ANALYTICAL METHOD DEVELOPMENT AND VALIDATION FOR AMLODIPINE ESTIMATION IN BULK AND PHARMACEUTICAL FORMULATION USING THE QBD APPROACH

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Abstract

A rapid, sensitive, robust, rugged and linear HPLC method is developed using QbD approach and validated as per ICH for the estimation of amlodipine impurities in tablet dosage form. Different concentration of mobile phase was used to get the satisfactory results, The mobile phase Buffer: Methanol: ACN (30:35:35) at pH to 4 is used as the mobile phase and 3µ particle size C18 column of 150 mm length and 4.6 mm internal diameter is used and it gives the extremely satisfactory results. Using photo diode array (PDA) detector, the compounds are monitored at 340 nm. The Design of Experiment Central Composite designs by Design expert 8 Software was used. HPLC methods were validated as linearity, precision, accuracy, specificity, system suitability, and robustness exceeded the limit. When compared to the previously reported method, the HPLC method is more sensitive, accurate, and precise. There was no excipient interference in the recovery study. The low percent RSD and molar extinction coefficient (L mol-1 cm-1) values indicated that the developed methods were sensitive. The proposed high-performance liquid chromatographic method was also evaluated for accuracy, precision, and robustness, and it was found to be convenient and effective for Amlodipine quality control. The developed method was found to be simple and cost effective for the quail.

Furthermore, the reduced solvent consumption results in a more cost-effective and environmentally friendly spectroscopic procedure. As a result, the proposed methodology is quick and selective, requires only a simple sample preparation procedure, and is suitable for Amlodipine.

Keywords

Amlodipine, HPLC, LOQ, QbD, linearity, precision, accuracy, specificity, system suitability etc.

Introduction:

Chromatography:- Chromatography is a technique for breaking down mixtures of substances into their constituents based on their molecular structure and composition. A stationary phase (a solid or a liquid supported on a solid) and a mobile phase are involved (a liquid or a gas)[1,2]. The mobile phase flows through the stationary phase, carrying the mixture's components with it. Sample components with stronger interactions with the stationary phase will move through the column more slowly than components with weaker interactions. The separation of various components is caused by the difference in rates. Chromatographic separations can be performed using a variety of stationary phases, including immobilised silica on glass plates (thin-layer chromatography), volatile gases (gas chromatography), paper (paper chromatography), and liquids (liquid chromatography) (liquid chromatography).[3,4,5]

 Amlodipine (chemically known as (RS)-3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate with molecular formulae $C_{20}H_{25}ClN_2O_5$ and molecular weight of 408.9 g/mol) is used to treat the high blood pressure by allowing the free flowing of blood through blood cells [6,7]. Amlodipine belongs to calcium channel blocker group. Many pharma companies are formulating and marketing amlodipine as single or in combination with other active ingredients under different brand names like Asomex, Istin, Norvasc, Caduet and Twynsta. Stability studies provide us with information on the quality of the drug product. The studies must include the tests, which can monitor the quality of the drug product [1] . Impurities can be generated by drug excipient interactions, storage conditions, hydrolysis etc. A sensitive, reproducible method is to be developed and validated to monitor the impurities in drug product.[8,9,10]

Literature survey reveals that some analytical methods are available for the estimation of amlodipine alone or in combination with other drugs using HPLC, HPTLC, and LC-MS [2] - [13] . Ph. Eur monograph method is also reported to estimate impurities in amlodipine besylate raw material. However, none of the analytical methods reported the estimation of all known and unknown impurities for amlodipine besylate. This paper describes the quantification of all impurities (IMP-A, IMP-B, IMP-D, IMP-E, IMP-F, IMP-G and IMP-H) of amlodipine besylate in amlodipine tablets.[11,12]

Materials And Methods:

1. **Material:**

Sr. No.	Name	Description
1.	Amlodipine	White powder, used to treat high blood pressure and coronary artery disease.
2.	Amidine 5	5.0 mg drug contain each tablet, Manufactured by Mylan Laboratories Limited, Marketed by Mylan Pharmaceuticals Pvt. Ltd.

Table 1: Active Pharmaceutical Ingredients.

SR NO.	NAME OF CHEMICAL	MOLECULAR FORMULA	PROPERTIES	MANUFACTURER
1.	Acetonitrile	C_2H_3N	Solvent, BP 76-81.6°C	Merck Life science
2.	Methanol	CH_3OH	Flammable Solvent	Merck Life science
3.	Distilled Water	H_2O	Universal Solvent, BP 100°C	

Table 2: List of Chemicals use in Research work

2. Methods [13,14,15,16]

1. Preliminary Analysis of Drug

a) Description

Color and texture of Amlodipine Besylate was compared with reported characters mentioned in drug bank.

b) Solubility

Solubility of Amlodipine Besylate was determined in various solvents like water, methanol, ethanol, Acetonitrile and dimethyl formamide or chloroform.

c) UV Analysis

UV analysis was carried out by scanning the solution of Amlodipine Besylate at 200-400 nm.

2. Design of Experiment

Central Composite designs by Design expert 8 Software

When the factor number is greater than 2, the number of experiments required for this design (calculated by expression N = 3k, where N is the experiment number and k is the factor number) is very large, reducing its efficiency in the modelling of quadratic functions. Because a complete Central Composite design with more than two variables necessitates more experimental runs than are typically available in practise, designs with a smaller number of experimental points are preferred. The vast majority of Central Composite factorial designs are used in chromatography.

Selection of Dependent factors

1. Mobile Phase

2. pH of Mobile phase

Selection of Independent factors

1. Retention Time

2. Theoretical Plate

3. Asymmetry

Following mobile phases selected

✓ Phosphate buffer : Acetonitrile: Methanol

✓ Water : Acetonitrile: Methanol

Central Composite Factorial design facilitate only one mobile phase at a time

✓ Phosphate buffer : Acetonitrile: Methanol

✓ Change pH Range: 3-5

Change Mobile phase proportion Range: 20-40% (Consider Aqueous)

3. Preparation of mobile phase

70 mL of HPLC grade Methanol and Acetonitrile (35:35) were combined with 30 mL of Buffer or Water (35:35:30). Acetonitrile: Methanol: Water

Orthophosphoric acid was used to adjust the pH to 3, 4, and 5. The solution was filtered through a 0.45 membrane filter and then sonicated for 10 minutes in a sonicator bath.

4. Preparation of stock solutions of Amlodipine Besylate

Stock solution was made by dissolving 10 mg Amlodipine Besylate in water and then diluting it with water in a volumetric flask of 10 ml to achieve a concentration of 1000 g/ml. 0.1 ml of the resulting solution was diluted to 10 ml with water to obtain a concentration of 10 g/ml of Amlodipine Besylate, which was labelled as standard stock. Besylate Amlodipine.

5. Selection of detection wavelength

Further dilutions of the standard stock solution were made with water and scanned over the range of 200-400 nm, with the spectra being overlain. It was discovered that the drug had a high absorbance at 210 nm.

Results of Trials:

Trials given by Design Expert software

Standard concentration of Amlodipine was taken 20 µg/ml. using Central Composite Factorial design gave 13 run at different pH, Solvent proportion two Solvent Combination with 13 runs for each Solvent Combination. Software give its 13 runs.

Table no 3: Run Suggested by Software for each Solvent.

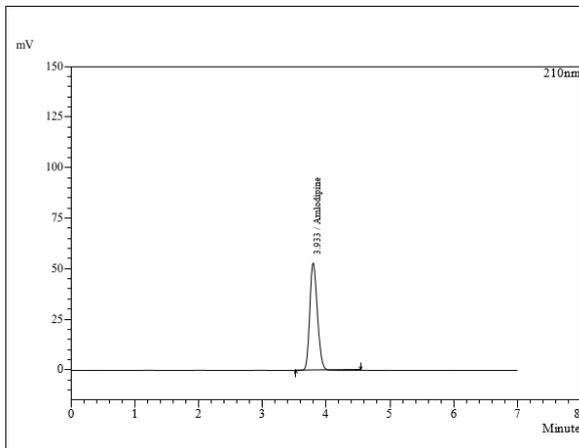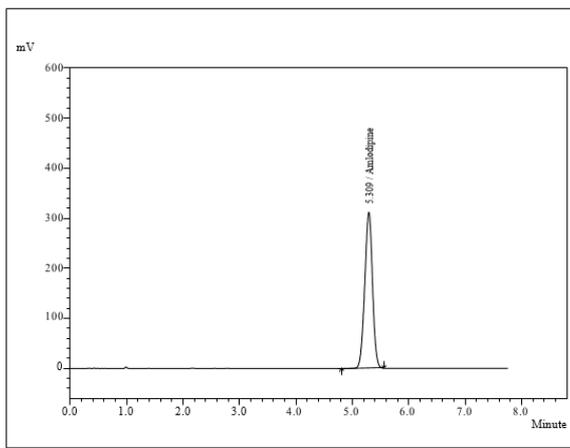| Sr. No	Mobile Phase Composition (Aqueous Phase)	pH of Buffer
1	44.14	4.00
2	30.00	4.00
3	40.00	5.00
4	30.00	2.59
5	30.00	5.41
6	20.00	5.00
7	30.00	4.00
8	40.00	3.00
9	20.00	3.00
10	30.00	4.00
11	30.00	4.00
12	30.00	4.00
13	15.86	4.00

Fig No. 1 Chromatogram of Amlodipine at Buffer (33:33:44) at pH 4.0

Fig .2 Amlodipine at ACN: MeOH: Buffer   ACN: MeOH: (35:35:30) at pH 4.0
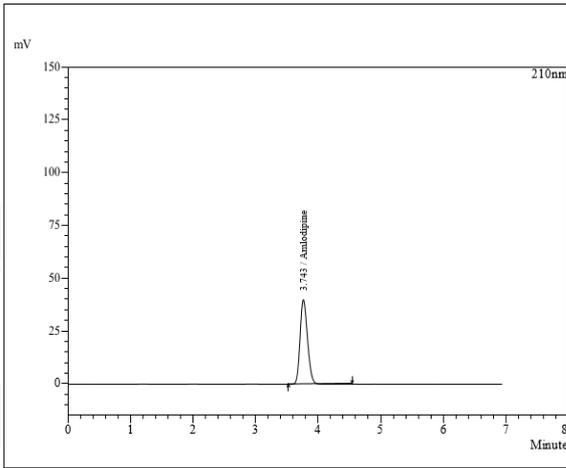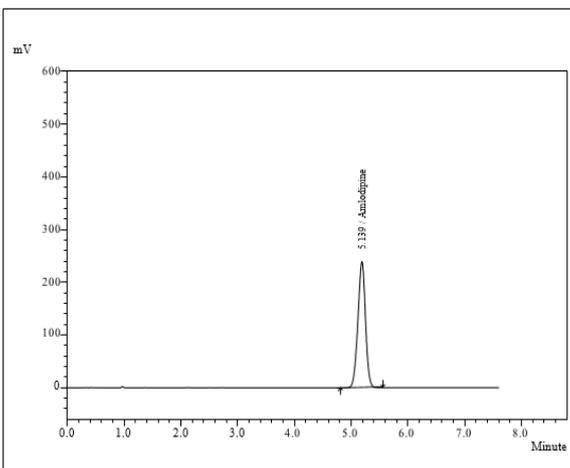

Fig 3 ACN: MeOH: Buffer (30:30:40) at pH 5.0

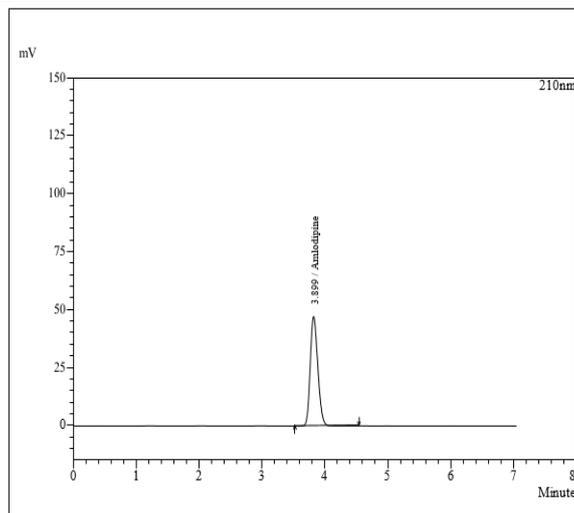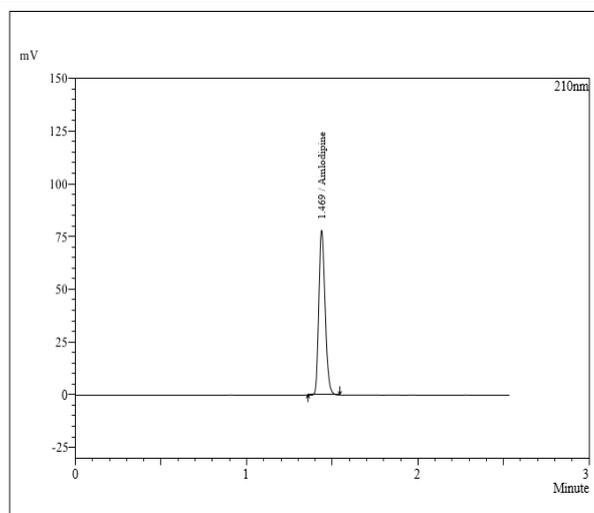**Fig 4: ACN: MeOH: Buffer (30:30:40) at pH 5.14**

Fig 5: ACN: MeOH: Buffer (40:40:20) at pH 5.0   **Fig 6:** ACN: MeOH: Buffer (35:35:30) at pH 4.0
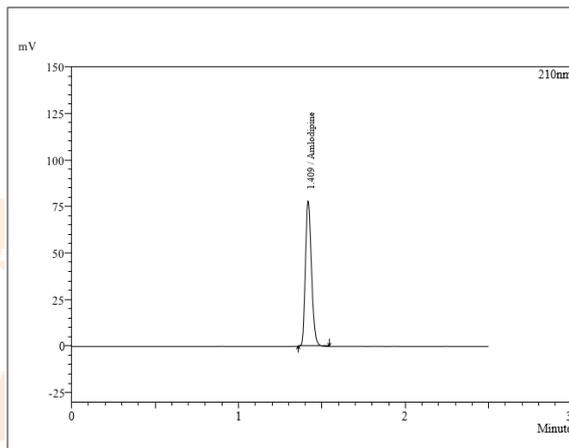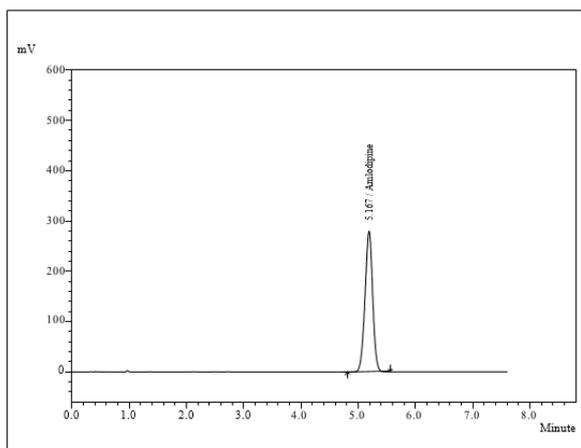

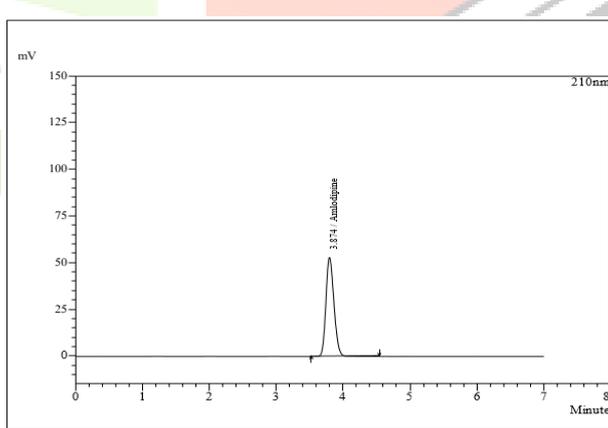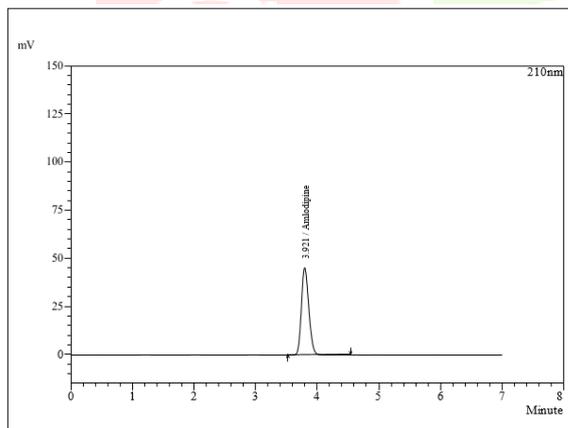**Fig 7:** ACN: MeOH: Buffer (30:30:40) at pH 3.0   **Fig 8:** ACN: MeOH: Buffer (40:40:20) at pH 3.0

Fig 10: ACN: MeOH: Buffer (35:35:30) at pH 4.0 **Fig 11:** ACN: MeOH: Buffer (40:40:30) at pH 4.0
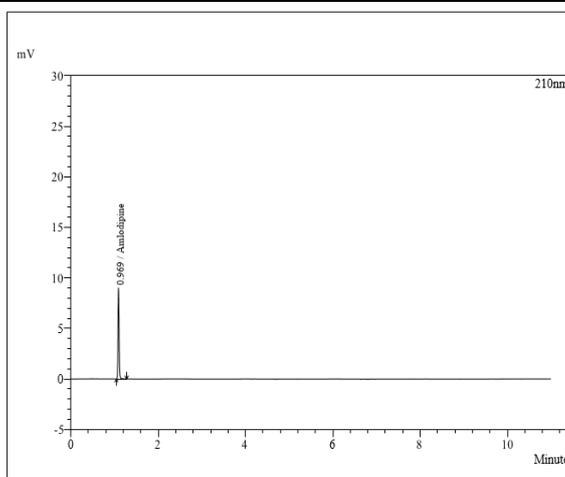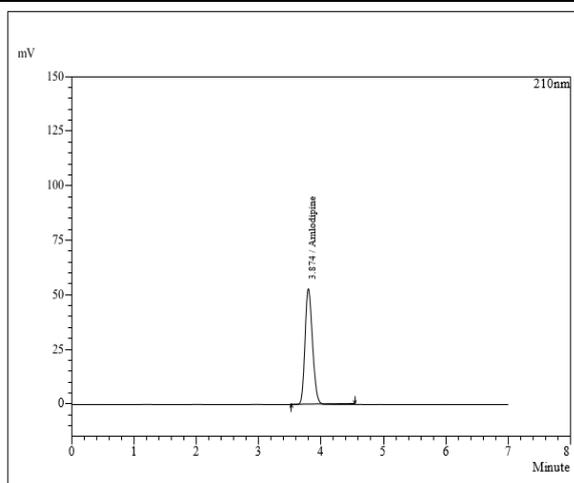
Fig 12: ACN: MeOH: Buffer (40:40:30) at pH 4.0   **Fig 13:** ACN: MeOH: Buffer (42:42:16) at pH 4.0

DESIGN EXPERT HAS OPTIMIZED THE FOLLOWING CHROMATOGRAPHIC CONDITIONS WITH RESPECT TO DESIRABILITY VALUE:

Table.4: Optimised Result of mobile phase (35:35:30 v/v) with aqueous phase Trials performed on C18 column at mobile phase (70:30 v/v) with aqueous phase pH 4.0 are extremely Satisfactory.

Sr. No	Mobile Phase Composition (Organic Phase)	pH of Buffer	Retention Time	Asymmetry	Theoretical Plates
1	44.14	4.00	5.339	1.32	4187
2	30.00	4.00	3.933	1.45	9687
3	40.00	5.00	5.126	1.85	5214
4	30.00	2.59	3.547	1.34	9684
5	30.00	5.41	3.784	1.79	9951
6	20.00	5.00	1.922	1.88	7462
7	30.00	4.00	3.899	1.21	8954
8	40.00	3.00	5.187	1.34	6528
9	20.00	3.00	1.752	1.26	3246
10	30.00	4.00	3.921	1.13	9564
11	30.00	4.00	3.935	1.34	9862
12	30.00	4.00	3.874	1.1	8914
13	15.86	4.00	0.984	1.26	4687

OPTIMIZATION:

- **Optimization Result**

Screening design for suitable chromatographic condition:

Peak parameters are used to select the best column and solvent system. Acetonitrile: Methanol: Water, Acetonitrile: Methanol: Buffered

Table 5. Trials performed on C18 column at mobile phase (15.86:42.04:42.04 v/v/v) with aqueous phase pH 4.

Sr. no.	Composition	Observation	Remarks
1	Water: Methanol: ACN (15.86:42.04:42.04 v/v/v)	Very Less Retention Time and small peak appeared	Not Satisfactory
2	Buffer: Methanol: ACN (15.86:42.04:42.04 v/v/v)	Very less Retention Time and more asymmetric factor	Not Satisfied

Table 6: Trials performed on C18 column at mobile phase (20:40:40 v/v) with aqueous phase pH 3

Sr. no.	Composition	Observation	Remarks
1	Water: Methanol: ACN (20: 40:40)	Less Theoretical Plates with very less Retention time	Partly Satisfactory
2	Buffer: Methanol: ACN (20: 40:40)	Less peak asymmetry but less theoretical plates	Satisfied

Table 7. Trials performed on C18 column at mobile phase (60:40 v/v) with aqueous phase pH 5

Sr. no.	Composition	Observation	Remarks
1	Water: Methanol: ACN (40:40:20)	Greater peak asymmetry with less theoretical plates	Very Dissatisfactory
2	Buffer: Methanol: ACN (40:40:20)	Very Less Retention time and more asymmetric factor	Satisfied

Table 8. Trials performed on C18 column at mobile phase (30:35:35 v/v/v) with aqueous phase pH 2.59

Sr. no.	Composition	Observation	Remarks
1	Water: Methanol: ACN (30:35:35)	Very Small Peak appeared	Not satisfactory
2	Buffer: Methanol: ACN (30:35:35)	Greater peak Asymmetry and lower theoretical plates	Not satisfactory

Table 9: Trials performed on C18 column at mobile phase (30:35:35 v/v/v) with aqueous phase pH 4

Sr. no.	Composition	Observation	Remarks
1	Water: Methanol: ACN (30:35:35)	Good Retention time but poor peak properties	Satisfactory
2	Buffer: Methanol: ACN (30:35:35)	Good peak properties, less retention time with higher theoretical plates	Extremely Satisfactory

Table 10. Trials performed on C18 column at mobile phase (40:30:30 v/v/v) with aqueous phase pH 5

Sr. no.	Composition	Observation	Remarks
1	Water: Methanol: ACN (40:30:30 v/v/v)	Small Peak Appeared	Not Satisfactory
2	Buffer: Methanol: ACN (40:30:30 v/v/v)	Poor peak properties	Not Satisfactory

Table 11: Trials performed on C18 column at mobile phase (80:20 v/v) with aqueous phase pH 6 are extremely Satisfactory. Design expert has optimized the following chromatographic conditions with respect to desirability value.

Sr. No	Mobile Phase Composition (Organic Phase)	pH of Buffer	Retention Time	Asymmetry	Theoretical Plates
1	44.14	4.00	5.539	1.32	4187
2	30.00	4.00	3.933	1.45	9687
3	40.00	5.00	5.626	1.85	5214
4	30.00	2.59	3.547	1.34	9684
5	30.00	5.41	3.784	1.79	9951
6	20.00	5.00	1.922	1.88	7462
7	30.00	4.00	3.899	1.21	8954
8	40.00	3.00	5.187	1.34	6528
9	20.00	3.00	1.752	1.26	3246
10	30.00	4.00	3.921	1.13	9564
11	30.00	4.00	3.935	1.34	9862
12	30.00	4.00	3.874	1.1	8914
13	15.86	4.00	0.784	1.26	4687

Table 12. Optimized trials suggested by software based on desirability value.

Sr. no.	Amount of Buffer	pH of buffer	Retention time	Tailing factor	Theoretical plates	Desirability
1	24.65	3.75	2.86741	1.208	8258.57	0.716

Optimized chromatographic conditions

Phase of mobility: Phosphate Buffer: Methanol: Acetonitrile (24.65: 37.67: 37.67 v/v/v), buffer pH: 3.75 Analytical column: Waters XBridge C18 column (4.6 250mm id. particle size 5m), UV detection: 210 nm, Flow rate: 1.00, injection volume: 10 LmL min $^{-1}$, Temperature: Ambient, Run time: 10 min.

Effect of independent variables on retention time (X):

The proposed Response Surface Linear Model was found to be significant after applying the experimental design, with a model F value of 289.78, a p value less than 0.005, and an R2 value of 0.9952. Only 0.09 percent of the time could a "Model F-Value" this large occur due to noise. The adjusted R2 value was 3.57, and the percent C.V. value was 0.9918. The model for response X (Retention time) is as follows:

The equation for response surface quadratic model is as follows

Retention Time = +3.91+1.73 * A+0.12 * B +0.067 * A * B -0.32 * A2-0.071 * B2   (1)

Fig.3 (b) depicts a graphical representation of the pH of the buffer (B) and the amount of ACN (A), with the flow rate (C) held constant at its optimum of 1 mL min-1. Changes in buffer pH resulted in a slight change in retention time (X), and decreases in buffer amount resulted in a decrease in retention time.
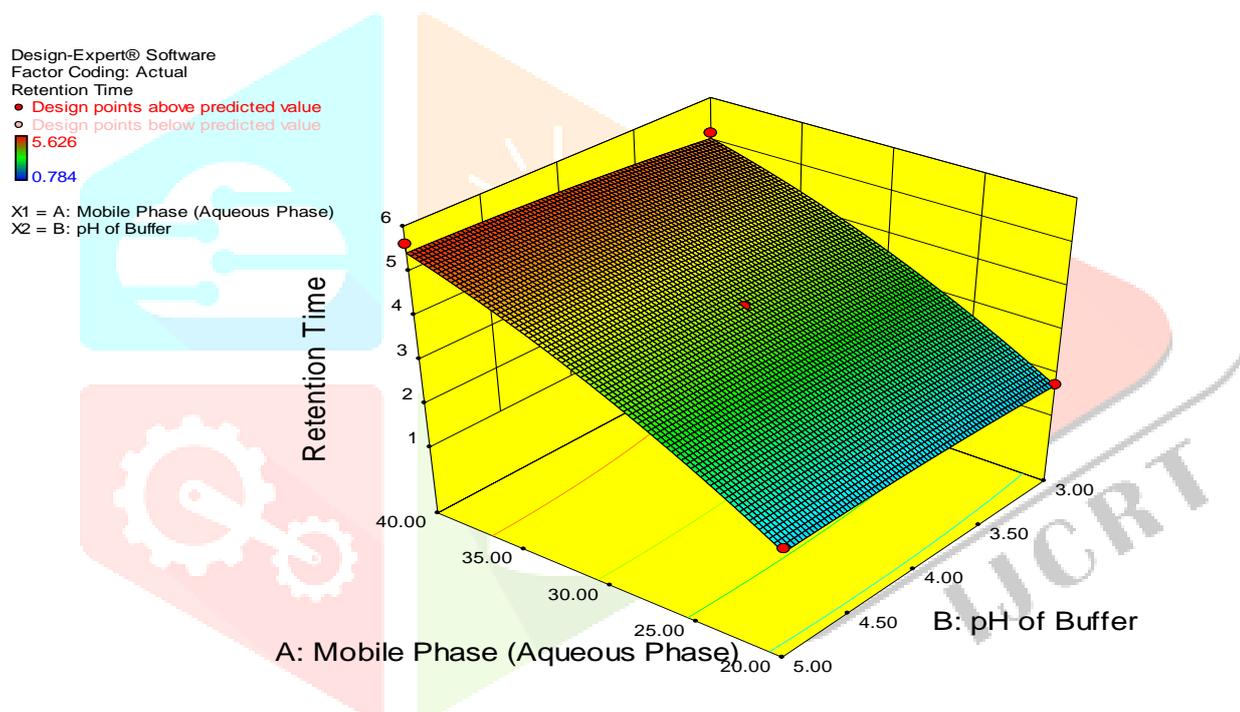

Fig. 14: Three-dimensional plot for retention time as a function of pH of buffer and amount of buffer. Constant factor (flow rate- 1mL min^{-1})

Fit summary: Linear model was suggested by the software.

ANOVA: ANOVA of developed Full three level factorial model for retention time (Y$_1$).

Model terms are significant when the "Prob > F" (p- value) is less than 0.0500. A and   B are

significant model terms in this case.

Table 14. Significance of *p* value on model terms of retention time.

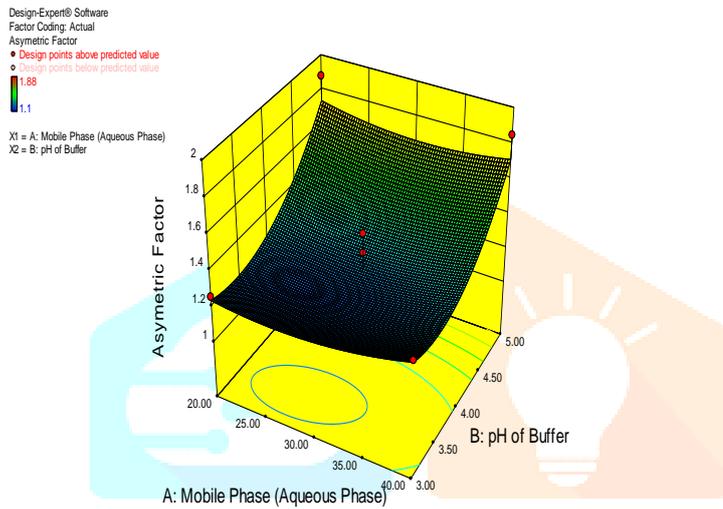| Model terms	p value	Effect of factor	Remarks
A	0.0001	1398.66	Significant
B	0.0383	6.49	Significant
AB	0.3389	1.05	Insignificant
A^2	0.0003	42.35	Significant
B^2	0.1940	2.06	Insignificant
Overall model	0.0001	-	Significant

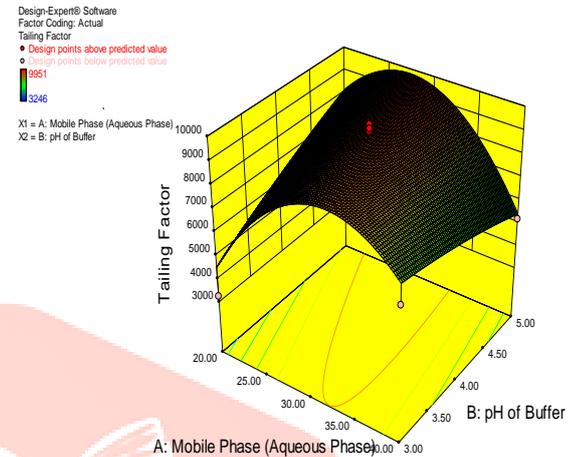**Fig 15: Three-dimentional plot for tailing factor**   **Fig.16 3D plot for theoretical plates**

**Table 15. Significance of *p* value on model terms of tailing factor.**

Model terms	p value	Effect of factor	Remarks
Model	0.0202	5.74	Significant
A	0.7653	0.096	Insignificant
B	0.0048	16.53	Significant
AB	0.7309	0.13	Insignificant
A^2	0.3316	1.09	Insignificant
B^2	0.0114	11.59	Significant
Overall model	0.0202		Significant

Table 16. Significance of *p* value on model terms of theoretical plates

Model terms	p value	Effect of factor	Remarks
A	0.9081	0.014	Significant
B	0.2687	1.44	Insignificant
AB	0.0242	8.21	Significant
A^2	0.0001	61.00	Significant
B^2	0.6600	0.21	Insignificant
Overall model	0.0015	14.20	Significant

VALIDATION:

Table 17: Linearity Result of Amlodipine.

Sr.No.	Concentration (µg/ml)	Peak Area
1	5	113879
2	10	219843
3	15	332801
4	20	431312
5	25	550069

Linearity

$y = 21677x + 4426.1$
$R^2 = 0.9994$
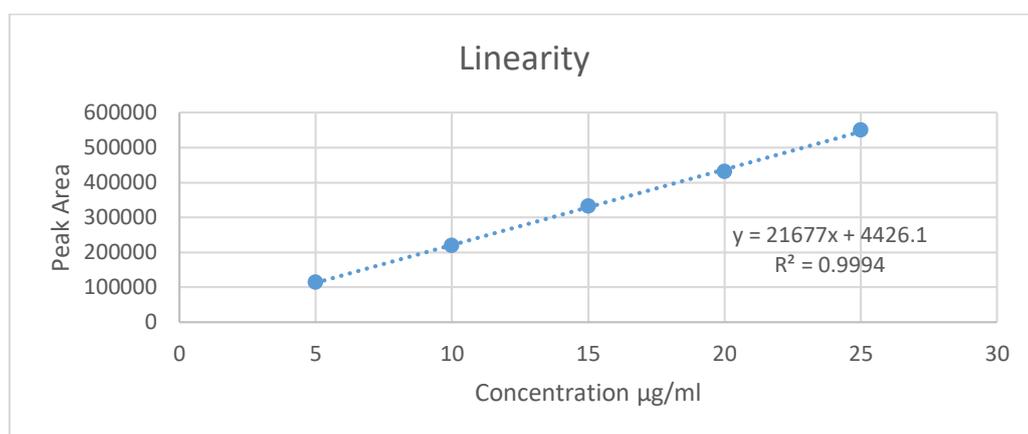
Fig No. 17 Calibration Curve of Amlodipine.
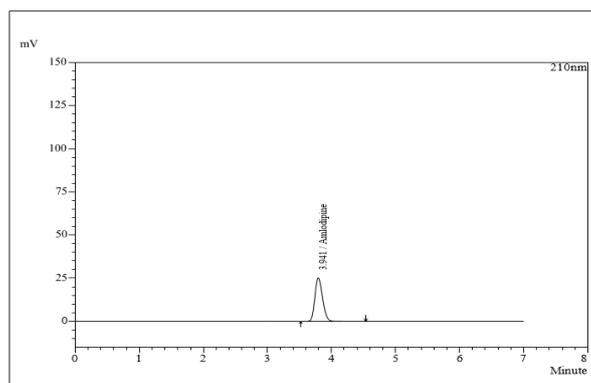
Fig 18: Amlodipine Standard

[Concentration 5µg/ml]
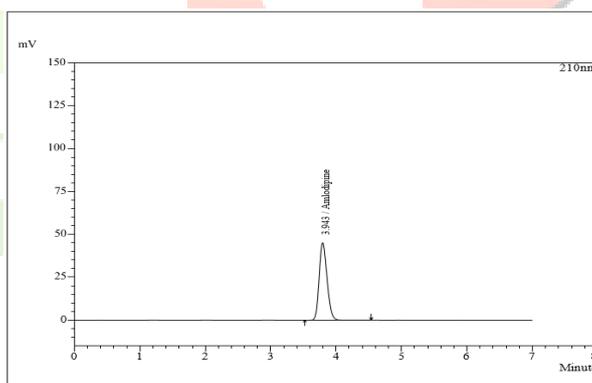
Fig 19: Amlodipine Standard

[Concentration 10µg/ml].

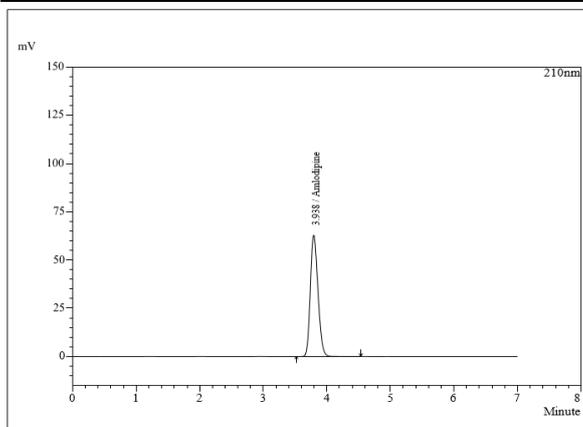**Fig 20: Amlodipine Standard**

[Concentration 15μg/ml]
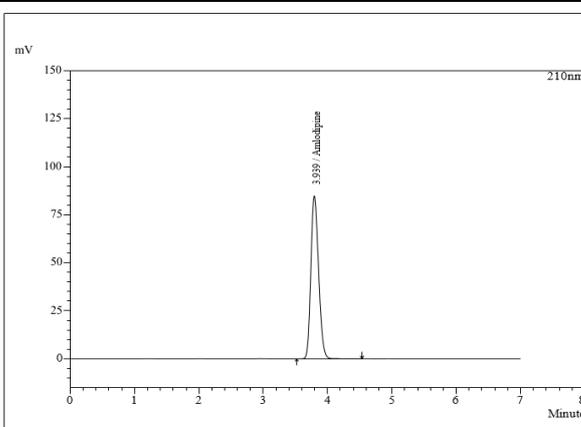
Fig 21: Amlodipine Standard

[Concentration 20μg/ml].

Table 22 Characteristic parameters of Amlodipine for the proposed HPLC method.

Parameter	Result
	Amlodipine
Calibration range (μg/ml)	5-25
Detection wavelength (nm)	210
Mobile phase	Methanol: Acetonitrile: Water (35:35:30 v/v/v)
Regression equation (y*)	y = 21677x + 4426.1
Slope (b)	21677
Intercept (a)	4426.1
Correlation coefficient(r2)	0.9994

Table 23. System suitability studies of Amlodipine by HPLC method.

Sr. No.	Properties	Values
1.	Retention time	3.943 min
2.	Area	434342
3.	Asymmetry	0.92

Table 24: Specificity of Amlodipine by HPLC method.

Concentration	API Area	Tablet Area
10	219855	219984
10	219971	219910
10	214238	214168
10	218973	218796
10	216153	216054
10	216841	216174
Mean	217672	217514
SD	2303.64	2391.99
RSD	1.06	1.10

Table 25: Intraday Precision of Amlodipine at 210nm

Concentration	Peak Area		
	0 Hrs	2 Hrs	3 Hrs
10	219855	219125	219992
10	219971	219845	220014
10	214238	216512	217674
10	218973	213785	213946
10	216153	215846	216473
10	216841	214979	215783
Mean	217672	216682	217314
SD	2303.64	2366.15	2407.74
RSD	1.06	1.09	1.11

Table No. 26 Interday Precision of Amlodipine at 210nm.

Concentration	Peak Area		
	1 day	2 day	3 day
10	219855	221432	224157
10	219971	220084	220173
10	214238	219988	226153
10	218973	222384	220493
10	216153	216134	220397
10	216841	216849	219982
Mean	217672	219479	221893
SD	2303.64	2489.35	2610.81
RSD	1.06	1.13	1.18

Table 28: Accuracy of Amlodipine at 210 nm.

Sr. No.	Concentration	Peak Area	recovery%
1	16	175912	100.16
2	16	175884	100.07
3	16	175998	100.21
4	20	219621	99.21
5	20	219774	99.75
6	20	219886	100.12
7	24	269826	99.98
8	24	269901	100.50
9	24	270124	100.66

Table 29: Robustness of Amlodipine at 210nm and 215nm

Conc. (µg/ml)	Area	
	210 nm	215 nm
10	219855	199284
10	219971	194682
10	214238	193541
10	218973	192973
10	216153	195546
10	216841	196487
Mean	217672	195419
SD	2303.64	2286.83
RSD	1.06	1.17

Summary:

The contents of the thesis have been divided into eight chapters and appropriate references have been placed after the 9th chapter.

Spectrophotometric method was developed for the estimation of Amlodipine in Pharmaceutical Formulation by QbD approach.

- Designed of Experiment by Design expert software.
- Optimized and Developed method for Spectrophotometry.
- Spectrophotometric method was validated for Linearity, Accuracy, Interday & Intraday Precision, Specificity & Selectivity, Sensitivity, Robustness.
- Designed of Experiment by Design expert software.
- Optimized and Developed method for Chromatography.
- Chromatographic method was validated for Linearity, Accuracy, Interday & Intraday Precision, Specificity & Selectivity, Sensitivity, Robustness.
- All the developed methods were successfully applied to determine the drugs in Pharmaceutical preparation.

Conclusion:

It is always necessary to develop methods capable of analysing a large number of samples in a short period of time with due accuracy and precision for routine analytical purposes. Amlodipine is listed in the Indian Pharmacopoeia.

HPLC, HPTLC, and UV- Visible spectrophotometric methods are among the few analytical methods that have been published in the literature for the determination of Amlodipine. In light of the foregoing, some simple analytical methods with sensitivity, accuracy, precision, and economy were planned to be developed. In the current study, an HPLC method (Using Quality by Design) was used to quantify Amlodipine in bulk drug and pharmaceutical formulations according to ICH guidelines. HPLC methods were validated as linearity, precision, accuracy, specificity, system suitability, and robustness exceeded the limit. When compared to the previously reported method, the HPLC method is more sensitive, accurate, and precise. There was no excipient interference in the recovery study. The low percent RSD and molar extinction coefficient (L mol-1 cm-1) values indicated that the developed methods were sensitive. The proposed high-performance liquid chromatographic method was also evaluated for accuracy, precision, and robustness, and it was found to be convenient and effective for Amlodipine quality control. The developed method was found to be simple and cost effective for the quail. Furthermore, the reduced solvent consumption results in a more cost-effective and environmentally friendly spectroscopic procedure. As a result, the proposed methodology is quick and selective, requires only a simple sample preparation procedure, and is suitable for Amlodipine.

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