intercept (c)	0.0834

Table 6. Linearity data for nicardipine HCl in phosphate buffer of PH 6.8

Concentration (µg/ml)	Absorbance of Nicardipine HCl in Phosphate Buffer of PH 6.8 at 235nm
0	0
15	0.369
25	0.475
35	0.592
45	0.719
55	0.835

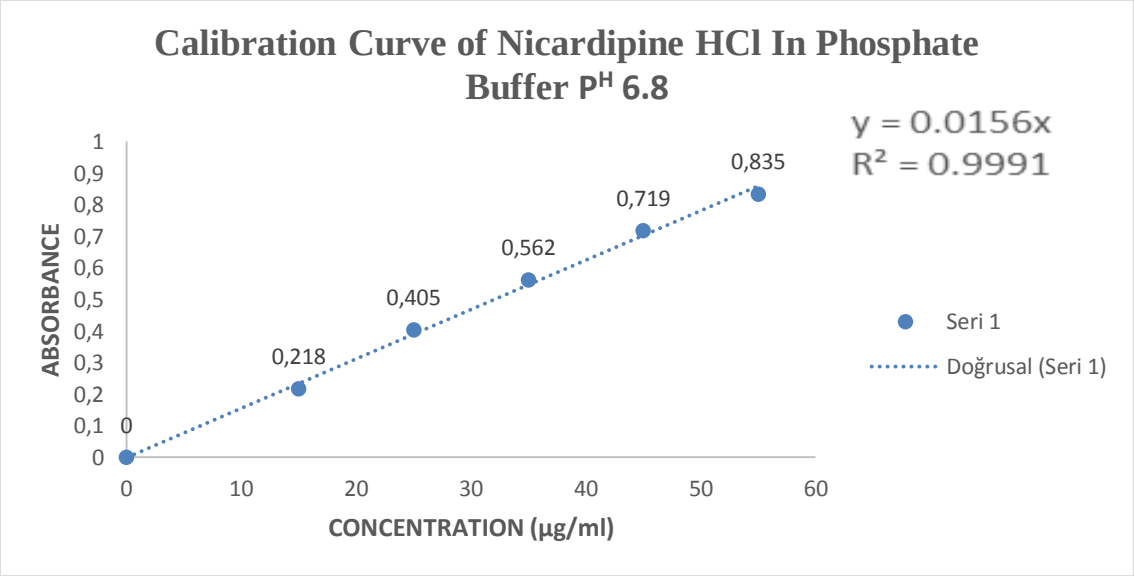

Figure 6. Linearity Curve of Nicardipine HCl in Phosphate Buffer of PH 6.8

Table 7. Beer- Lambert´s law data of Nicardipine HCl in phosphate buffer PH 6.8

Parameters	**Nicardipine HCl in Phosphate Buffer of PH 6.8 at 235nm**
Linearity Range	15-55 µg/ml
Correlation coefficient	0.999
Slope (m)	0.0156
Intercept (c)	0.1864

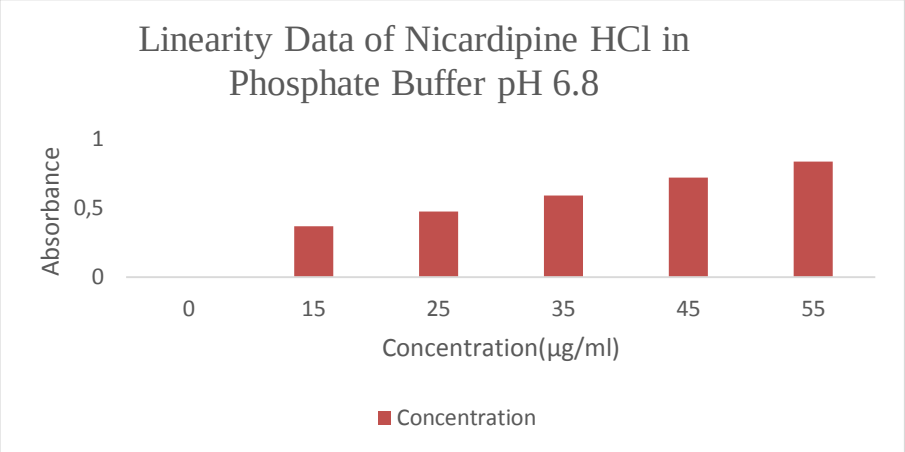

Figure 7. Linearity plot of nicardipine HCl in phosphate buffer of PH 3.6

2.2.2 *Accuracy:* The results are shown in Table 8.
Conclusion: The percentage recovery fell within acceptable limits, affirming the method's accuracy.

Table 8. Accuracy data at 235 nm for Nicardipine HCl

Concentration	Amount spiked	Total amount	Amount found	%Recovery
25µg	1µg	26	25.8	99.23
35µg	1µg	36	35.7	99.16
45µg	1µg	46	45.8	99.56

2.2.3 *Precision:* The results are shown in Table 9, 10,11 and 12
Conclusion: The percentage of relative standard deviation (%RSD) was within acceptable ranges, suggesting that the method demonstrated precision.

Table 9. Intraday Precision of Nicardipine HCl

S.NO	Sample (35µg/ml)	ABSORBANCE		
		METHANOL	BUFFER PH 3.6	BUFFER PH 6.8
1	1	0.375	0.422	0.592
2	2	0.374	0.421	0.590
3	3	0.373	0.420	0.591
4	4	0.374	0.422	0.593
5	5	0.375	0.422	0.592
6	6	0.373	0.423	0.591
7	**MEAN**	**0.374**	**0.4216**	**0.5915**
8	**SD**	**0.000894**	**0.001033**	**0.001049**
9	**%RSD**	**0.08994**	**0.1033**	**0.1049**

Table 10. Inter day precision of nicardipine HCl in methanol

SAMPLE S. No	ABSORBANCE Day-1	ABSORBANCE Day-2
1	0.375	0.378
2	0.374	0.370
3	0.373	0.375
4	0.374	0.372
5	0.375	0.377
6	0.373	0.375
Mean	**0.374**	**0.3745**
SD	**0.000894**	**0.003017**
%RSD	**0.0894**	**0.3017**

Table 11 . Inter day precision of nicardipine HCl in phosphate buffer of PH 3.6

SAMPLE S. No	ABSORBANCE Day-1	ABSORBANCE Day-2
1	0.422	0.425
2	0.421	0.426
3	0.420	0.423
4	0.422	0.426
5	0.422	0.425
6	0.423	0.424
Mean	**0.4216**	**0.4248**
SD	**0.001033**	**0.001169**
%RSD	**0.1033**	**0.1169**

Table 12. Inter day precision of nicardipine HCl in phosphate buffer of PH 6.8

SAMPLE	ABSORBANCE	ABSORBANCE
S. No	**Day-1**	**Day-2**
1	0.592	0.593
2	0.590	0.594
3	0.591	0.592
4	0.593	0.595
5	0.592	0.591
6	0.591	0.590
Mean	**0.5915**	**0.5925**
Sd	**0.001049**	**0.001871**
%RSD	**0.1049**	**0.1871**

2.2.4 *LOD and LOQ:* The results are shown in Tables 13,14 and 15.

LOD and LOQ data of Nicardipine HCl at 235nm.

Table 13. Methanol

Parameters	At 235nm
LOD	0.458µg/ml
LOQ	1.34µg/ml

Table 14. Phosphate Buffer PH 3.6

Parameters	At 235nm
LOD	0.318µg/ml
LOQ	1.13µg/ml

Table 15. Phosphate Buffer PH 6.8

Parameters	At 235nm
LOD	0.230µg/ml
LOQ	1.09µg/ml

2.2.5 *Specificity:* The blank (Methanol, Phosphate Buffer PH 3.6**,** Phosphate Buffer PH 6.8 showed no absorbance at maximum wavelength.

Conclusion: There is no solvent interference.

3. CONCLUSION

Based on the results and discussion it was found that the solubility of the Nicardipine HCl was best in case of Phosphate Buffers of PH 3.6 and PH 6.8 when compared to methanol. The stability of the drug was good in case of buffers and estimation of the drug was being simple and affordable. The results indicate that the proposed method is simple, precise and accurate. The results comply the method validation in line with ICH guidelines. Moreover, Spectroscopical analysis are readily available and affordable. Validated parameters are summarized in the Table 16.

4. MATERIALS AND METHODS

4.1 Chemicals and Reagents: Nicardipine Hcl, Methanol, Phosphate Buffer, Citric Acid Monohydrate, disodium hydrogen phosphate, dihydrogen sodium phosphate and Distilled water.

4.2 Procedure for Method Development of Nicardipine Hydrochloride by UV - Visible Spectrophotometry

*4.2.1 Parameters Fixation***:** Through a series of initial experiments, the ideal conditions for the quantitative determination of the drug were identified [15,16].

4.2.2 Selection of Solvent: Solubility Charataristics of Nicardipine Hydro chloride solubility was assessed in various solvents in accordance with Pharmacopeial standards. and from the literature survey. Nicardipine HCl is freely soluble in Methanol and Phosphate Buffer Solutions of PH 3.6 and 6.8[17,18]. The value is shown in Table 1.

Table 16. Summarized table for nicardipine HCl.

PARAMETER	RESULTS		
	Methanol	**Phosphate Buffer (PH 3.6)**	**Phosphate Buffer (PH 6.8)**
Wavelength(nm)	235	235	235
Linearity Range	15 - 55µg/ml	15 - 55µg/ml	15 - 55µg/ml
Regression Equation	0.991	0.993	0.999
Slope (m)	0.0109	0.0099	0.0118
Intercept (c)	0.0197	0.0834	0.1864
LOD	0.438 µg/ml	0.458 µg/ml	0.530 µg/ml
LOQ	1.26 µg/ml	1.27 µg/ml	1.29 µg/ml

4.3 Preperation of Solutions:

4.3.1 Preparation of standard solution (STOCK A): Weigh accurately 0.1gm of Nicardipine HCl into 100ml volumetric flask and dissolve in Methanol [19,20].

4.3.2 Preparation of standard solution (STOCK B): Transfer 10 ml of stock solution A into a 100 ml volumetric flask, then dilute to the mark with Methanol [21,22].

4.3.3 Preparation of working standards: Dispense 1.5 ml, 2.5 ml, 3.5 ml, 4.5 ml, and 5.5 ml into five separate volumetric flasks. Then, add 2 ml of Methanol to each flask and adjust the volume to 10 ml with Methanol [23,24].

4.3.4 Preparation of Standard solution (STOCK A) with Phosphate Buffer Solution of P H 3.6: Weigh accurately 0.1gm of Nicardipine HCl into 100ml volumetric flask and dissolve in Phosphate Buffer Solutions of PH 3.6[25,26].

4.3.5 Preparation of Standard solution (STOCK B) with Phosphate Buffer Solution of P H 3.6:
Transfer 10 ml of stock A solution into a 100 ml volumetric flask, and then fill it up to the mark with Phosphate Buffer Solution at pH 3.6 [27,28].

4.3.6 Preparation of Working Standards: Pipette out 1.5ml, 2.5ml, 3.5ml, 4.5ml, 5.5ml into five different volumetric flasks and add 2ml of Phosphate Buffer Solutions of PH 3.6 and make up the volume up to 10ml with Phosphate Buffer Solutions of PH 3.6[29,30].

4.3.7 Preparation of Standard Solution (STOCK A) with Phosphate Buffer Solution of P H 6.8:
Weigh accurately 0.1gm of Nicardipine HCl into 100ml volumetric flask and dissolve in Phosphate Buffer Solutions of PH 3.6 [31,32].

4.3.8 Preparation of Standard Solution (STOCK B) with Phosphate Buffer Solution of P H 6.8:
Measure 10 ml of stock A solution and transfer it into a 100 ml volumetric flask. Then, fill the flask to the mark with Phosphate Buffer Solution of pH 6.8 [33,34].

4.3.9 Preparation of working standards: Pipette out "1.5ml, 2.5ml, 3.5ml, 4.5ml, 5.5ml" into five different volumetric flasks and add 2ml of Phosphate Buffer Solutions of PH 6.8 and make up the volume up to 10ml with Phosphate Buffer Solutions of PH 6.8 [35,36].

4.3.10 Preparation of Phosphate Buffer Solution of PH 3.6: Dissolve 0.900 g of anhydrous disodium hydrogen phosphate and 1.298 g of citric acid monohydrate in an adequate amount of water to make a final volume of 1000 ml [37,38].

4.3.11 To prepare a Phosphate Buffer Solution with a pH of 6.8: Dissolve 28.80 g of anhydrous disodium hydrogen phosphate and 11.45 g of potassium dihydrogen phosphate in an appropriate amount of water to yield a final volume of 1000 ml [39,40].

Choosing the appropriate wavelength is crucial for ensuring the sensitivity of the method, as it determines the optimal response for all detectable components. In this case, the wavelength selected for analysis is 235 nm [41,42]. The value is shown in table no 1.

4.4 Validation of the developed method:

4.4.1 Linearity: In each instance, the calibration curve was created by assessing the absorbance at five concentration levels of Nicardipine HCl (ranging from 15 to 55 µg/ml) using the least squares method. A line of best fit was then determined, and calculations were performed to obtain the correlation coefficient, slope, and y-intercept[43,44].. The resulting calibration curve was depicted in Figure 2, 3, 4, 5, 6,7 and Table 2, 3, 4, 5, 6, 7.
Acceptance criteria: R ² value should not be less than 0.98

4.4.2 Accuracy: The accuracy of the method and the assessment involved conducting recovery experiments at the level of 3 concentrations 35µg, 45µg, 55µg of the intended or target concentration from the test solution. All the 3 concentrations were prepared and subjected to the developed procedure. % recovery was calculated for the 3 concentrations [45,46].. The values are shown in Table 8.

Acceptance Criteria: The average percentage recovery should be between 99-101% and the values are shown in Table 8.
4.4.3 Repeatability: The precision of the method was evaluated by conducting measurements on six replicates sample containing 35µg/ml of Nicardipine HCl[47,48]. The % relative standard deviation and standard deviation was calculated and presented in respective tables 9, 10, 11, 12.
Acceptance criteria: % RSD: Not More Than 2%

4.4.4 Inter day precision: Is checked on 2 consecutive days by preparing 35µg/ml concentration and the absorbances were checked [49]. %RSD was calculated in the table 10, 11.

Acceptance criteria: %RSD: Not More Than 2% the values are given in Table 10.
4.4.5 Specificity: The absorbance of the blank solution was measured and found to be extremely low, at 0.014, indicating no interference with the blank solution. This observation suggests the method's specificity for the drug [49].

4.4.6 LOD and LOQ: The "limit of detection" and "limit of quantification" of Nicardipine HCl were calculated from the calibration curve, by using formula [49]. The values are shown in Tables – 3, 4, 5.

LOD = $\boldsymbol{3.3\sigma/S}$
LOQ = $\boldsymbol{10\sigma/S}$
$\boldsymbol{\sigma}$= Standard deviation of responses.
S = Slope of calibration curve
An attempt was made to develop and validate a simple, precise, accurate and economical Spectrophotometric method using Phosphate Buffers of P^{H} 3.6 and 6.8 and Methanol as solvent for the estimation of Nicardipine HCl in bulk as per ICH guidelines.

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Conflict of interest statement: "No conflict of interest" in the manuscript

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