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Estimation of Lercanidipine HCl By AUC of UV-VIS Spectrophotometry Technique & RP-HPLC Method

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KEYWORDS
Lercanidipine HCl, AUC method, Liquid Chromatography, Validation, ICH guidelines.

ABSTRACT

An attempt was made to develop a validated method for the estimation of Lercanidipine HCl in bulk and its dosage form by using the area under curve and the RP-HPLC method. **In Method 1,** the Area Under the Curve method using UV-VIS spectroscopy was performed at a wavelength between 350-360 nm. The linearity was obtained at a concentration range of 5-30 µg/ml. The linear regression equation was Y = 0.1083 x – 0.0310, and the Co-relation Co-efficient was $r^2 = 0.9996$. The sample solution and standard solution are prepared by using water as a diluent. The % RSD was found to be less than 2 in the tablet assay and recovery study. **In Method 02**, the RP-HPLC method is used. The stationary phase is a C_{18} column (250 mm × 4.6 mm, 5 µm), and the mobile phases are a 90:10 mix of methanol and water. The mobile phase flow rate of 1 ml/min, with detection at 237 nm, was used for analytical purposes. Its retention time was 6.48 min. Linearity was obtained at a concentration range of 5–80 µg/ml. The linear regression equation was found to be Y = 49,901.5198 x + 27,678.7201, and the correlation coefficient $R^2 = 0.9999$. The %RSD was found to be less than 1.5 in precision, recovery, and robustness studies. The students 't' test values were within the acceptable limit for both the methods. Method 2 is more accurate and highly sensitive in comparison to Method-1.

INTRODUCTION

Lercanidipine hydrochloride is a calcium channel blocker related to the 1,4-dihydropyridines.Chemically it is 5-O-[1-[3,3-diphenylpropyl(methyl)amino]-2-methylpropan-2-yl] 3-O-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate hydrochloride. It is used to treat hypertension and chronic stable angina pectoris. The drug is official in Martindale [1] and Merck index. [2] It is a poor water soluble drug with absolute bio availability of 10%, its purity was 99.81%.

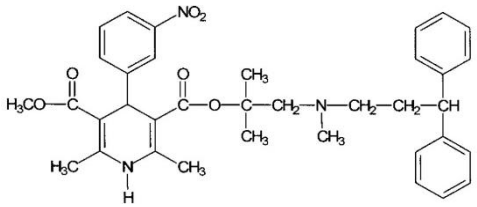

Fig-01: Chemical Structure of Lercanidipine

Table-1: UV-VIS Spectrophotometric literature

Sl. No.	Solvent system	ƛ max	Linearity (µg/ml)	Reference
1	Methanol	332	7.5-60	3
2	Methanol	236	2.5-60	4
3	Methanol	353.93	5-60	5
4	0.1N HCL	242	10-50	6

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5	drug and 1,2-naphthaquinone-4-sulphonic acid sodium salt (NQS) by means of nucleophilic substitution reaction.	460	20–100	[7]

Table-2: Reported research articles of RP-HPLC

Sl. No.	Analytical Method	Column	Mobile Phase Composition	Rt	Reference
1	RP-HPLC	Promosil C-18	ACN : CH_3 OH: H_2O (35:35:30, v/v/v) (pH 3.2)	6	[8]
2	RP-HPLC	Water C-8	Na Perchlorate H_2O & ACN (50:50 v/v) (pH 4.0)	20	[9]
3	RP-HPLC	X-Terra C-18	ACN: CH_3OH: 0.02m KH_2PO_4 (pH 5) (50:10:40)	3.5	[10]
4	RP-HPLC	Luna C-18	ACN & Phosphate Buffer (pH 3.6)	5.97	[11]
5	RP-HPLC	C-18	ACN: Acetate Buffer (pH 4)	…..	[12]
6	RP-HPLC	HibarC-18	ACN:CH_3OH:H_2O: O-H_3PO_4 (35:35:30:0.2) (pH 3)	4.6	[13]
7	RP-HPLC	Phenomenox Gemini C-18	ACN And 10mm Ammonium Acetate Buffer (pH 3.2) (80:20 v/v)	6.6	[14]
8	RP-HPLC	Kromasil C-18 Column	Acetate Buffer (4.5) 20 Mm & ACN (10:90, v/v)	7.7	[15]
9	HPLC	Phenomenex Gemini C-18	ACN &20 Mm KH_2 Phosphate Buffer (pH 3.5) (55:45, v/v)	6	[16]
10	HPLC	Chromasil YMC Pack C-8	0.02 m Ammonium Dihydrogen Phosphate Buffer: CH_3OH (35:65, v/v) (pH 3.5)	4.2	[17]
11	RP-LC	X terra RP-18	CH_3OH: H_2O (70:30 v/v) with 15 mM tri-fluoroacetic acid (pH 3)	6.56	[18]
12	HPLC	Princeton C18	ACN: H_2O (55:45 v/v) (3.5)	5.31	[19]
13	RP-HPLC	Agilent Tc-C18	ACN & Disodium Hydrogen Phosphate (pH 4) (55:45 v/v)	8.36	[20]
14	RP-HPLC	Phenomenex Gemini C18	CH_3 OH: H_2O (95:5 v/v)	5.38	[21]
15	RP-HPLC	Zorbax Sb C18	0.01 m K H_2 PO4 (pH 3.5) & ACN. (60:40, v/v)	5.3	[22]
16	RP-HPLC	Symmetry C18	H_2 PO_4:CH_3 OH: ACN (40:40:20)	4.77	[23]
17	RP-HPLC	Waters ODS (C18)	ACN: Buffer (pH-3.4) With Opa & (40:60)	2.26	[24]

Previous work showed that few UV-Vis Spectroscopy and RP-HPLC methods have been developed for getting the Lercanidipine Hcl content in dosage form (summarized in Table 1 & 2). In these methods different columns, mobile phase systems were taken. The retention time was also varied.Literature reveals that several methods such as High Performance Liquid Chromatography with other compounds (HPLC), [25], [26] LC-ESI-MS/MS, [27], [28], [29], [30], [31] voltammetric method, [32] HPTLC, [33] are used for estimation of Lercanidipine. Therefore, this study can describe a simple, rapid, precise, economical and accurate AUC method and Reverse Phase High Performance Liquid Chromatography (RP-HPLC) method for the development and validation of Lercanidipine hydrochloride in the pharmaceutical dosage form.

MATERIAL & METHOD

Instruments:

Apparatus and Chromatographic conditions

Shimadzu UV-visible spectrophotometer (1900i) with 1cm matched quartz cells, Contech precision balance (CAS-54), Shimadzu (LC-10AT vp) equipped with a SPD-10 AT vp UV detector, manual injector with 20 µL loop and Lab solution software was used. Stationary Phase used was Enable (Torrance, CA) Luna C-18 Column (250mm × 4.6 mm i.d, 5µm) and the mobile phase was Methanol- water (90:10, v/v). The mobile phase was filtered through nylon 0.45 µm membrane filters (Millipore Pvt., Ltd, Bangalore, India). The mobile phase flow rate was 1 ml/min and injection volume was 20 µL. All weighing were done on single electronic pan balance (Con-tech, India).

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Reagents and chemicals:
Lercanidipine HCl is pure powder with 99.96% purity was obtained as a gift sample from Cipla Ltd (Mumbai, India). Lercanidipine HCl tablets (10.0 mg/tablet) were procured from the local market. HPLC grade Methanol (S.D. Fine Chemicals, Ahmedabad, India) water (Finar chemicals Ltd., Ahmedabad, India) and nylon filter (Millipore Pvt., Ltd, Bangalore, India) were used for study. Methanol and water are purchased from the distributor of Cuttack having HPLC Analytical Grade.

Method 1:

Preparation of a standard solution: Weighed accurately about 10 mg of Lercanidipine HCl working standard into a 100-mL volumetric flask containing 40 ml of double-distilled water. Sonicate for 3 minutes to dissolve. Then make up the volume with diluent in order to get 100 µg/ml.

Preparation of working standard solution: From stock solution, aliquots of 0.5, 1, 1.5, 2, 2.5, and 3 ml were transferred into six different 10 ml volumetric flasks and diluted up to the mark with blank or diluent to produce the final concentration in the range mentioned in Table 3.

Table -3: Observed value for linearity curve of Method – 1.

Sl. No.	Conc (µg/ml).	Area
1	0	0
2	5	0.493
3	10	1.017
4	15	1.606
5	20	2.145
6	25	2.658
7	30	3.234

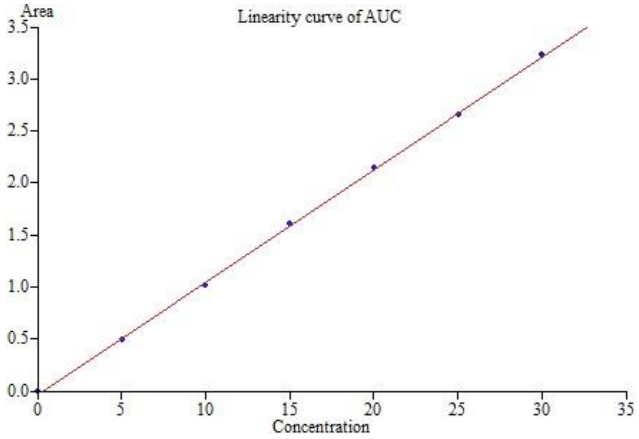

Fig 2: The linearity curve of Method 1.

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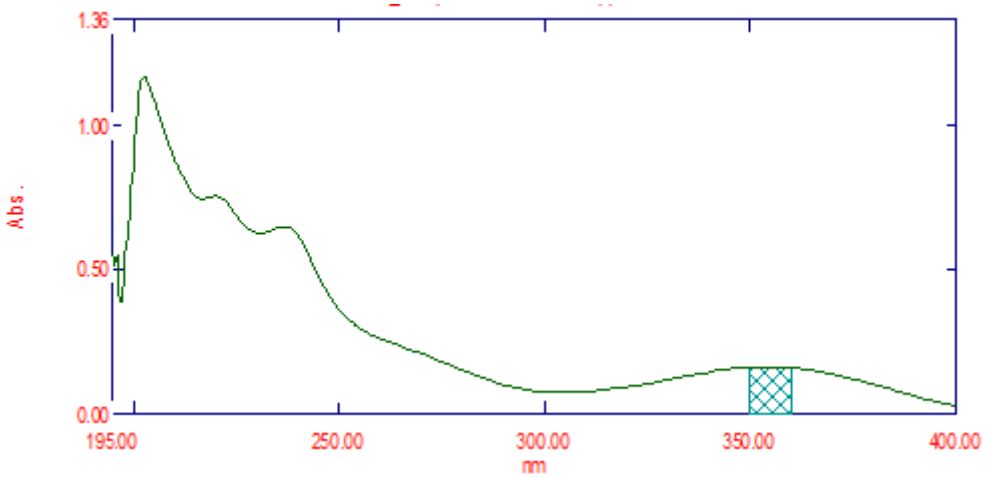

Fig 3: UV Spectrum of Lercanidipine (AUC Method) (15 µg/ml)

Method 2:

Preparation of Standard Solution: Accurately weighed standard Lercanidipine (10mg) was transferred to a 100-ml volumetric flask previously containing a 40-ml mobile phase. The content was sonicated for thirty minutes after making up the volume of 100 ml with the mobile phase to obtain a standard stock solution (100 µg/ml).

Preparation of Working Standard Solution: The HPLC method was performed by preparing eight different concentrations of Lercanidipine HCl Standard Solution in diluent (mobile phase) from their stock solution individually, and the final concentration is mentioned in Table 4.

Table 4: The linearity Data of the Method 2

Sl. No.	Conc. (µg/ml)	Area
1	0	0
2	5	274213
3	20	1049549
4	30	1554808
5	40	2013020
6	50	2516925
7	60	3034143
8	70	3506678
9	80	4014812

ASSAY METHOD

Method-1: In the UV-Spectrophotometric method, two wavelengths (350nm - 360 nm) were selected for the determination of Area Under Curve [AUC] using scaling factor 1. The UV spectrum of the drug (15µg/ml) under the AUC method is shown in Fig 3. The linearity curve of method 1 is shown in Fig. 2**.** For the selection of the analytical wavelength range for the area under curve method, a 15µg/ml solution of Lercanidipine was scanned in the spectrum mode from 400nm to 200nm against double-distilled water as a blank. The wavelength range was selected around wavelength maxima. Different working standards were prepared between 05, 10, 15, 20, 25, and 30 µg/ml.

Preparation of Calibration Curve for Lercanidipine HCl

From the stock solution, aliquots of 0.5, 1, 1.5, 2, 2.5, and 3 ml were transferred into 10 ml volumetric flasks and diluted up to the mark with diluent to get the final concentration in the range of 5, 10, 15, 20, 25, and 30 µg/ml. These solutions were scanned from 400 to 200 nm, and area under curve (AUC) values were integrated in the range of 350 to 360 nm. The calibration curve was plotted between areas under curve values against concentration. The linear regression equation of method 1 was found to be Y = 0.1083 x - 0.0310 and the Co-relation Coefficient r^2 = 0.9996.

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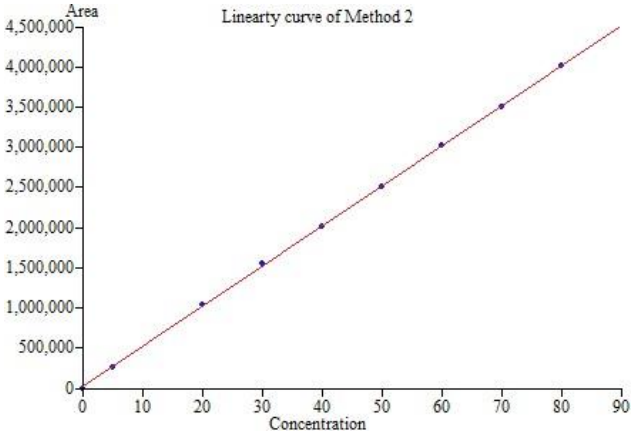

Fig 4: The linearity curve of Method 2 is shown in.

Assay of Tablets:

Method 1: To determine the content of Lercanidipine HCl from marketed product: Twenty tablets of Lercanidipine HCL were accurately weighed and average weight per tablet was determined. Tablets were ground to fine powder and weighed tablet powder equivalent to 10 mg transferred to 100 ml volumetric flask. The powder was dissolved in 40 ml double distilled water. The flask was sonicated for 10 min and then the solution was filtered using Whatman filter paper and the volume was made up to the mark with blank. Appropriate volumes of the aliquot were transferred into four different 10ml volumetric flasks and the volume was made up to the mark with diluent to prepare the formulation concentration for the measurement.

Method -2

i. Optimized chromatographic condition.

The mobile phase, consisting of methanol and water in a ratio of 90:10, was used to obtain clear peaks of Lercanidipine HCl. Then the mobile phase was degassed with the help of an ultra sonicator to eliminate the dissolved gases. Injection volumes of 20 µl for each standard solution were injected into the column. The detection wavelength and chromatographic run times were selected at 237nm and 10 min, respectively. Analytical column used: Enable Column C-18, temperature: 22^0 C, Elution: isocratic, Diluents: Mobile Phase.

ii. Selection of wave length.

The UV Wavelength was selected by running the different concentration of drug by using the wavelength between 200 to 400nm. The maximum wavelength was found to be 237nm. The overlay UV spectrum of the drug is shown in the below Fig: 5.

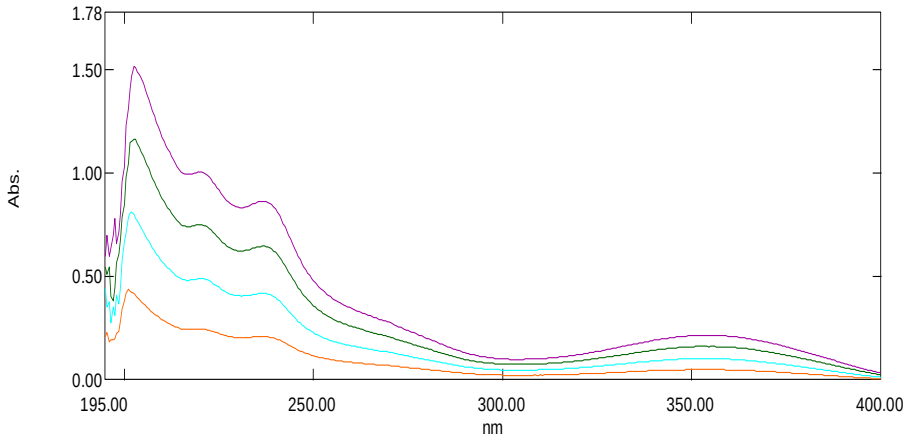

Fig: 5: The overlay UV spectrum of the drug

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iii. Preparation of standard Calibration curve for RP-HPLC:

In order to make the HPLC method's calibration curve, eight different concentrations of Lercanidipine HCl standard solution were mixed with mobile phase from their stock solution. The calibration curve was constructed by taking area on the Y-axis and concentration on the X-axis. The representative chromatogram of Lercanidipine HCl is shown in Figs. 6 and 7. The linearity curve of Lercanidipine HCl is shown in Fig. 4, and the linearity data is shown in Table 4. The linear regression equation was found to be Y = 49,901.5198 x + 27,678.7201, and the Correlation co-efficient R^2 = 0.9999.

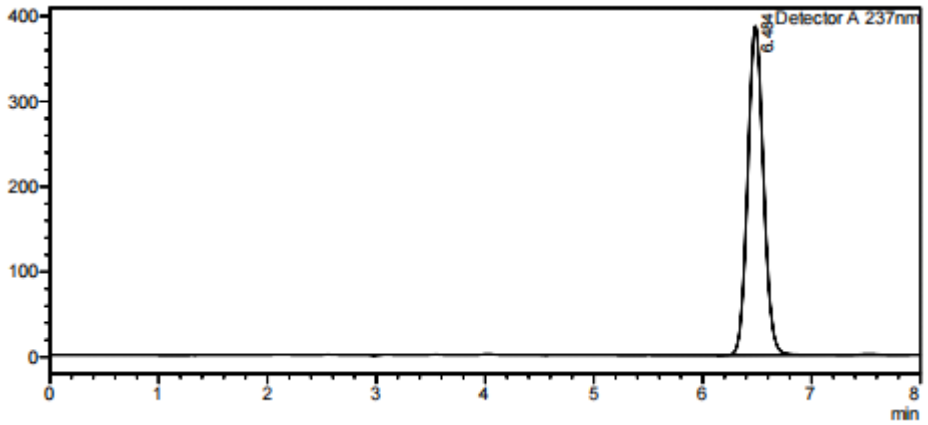

Fig: 6: Representative chromatogram of Lercanidipine HCl (80µg/ml)

Assay of Tablets

Twenty tablets were weighed and crushed to form a fine powder. The accurately weighed quantity of powder equivalent to 10.0 mg Lercanidipine HCl was transferred to a 100-ml volumetric flask containing a 40-ml mobile phase. The solution was sonicated for 10 minutes, and the volume was diluted to the mark with the mobile phase to obtain the sample stock solution (100µg/ml). The solution was filtered through a 0.45µm membrane filter paper. Appropriate volumes of the aliquot were transferred into five different 10 ml volumetric flasks, and the volume was made up to the mark with mobile phase to obtain 20µg/ml of Lercanidipine HCl. The solution was injected under the above chromatographic conditions, and peak areas were measured. The concentration of the formulation is measured by utilizing the linear regression equation. The results are shown in Table 5.

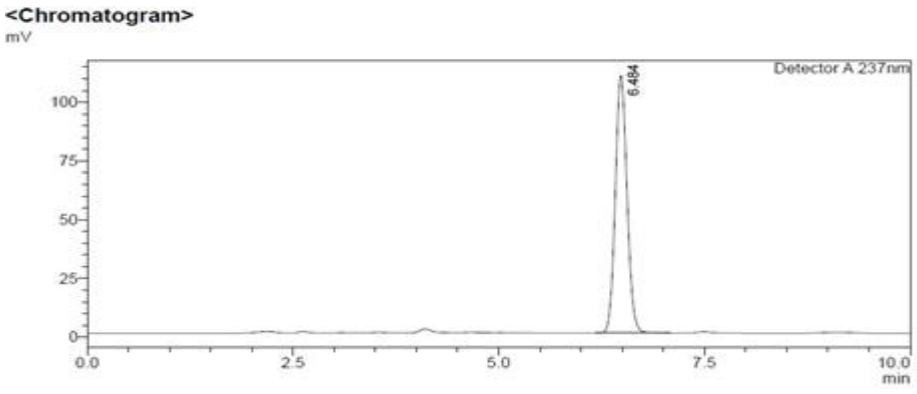

Fig 7 Chromatogram of Lercanidipine Hcl (20µg/ml)

Table-5 : Analysis of marketed tablet formulation (Lotensyl®10) (Sun Pharma) (n=5)

Method	Formulation	Label claim (mg/tab)	Amount found (mg/tab)	C.I.	% RSD	SE	t
2	20	10	10.072	100.7250 ± 1.157	0.721	0.363	1.993
1	10	10	10.12	100.7 ± 0.811	0.353	0.177	2.245

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SD: Standard deviation, SE: standard error, C.I.: Confidence Interval within which true value may be found at 95% confidence level = R ± ts/√n, R: Mean percent result of analysis of Recovery study (n = 4). Theoretical't' values at 95% confidence level for n - 1 degrees of freedom t (0.05, 3) = 3.182

METHOD VALIDATION

The method was validated according to International Conference on Harmonization guidelines for validation of analytical procedures.[34],[35],[36],[37]

System Suitability: System-suitability tests are an integral part of method development and are used to ensure adequate performance of the chromatographic system. Such Parameters like Retention time (Rt), peak area, number of theoretical plates (N), tailing factor (T), Asymmetry factor and resolution were evaluated. Six duplicates standard stock solution of drug Lercanidipine HCl was taken (50µg/ml) and analysis was performed at the optimized chromatographic conditions. The results are discussed in Table 6.

Table 6: Results of System suitability Parameter

Parameters	Lercanidipine	Limits
Repeatability (% RSD)	0.5671	<1.5
Asymmetry factor	1.14	<1.5
RetentionTime (mins)	6.48	———
Theoretical plates (N)	3084.693	(>2000)

Peak purity: The peak purity of Lercanidipine HCl was assessed by comparing the retention time (R_t) of standard Lercanidipine HCl. Good correlation was also found between the retention time of standard and sample of Lercanidipine HCl.

Precision: The intra-day and inter-day precision of the proposed methods were determined by measuring the responses four times on the same day and four different days over a period of one week for the same concentrations of Lercanidipine HCl (20 µg/ml). It was found to be less than 1% for within-day and day-to-day variations, which proves that the method is precise.

Recovery study: An accuracy study was performed by adding a known amount of standard solution into the test solution, called the spiking method. A known amount of the standard drug was added to pre-analyzed tablet samples at a level of 50%, 100%, and 150% in methods 1 and 2. The results of the recovery studies are shown in Table 7.

Table 7: Results of the Recovery Study

Method	% Level of recovery	Formulation (µg/ml)	Amount of pure drug added	Amount of drug found (µg/ml)	C.I.	% RSD	SE	t
2	50	20	10	29.962	99.875±1.436	0.901	0.45	0.276
	100	20	20	39.955	99.88±1.09	0.682	0.343	0.327
	150	20	50	70.072	100.10±1.26	0.793	0.397	0.26
1	50	10	5	15.025	100.20±1.96	20.371	10.206	0.323
	100	10	10	20.222	101.11±2.36	1.472	0.744	1.494
	150	10	15	24.97	99.88±1.21	0.765	0.382	0.313

Robustness: It was done by making small changes in the chromatographic conditions and found to be unaffected by small changes like ± 2% change in volume of the mobile phase, ± 2^0 C Temperature and ± 2% flow rate, & ± 2nm wavelength**.** In each conditions % RSD were found to be less than 1. So the method is robust.

LOD & LOQ : The sensitivity of method was estimated in terms of Limit of Detection (LOD) and Limit of Quantification (LOQ). LOD and LOQ of the newly proposed methods were calculated using the formula of ICH guideline;

Limit of Detection (LOD) = 3.3 × σ/S….Eq. 1

Limit of Quantitation (LOQ) = 10 × σ/S….Eq. 2

Where, "σ" is standard deviation of y intercepts of regression lines, "S" is Slope of calibration curve. The lower limit of detection and the limit of quantitation were found to be 0.199 and 0.341µg/ml respectively.

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Table 7: Summary of Validation Parameters

Parameter	AUC METHOD	RP-HPLC
λ_1& λ_2 range	350-360nm	237 nm
Linearity & range	5-30µg/ml	5-80 µg/ml
Slope	0.1083	49,901.5198
Intercept	- 0.0310	27,678.7201
Correlation coefficient (r^2)	0.9996	0.9999
LOD & LOQ (µg)	2.45 & 4.67	0.199 & 0.341

Results and Discussion: Two methods were developed and validated on the basis of ICH guidelines for the estimation of Lercanidipine HCl in pure form and in tablets. Double-distilled water is used as a diluent in Method 1. Methanol and water (90:10) were used as the mobile phase in method 2.

Method 1: The linear regression equation was found to be Y = 0.1109X-0.071 and r 2 = 0.998. The linearity and range were found to be 5 to 30 µg/ml. The % RSD was less than 2. The lower limit of detection and the limit of quantitation were found to be 2.45 and 4.67 µg/ml, respectively. It indicates that Method 1 is an accurate and precise.

Method 2:
The modalities adopted in experimentation were successfully validated as per the analytical procedures laid down in routine. A preliminary analysis of a typical sample and recovery studies served to validate the proposed method. The detection wavelength and chromatographic run times were selected at 237 nm and 10 min, respectively. The linear regression equation was found to be Y = 50865.49 x + 48544.27, with a correlation coefficient (r2) of 0.9999. The percentage of recoveries was obtained in the range of 99 to 102. The results of Student't' test are within the acceptable limit in the tablet assay and recovery study of this proposed method 2. In the robustness study, the normal result was unaffected by small changes like ± 2% change in organic solvent in the mobile phase, ± 2°C in temperature, ± 2% in flow rate, and ± 2nm of wavelength. Every parameter of robustness was found to be less than 1.5. The absence of additional peaks in the chromatogram indicates non-interference of the common excipients used in the tablets. The lower limit of detection and the limit of quantization were found to be 0.199 µg/ml and 0.341 µg/ml, respectively. Good correlations were found between the retention times of the standard and tablet samples of drugs.

CONCLUSION
The proposed AUC method for the estimation of Lercanidipine HCl in bulk and tablet dosage form is a new method along with highly selective and sensitive. The value of the % RSD was within the acceptable limit, indicating the reproducibility and accuracy of the proposed method. The developed RP-HPLC method was simple, sensitive, precise, and accurate; hence, it can be used routinely for the determination of Lercanidipine HCl in bulk and pharmaceutical dosage form. This demonstrates that the developed RP-HPLC method is new, simple, linear, accurate, robust, sensitive, and reproducible. Thus, the developed method can be easily used for the routine quality control of bulk and tablet dosage forms. Method 2 is more accurate and highly sensitive in comparison to Method-1.

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